 DOI: 10.18231/2394-4994.2017.0044

Comparison of Ketamine versus Fentanyl as an adjuvant with Propofol for inserting Laryngeal Mask Airway

Mohan Kumar RM[1], Muralidhara Danappa Patel[2,*], Hemavathi Balachander[3], Satyen Parida[4]

[1]Assistant Professor, ESIC-PGIMSR & Medical College, Rajajinagar, Bangalore, [3]Professor, [4]Associate Professor, Dept. of Anaesthesia & Critical Care, JIPMER, Puducherry, [2]Associate Professor, Dept. of Anaesthesia, Shridevi Institute of Medical Sciences & Research Hospital, Tumkur

***Corresponding Author:**
Email: binmurali@gmail.com

Abstract

Materials and Methods: 120 adult, ASA 1 and 2 patients were randomly allocated into two groups, propofol-ketamine (PK) and propofol-fentanyl (PF), (n=60 in each group) Baseline parameters- oxygen saturation (SpO2), Mean Blood Pressure (BP), Pulse Rate (PR) and End Tidal carbon dioxide (EtCO2), were recorded following which 1µg/ kg Fentanyl to the PF group & 0.5 mg/kg Ketamine to the PK group was given intravenously. Induction was initiated with infusion of 1% Propofol @ 1mg/ kg/ min with a syringe pump to avoid apnea. Tolerance to jaw thrust was regarded as end point for LMA insertion. Statistical analysis done by Parametric and non parametric values were analyzed using student's unpaired t-test and Mann Whitney's U test respectively. Intragroup differences analyzed by one-way ANOVA with significance using Tukey's method. The incidence of apnea was analyzed using Chi- square test. $P<0.05$ was considered significant.

Results: There was a significant($P<0.05$) fall in heart rate, the systolic, diastolic & mean arterial pressures, from baseline to LMA insertion in the propofol-fentanyl group when compared to propofol-ketamine group. No significant difference in the insertion conditions was noted between the two groups. None of the patients in either of the two groups had any significant adverse events.

Conclusion: we conclude that propofol-ketamine preserves hemodynamic and ventilatory stability compared to propofol-fentanyl, while providing similar LMA insertion conditions.

Key Message: Infused Propofol - ketamine combination can be a better alternative to Infused propofol fentanyl for induction and insertion of LMA in selected group of patients where maintenance of blood pressure and ventilation are utmost important during induction.

Keywords: Propofol, Ketamine, Fentanyl, Laryngeal mask airway, General anaesthesia

Date of Acceptance: 27th January, 2017 **Date of Manuscript Receive:** 7th November, 2016

Introduction

The laryngeal mask airway (LMA) is often inserted without using neuromuscular blocking agents. Anesthesia, which is deep enough to obtund the airway reflexes, is essential to obtain optimal conditions for insertion of LMA. Propofol depresses both pharyngeal and laryngeal reflexes more than thiopentone[1,2,3] and thus facilitates insertion of LMA.

Many adjuvants have been used to further improve the insertion conditions, of which opioids have been commonly studied. Addition of fentanyl to propofol provides excellent LMA insertion conditions. However, this combination is more often associated with significant hypotension, bradycardia and respiratory depression.[4] This might be critical in hemodynamically unstable patients. Addition of ketamine to propofol has been shown to be additive at both the end points of hypnosis and anesthesia. This may be beneficial for LMA insertion which needs sufficient depth of anesthesia to obtund airway reflexes to prevent patient responses like gagging, coughing and movement. Ketamine, with its cardio stimulant effects due to sympathomimetic actions, when used with propofol for induction of general anesthesia, balances the cardio depressant effects of propofol thereby maintaining hemodynamics better than fentanyl,[5] Hence this study was designed with the objective of evaluating the use of combination of propofol-ketamine and propofol- fentanyl for LMA insertion, both with respect to insertion conditions as well as hemodynamic stability.

Materials and Methods

This study was conducted in Jawaharlal Institute of Post Graduate Medical Education and Research **(JIPMER)** Puducherry. After approval of institutional research and ethics committee. 120 ASA 1 and 2 adults scheduled for elective surgical procedures under general anesthesia were recruited for the study after obtaining a written informed consent. All patients were comparable with respect to the demographic characteristics **(Table 1).** Patients who had any contraindications for LMA usage like mouth opening <2 cms, complete upper airway obstruction, those with increased risk of aspiration(pregnancy, full stomach patients), those with high airway pressure (bronchospasm) &/ low pulmonary compliance(morbid

obesity) and history of allergic reactions to any of the study drugs were excluded from the study.

