European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 04, 2022

**ORIGINAL RESEARCH**

# A COMPARISON OF PROPOFOL VERSUS KETOFOL PLUS FENTANYL AS INDUCTION AGENTS ON HEMODYNAMIC PARAMETERS IN PATIENTS UNDERGOING ELECTIVE SURGICAL PROCEDURES UNDER GENERAL ANESTHESIA

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## ABSTRACT

**Background: Propofol has gained a lot of popularity and is very commonly used in elective surgeries due to its solubility, rapid induction, quick recovery time along with its amnestic and antiepileptic properties make a potent anesthetic agent. Exclusive uses of propofol to provide LMA might be associated with some undesirable effects which are dose-dependent are like hypotension, respiratory depression, coughing, hiccups, laryngospasm, and movements. Forgoing studies reveled that a combination of ketamine and propofol decreased patients' use of propofol and opioids and improved hemodynamic and respiratory stability. The prime objective of our study is to substantiate the earlier results regarding whether the efficacy of the ketamine-Propofol-Fentanyl combination has more favorable hemodynamics than the gold standard prototypic induction drug (Propofol) in a cohort of healthy patients and to compare the additional post-operative analgesia requirements between the two groups.**

**Materials and Methods: The clinical prospective observational study was done on 240 individuals which were divided in to 2 equal groups (120 each group), the, Group A (Propofol) received 2.5 mg/kg Propofol for induction and the Group B (Ketamine-Fentanyl-Propofol) of 120 subjects, provided with 0.8mg/kg of ketamine + 0.2mg/kg fentanyl + 1mg/kg of Propofol. Patients in both - groups were maintained with O2, N2O, Sevoflurane and measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) was done before induction and 10 minutes after induction before the surgical stimulus. Additional analgesia (0.2 mg/kg ketamine, 0.1mg/kg fentanyl and 0.3 mg/kg propofol, for a total of 1mg/kg**

**ketamine, 0.3 mg/kg fentanyl and 1.3 mg/kg propofol) was supplied to all patients with a VAS > 3 who reported pain. Independent samples t-test and paired t-test were employed for analysis of the collected data.**

**Results: In Group B (KP), the systolic, diastolic, mean arterial blood pressure, and heart rate changes following LMA implantation were considerably greater than in Group A (P). Group B had longer recovery durations, lower VAS scores immediately following surgery, and less analgesic needs. There was no incidence of apnea, hypoventilation, or emerging responses.**

**Conclusion: Ketofol (0.8mg/kg ketamine and 1 mg/kg propofol) + 0.2mg/kg fentanyl has multiple advantages than relaying propofol (2.5mg/kg) alone Hemodynamic stability, absence of respiratory depression, rapid recovery, and potent postoperative analgesia. We thus advocate intravenous ketofol as an induction drug, particularly for patients undergoing short surgical operations.**

**Keywords: Ketofol; Propofol; general anesthesia; induction; hemodynamic changes.**

## INTRODUCTION

In plethora of elective procedures propofol is familiar for effective sedation and analgesic agent owing to its rapid start and recovery, as well as the fact that it has less undesired side effects than its homologues. Though, a limited therapeutic index, cardiorespiratory depressant events, and low analgesic property hampers its advantage as a dynamic anesthetic means,[1-3] grievously, no single medication fulfilling above exists so anesthesiologists use a concoction of different drugs in standardized doses to get maximal benefits.[4]

To mitigate these constraints, various other anesthetic agents with good analgesic activities such as ketamine, fentanyl, or sevoflurane are co-administered with propofol. withal, the search for an ideal co- induction agent with propofol is an area of constant and active medical research. In the context of general anesthesia, ketamine (NMDA receptor antagonist) and fentanyl (a potent lipid-soluble opioid) have emerged as effective co-induction agents used with propofol.[5,6]

Fentanyl or ketamine are combined with propofol to achieve balanced anesthesia with reduced side-effects. It is assumed that combining propofol with ketamine (ketofol) at low doses results in the rapid achievement of targeted sedation.[7] Similarly, fentanyl is also frequently co-administered with propofol due to its exceptional analgesic potential and short duration of action.[8] when ketamine is used as the solitary induction agent, it has the ability to cause an accountable decrease in arterial blood pressure and cardiac output.[9] furthermore, it leads to a higher reduction in systemic arterial pressure than a synonymous dosage of thiopentone.[10] Reduced cardiac contractility and decreased systemic vascular resistance are both contributory agents of the foreseen reduction in blood pressure.