The current study was designed to test the hypothesis that propofol-ketamine provides better hemodynamic stability and insertion conditions for LMA insertion as compared to propofol-fentanyl.

The sample size was calculated using power analysis to get an expected 20% difference between the two groups in hemodynamic response, for insertion of LMA, on first attempt, with alpha= 0.05 and power of beta=0.8.

The patients were randomly assigned to group PK (propofol-ketamine, n = 60) and group PF (propofol-fentanyl, n = 60) by sealed envelope technique by a person other than the anaesthesiologist involved in the study.

All patients were premedicated with intramuscular injection of Glycopyrrolate (0.3 mg) given 30 min before surgery. In the operating room, baseline cardiorespiratory parameters (pulse rate, non-invasive blood pressure, oxygen saturation at room air, End tidal CO_2 tension and electro-cardiogram) were recorded. Following preoxygenation for 3 min, injections of midazolam(20µg/kg) followed immediately by drugs 1 and 2, given at 4 mins and 1 min prior to induction of anesthesia respectively (composition of both drugs were unknown to the anesthesiologist involved in the study, and was revealed only on completion of the study), were administered intravenously. Drug 1, given at 4 mins prior to induction, constituted fentanyl (1µg/kg) in group PF and placebo (normal saline) in group PK while drug 2, given at 1 min prior to induction, constituted ketamine (0.5mg/kg) in group PK and placebo (normal saline) in group PF. Induction of anaesthesia was achieved with propofol @ 1 mg/kg/min using a syringe driver pump. During the process of induction, jaw thrust manoeuvre was applied by progressively lifting the jaw forwards when the verbal contact with the patient was lost. Jaw thrust was relaxed to a previously tolerated level if a motor response was noticed and infusion was resumed until there was no motor response to a full forward thrust which was defined as the end point of induction to perform LMA insertion. LMA was inserted by the same anaesthesiologist, for all cases, in order to avoid inter-observer variations with respect to LMA insertion conditions, using classical approach as described by Brain. However, if patient showed any movement, an additional 0.5 mg/kg of propofol was administered as a bolus over 10 seconds. Successful LMA insertion was confirmed by clinical [ascertained by the ability to easily ventilate the lungs (assessed by chest movement), without any significant resistance or leak and no significant resistance to expiration with rapid refilling of the reservoir bag] and Etco2 trace. Airway was secured with an endotracheal tube if proper LMA positioning was not achieved after two attempts. Number of attempts for proper insertion of LMA were noted, the total dose of propofol needed at LMA insertion, the time taken to reach the end point and that for successful LMA insertion were noted. Patient acceptability for LMA insertion was assessed using a 6 variable 3 point scoring system (Table 2) Maintenance of anaesthesia was continued with 66% nitrous oxide in 33% oxygen and propofol infusion @ 200 □g/kg/min for first 10 min. Cardio-respiratory variables were recorded at insertion of LMA and every min thereafter for first 10 minutes. Surgery wasn't allowed to be started during these 10 minutes as we didn't wanted the study to be influenced by the surgical procedure.

Incidence of adverse events in the form apnea, desaturation and failure to position the LMA properly after 2 attempts were recorded. Any Apnea (cessation of spontaneous respiratory efforts) for more than 20 seconds and desaturation (below 92%) would be treated with artificial ventilation using 100% oxygen. In case of failure to insert LMA successfully, airway would be secured with endotracheal tube. In the event of severe fall in BP, propofol infusion would be stopped, IV fluid bolus (200ml) would be given and if still not responding, then vasopressor (mephenteramine 3mg aliquots, i.v) would be administered and these patients would be excluded from the study.

Data was analyzed using the SPSS statistical software, version 16.0. Parametric and non-parametric values were analyzed using student's unpaired t-test and Mann Whitney's U test respectively. Differences within the group for parametric variables at different time points were analyzed by one-way ANOVA with significance using Tukey's method. The incidence of apnea was analyzed using Chi- square test. $P<0.05$ was considered significant.

Results

The two groups were comparable with respect to the demographic characteristics **(Table 1).** There was no significant difference between the two groups. Total Propofol Dose at LMA Insertion(mg) and Time taken to achieve the end point of induction (loss of motor response to jaw thrust) & the time taken for LMA insertion were similar between the two groups **(Table 3)**. No difference in failure of LMA insertion between the groups. Regarding hemodynamics there was a significant fall in heart rate, the systolic, diastolic & mean arterial pressures, from baseline to LMA insertion in the propofol-fentanyl group when compared to propofol-ketamine group **(Table 4)**, A significant fall ($p<0.05$) in heart rate and mean percentage change in heart rate was noted at all intervals except at baseline, in propofol-fentanyl group, both within the group and in comparison to propofol-ketamine group **(Fig. 1).** The mean arterial pressure drop from baseline was significant in PF group (**Fig. 2**) and mean percentage changes in the mean arterial pressures were also found to be statistically different between the two groups only at LMA insertion and for the first four minutes

thereafter **(Table 6).** There was no significant change in the mean SpO_2 between the two groups **(Table 5).** Ventilatory parameter showed significant rise in $EtCO_2$ (mean) from baseline to LMA insertion, between the two groups, the rise being much more in propofol-fentanyl group **(Table 5).**

There was no significant difference in the patient response to LMA insertion (coughing, movement) while the incidence in apnea was more in the propofol-fentanyl group

Table 1: Demographic data

	Group PK (n=60)	Group PF (n=60)	Statistical significance
Age (years)#	28.4 ±8.6	30.1 ± 8.3	NS
Weight (kg)#	52.9 ±11.2	54.1 ± 9.9	NS
Gender	4/56	3/57	NS
Baseline Mean arterial pressure(MAP)	92.76±14.78	89.70±16.48	NS (P=0.3156)
Data expressed as Mean± 2 Standard Deviation and Percentages			

Table 2: LMA insertion scoring

Variables	0	1	2
Mouth opening	Full	Partial	Nil
Ease of insertion	Easy	Difficult	Impossible
Swallowing	Nil	Slight	Gross
Coughing	Nil	Slight	Gross
Laryngospasm	Nil	Partial	Total
Movement	Nil	Slight	Gross
Acceptability for LMA insertion was assessed using a 6 variable 3 point scoring system			

Table 3: LMA Insertion conditions

Parameter	Group PK (n=60)	Group PF (n=60)	Statistical significance
Total Propofol Dose at LMA insertion(mg)#	160.5 ± 76.4	164.3 ± 73.2	NS
Time to achieve End Point(sec)#	182.8 ±83.3	184.0 ± 89.1	NS
Time for LMA Insertion(sec)#	16.1 ± 2.5	17.1 ± 3.9	NS
Insertion Score: Median (Range)	0.50 (0 – 5)	0.00 (0 – 5)	NS
Failure of LMA Insertion	2/60 (3.3%)	1/60 (1.7%)	NS
Data expressed as Mean ± 2SD, Median (Insertion score) and Percentages			

Table 4: Changes in Hemodynamics from baseline after induction and LMA insertion

Parameter	Group PK (n=58)	Group PF (n=59)	Statistical significance
HR (bpm)#	-1.7±6.9	-9.3±8.2	P<0.05
SBP(mm of Hg) #	-1.8±9.8	-15.9±9.3	P<0.05
DBP(mm of Hg)#	-1.5±9.2	-11.7±9.7	P<0.05
MAP(mm of Hg)#	-1.8±9.1	-13.2±9.8	P<0.05
Decrease in Hemodynamics (HR, SBP, DBP, MAP) from the baseline expressed in – Mean ± 2SD and P value			

Table 5: Ventilatory parameters at LMA insertion

Parameter	Group PK (n=58)	Group PF (n=59)	Statistical significance
SpO_2 (mean)	99%	99%	NS
$EtCO_2$(mm of Hg)#	34.2±1.8	35.5±3.3	P<0.05
Data s expressed in percentages, ETCO2 as (Mean ±2 SD) & P value			

Table 6: Mean % change in MAP at different intervals

Mean % change in MAP at	Group PK (n=58)	Group PF (n=59)	P Value
0 min(LMA Insertion)	-1.6±10.2	-14.2±10.0	0.00
1 min	-3.0±10.3	-13.1±14.7	0.00
2 min	-5.4±10.1	-14.7±14.0	0.00
3 min	-7.8±10.3	-14.8±14.3	0.00
4 min	-7.5±10.9	-14.6±14.7	0.00
5 min	-9.8±10.7	-14.0±15.5	0.09

6 min	-9.0±10.4	-12.8±16.6	0.15
7min	-9.2±11.0	-9.5±17.3	0.91
8 min	-9.1±11.6	-9.3±16.8	0.93
9 min	-7.7±10.7	-8.5±16.6	0.77
10 min	-6.8±10.8	-5.5±18.1	0.64
Data expressed Mean ± 2SD and P value (<0.05) significant till 4 minutes			

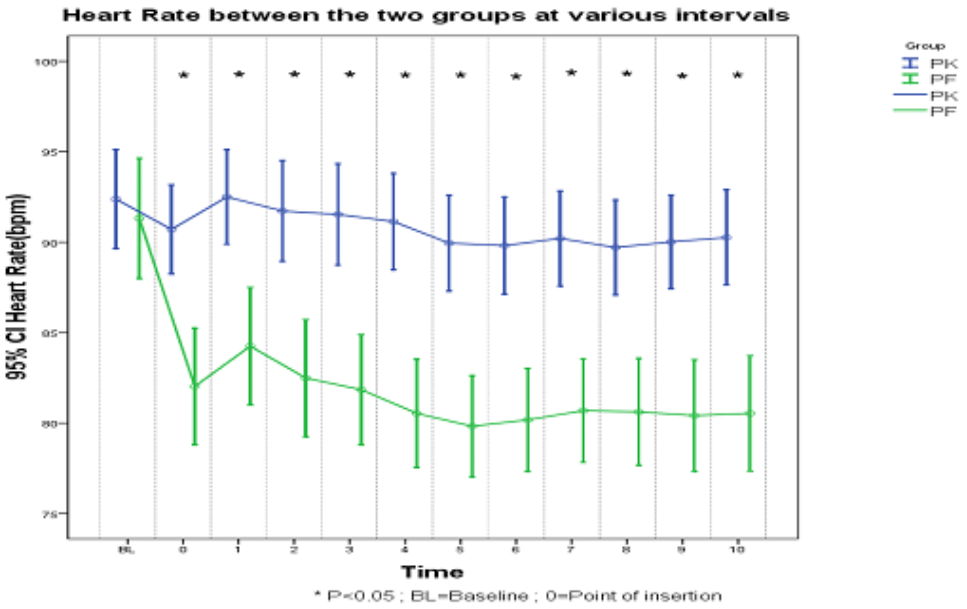

Fig. 1

***P<0.05, BL = Baseline, 0 = Point of LMA insertion, 1 – 10 = Time in mins after LMA insertion**

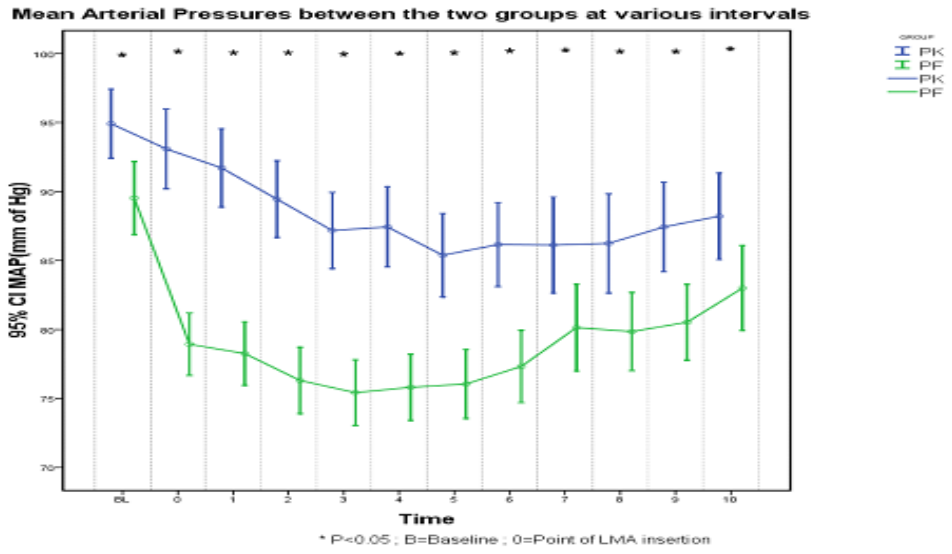

Fig. 2

Discussion

In this study, we studied side effect profile by comparing the hemodynamic & ventilatory stability with the combination of propofol- ketamine versus propofol- fentanyl.

Propofol is the preferred agent for insertion of LMA compared to thiopentone.[1,2,3] However, when used alone in unpremedicated patients, it provides unsatisfactory insertion conditions, giving rise to gagging, coughing, movement and even laryngospasm in the patient. Addition of fentanyl to propofol provides excellent conditions for LMA insertion.[4] However, this combination is more often than not associated with significant hypotension, bradycardia, respiratory depression and an increase in the incidence and duration of apnea,[5] above study showed prolonged

apnea in 23.1% in PF group whereas our study showed decreased incidence of apnea (8% in PK and 13.3% in PF group) in both the groups possibly due to infusion of propofol which caused slower rate of plasma effect site equilibration as mentioned in other studies.[6] This might be critical in hemodynamically unstable and cardiac patients.

Huit et al[7] showed the combination of ketamine and propofol has been shown to be additive at both the end points of hypnosis and anesthesia without an effect on ED 50 of Propofol on apnea with advantages of its cardio stimulant effects due to sympathomimetic actions, which balances depressant effects of propofol. We compared ketamine and fentanyl as an adjuvant with propofol for side effects during the insertion of LMA where propofol ketamine (PK) combination had decreased incidence of apnea (3/60) 5% compared to PF (8/60) 13.3%. Also, when used for total intravenous anesthesia during monitored anaesthesia care it has superior analgesia with less respiratory depression needing a lesser opioid requirement as rescue analgesia.[8] However, during our pilot study, increased secretions were observed in patients receiving ketamine, and in few of those cases, gross swallowing, coughing and even laryngospasm were also noted. As a result of this, we decided to give inj.glycopyrrolate, 0.3mg, im, 30 minutes before the procedure as premedication. We observed that there was significant reduction in these adverse events on addition of glycopyrrolate as premedication and we added this in our study.

In our study, MAP and mean percentage change in MAP was compared and analyzed. MAP continued to remain below baseline at all time intervals in both the groups. We noted that the decline in MAP in Group PF was consistently more than those observed in Group PK at all the time intervals studied. However, the difference between the two groups was found to be statistically significant only at LMA insertion and first four minutes following LMA insertion. The initial drop in MAP in the Group PF can be attributed to the combined cardio depressant effect of fentanyl and propofol used for induction of anesthesia. While the sympathomimetic action of ketamine was probably effective in countering the hypotensive effect of the induction dose of propofol in Group PK, thereby maintaining MAP closer to the values observed at baseline. With the continued use of propofol as an infusion for maintenance of anesthesia, MAP showed a decline in Group PK despite ketamine, as a result of which, no statistically significant difference could be demonstrated at the later time intervals. This observation is concurring with the findings of Tomatir et al[9] and khutia et al[10] which were done on pediatric group of patients also in other studies have shown efficiency of propofol ketamine combination for insertion of airway equipment with better control of hemodynamics[11] also combination has been studied for LMA insertion in elderly where maintenance of hemodynamics is very important,[12] combination was studied for TIVA where propofol and ketamine combination had better hemodynamic compared to propofol fentanyl group.[13] Our study included middle aged group but correlated well with the above studies in maintaining mean arterial pressure in PK group compared to the other group. Regarding oxygen saturation, we found no significant difference in either groups and none of the patients desaturated. The $EtCO_2$ values observed at LMA insertion were noticeably higher from the baseline in both the groups. However this increase was more significant in the PF group. This is probably because the fentanyl induced respiratory depression could have compounded the depression of ventilatory drive produced by propofol during the period of induction. This is also evident by the higher incidence of apnea in Group PF, though it was not found to be statistically significant. However, none of the patients in either of the groups desaturated during the study. Akin et al[14] & Mortero et al[15] have also demonstrated similar findings.

In our study, we found that more number of patients in PK Group needed additional boluses of propofol for LMA insertion as compared to the patients in PF Group. Regarding the three cases of failure to insert LMA in our study, LMA insertion was impossible in two of the patients in Group PK as there was gross movement & coughing at the time of insertion. In the PF Group, there was only one incidence of failure to insert LMA, the reason here being, inability to position the LMA properly rather than patient movement during LMA insertion. Though addition of ketamine might have been additive at anesthetic end point of loss of motor response to jaw thrust, it might have had a lesser degree of suppression of pharyngeal & laryngeal reflexes, accounting for movements in the two patients of failure in group PK in our study, despite similar propofol dose requirements in both the groups.

The insertion conditions were assessed by six variable three point score. The median insertion score was similar between the two groups (Table 3). However, the ease of insertion, as assessed by the anaesthesiologist inserting the LMA, was found to be better in the PF Group.

Though the total propofol dose (mean value) needed for induction and LMA insertion, was lesser in PK Group as compared to PF Group (160.5 ± 76.4mg Vs 164.3 ± 73.2mg), number of patients needing additional bolus doses of propofol were more in the former group. However, this difference in total dose requirement between the two groups was not found to be statistically significant. This is consistent with one of the previous studies wherein, Goh et al[5] in their study comparing propofol-ketamine with propofol-fentanyl for LMA insertion, had found that the total propofol dose needed was lesser in PK Group as compared to PF Group (152 ± 33.9mg vs 158 ± 38.5mg). It was also

found in our study, that the time needed to reach the end-point and the time taken for LMA insertion were similar for the two groups.

Limitations of the study

Side effects of the study drugs like hallucinations, post operative nausea and vomiting, excessive dry mouth, post operative sore throat were not recorded/followed up. Also, since we included ASA 1 & 2 patients in our study, the effects of anti-hypertensives/beta blockers or the disease(hypertension) per se on hemodynamics, have been overlooked upon. This is another limitation of our study.

Conclusion

We conclude that propofol-ketamine preserves hemodynamic and ventilatory stability compared to propofol-fentanyl, while providing similar LMA insertion conditions.

Conflict of interest: Nil

References

1. McKeating K, Bali IM and Dundee JW. The effects of thiopentone and propofol on upper airway integrity. Anaesthesia 1988;43:638-40.
2. Brown GW, Patel N and Ellis FR. Comparison of Propofol and thiopentone for Laryngeal mask insertion. Anaesthesia 1991;46:771-2.
3. Scanlon P, Carey M, Power M and Kirby F. Patient response to LMA insertion after induction of anaesthesia with propofol or thiopentone. Can J Anaesth 1993;40:816-8.
4. Tagaito Y, Isono S and Nishino T. Upper airway reflexes during a combination of Propofol and Fentanyl anesthesia. Anesthesiology 1998;88:1459-66.
5. Goh PK, Chiu CL, Wang CY, Chan YK and Loo PL. Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions. Anaesth Intensive Care 2005; 33:223-8.
6. Struys MM , Coppens MJ, De Neve N, Mortier EP, Doufas AG, Bocxlaer VJF et al. Influence of administration rate on propofol plasma-effect site equilibration. Anesthesiology. 2007 Sep;107(3):386-96.
7. Huit TW, Short TG, Hong W, Suen T, Gin T and Plummer J. Additive interactions between propofol and ketamine when used for anaesthesia induction in female patients. Anesthesiology 1995;82:641-8.
8. Badrinath S, Avramov M N, Shadrick M, Witt TR and Ivankovich AD. The use of a ketamine-propofol combination during monitored anaesthesia care. Anesth Analg 2000; 90:858-62.
9. Tomatir E, Atalay H, Gurses E, Erbay H and Bozkurt P. Effects of low dose ketamine before induction on propofol anesthesia for paediatric magnetic resonance imaging. Paediatric Anaesthesia 2004;14:845-850.
10. Khutia S K, Mandal MC, Das S and Basu SR. Intravenous infusion of ketamine-propofol can be an alternative to intravenous infusion of fentanyl-propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures. Indian J Anaesth. 2012 Mar-Apr;56(2):145–150.
11. Ozgul U, Begec Z, Karahan K, Erdogan MA, Aydogan MS, Colak C, et al. Comparison of Propofol and Ketamine-Propofol Mixture (Ketofol) on Laryngeal Tube-Suction II Conditions and Hemodynamics: A Randomized, Prospective, Double-Blind Trial. Curr Ther Res 2013 Dec;75:39–43.
12. Erdogan MA, Begec Z, Aydogan MS, Ozgul U, Yucel A, Colak C et al. Comparison of effects of propofol and ketamine-propofol mixture (ketofol) on laryngeal mask airway insertion conditions and hemodynamics in elderly patients: a randomized, prospective, double-blind trial. J Anesth. 2013;27:12–17.
13. Bajwa SJS, Bajwa SK and Kaur J. Comparison of two drug combinations in total intravenous anesthesia: Propofol–ketamine and propofol–fentanyl. Saudi J Anaesth. 2010 May-Aug;4(2):72–9.
14. Akin A, Guler G, Esmaoglu A, Bedirli N and Boyaci A. A comparison of fentanyl-propofol with a ketamine-propofol combination for sedation during endometrial biopsy. J clin Anesth 2005;17:187-90.
15. Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K and Sheppard RA. The effects of small dose ketamine on propofol sedation, respiration, postoperative mood, perception, cognition and pain. Anesth Analg 2001;92:1465-9.