Though arterial pressure has decreased, suppression of baroreceptor response is the cause of stable heart rate.[11,12]

On the results of contemporary research direct stimulation of the central nervous system lead to elevated sympathetic nervous system output, seems to be the most acceptable mechanism of cardiovascular stimulation as evident from Infusion of ketamine.[13]

The present trend of using a combination of ketamine, fentanyl or sevoflurane with low doses of propofol for efficient maintenance of hemodynamic stability is mostly due to additive

effect of Gamma-aminobutyric acid (GABA) agonism by propofol and N-Methyl-D-Aspartate (NMDA) antagonism by ketamine.[14] Potential efficacy of this anesthetic drug combination, propofol with ketamine and fentanyl will help anesthesia and health care professionals to provide safe and effective alternative induction agent for better LMA insertion conditions and improved hemodynamic stability, enhancing better patient outcome.

**Aims and objectives**

A clinical observational cohort study conducted at Vijay Marie Hospital & Educational Society hospital from Jan 2018-Mar 2022 after ethical approval and patient consent was to study the efficacy of the ketofol - Fentanyl combination would have much potent haemodynamics than the gold standard regular induction agent propofol alone in a healthy patient population.

## MATERIALS & METHODS

240 subjects of 20-65yr age range meeting ASA status I and II were separated into two groups (P and KFP, 120 in each group) undergoing short elective surgical procedures after discussing the treatment and obtaining written informed consent from the patients.

- Propofol Group A (Group P).
- Ketamine-Fentanyl-Propofol Group B (KFP).
- Data were collected using a pretested observational checklist. Data collectors were three bachelor degree holder anesthetist and they supervised by one master degree holder anesthetist. All anesthetists participating in the study including anesthetists who inserts the LMAs and administers the medications had at least 2 years of experience in conducting anesthesia.
- **Group A (Propofol):**

Patients in this group will get 2.5mg/kg propofol as part of their induction. If the patients respond to the stimulus following induction, they will be given an additional 1mg/kg of propofol, for a total of 3.5mg/kg. Following induction, patients in either group will receive O2 33%, N2O 66%, and 1 MAC of Sevoflurane (age related iso-MAC values) as anaesthetic maintenance. The patient will be ventilated using aided or spontaneous breathing via the Bains circuit.

The baseline hemodynamics, heart rate, NIBP, oxygen saturation, and respiratory rate will all be recorded (0th interval). Laryngeal Mask Airway (LMA) and ETCO2 are coupled to secure the airway. On insertion of the LMA, any apnoeic occurrence, secretions, or adverse events are noted. The patient will be ventilated either aided or spontaneously, and anaesthesia will be maintained with 1MAC Sevoflurane. For the next 15 minutes, baseline hemodynamics are measured at 3 minute intervals.If there is any laryngospasm, it is treated with intravenous succinylcholine (Sch) and the research is continued.

If the airway cannot be secured with LMA, I.V. Inj. Sch is given, the patient's trachea is intubated with an Endo Tracheal Tube (ETT), and the patient is removed from the research.If the LMA ventilation is found to be inadequate, the LMA is removed, I.V. Vecuronium (dosage 2ED95) is provided, the airway is secured with ETT, and the patient is removed from the research.Surgical stimulus is avoided during the first 15 minutes of LMA placement (study period).

After 15 minutes of LMA insertion, surgery begins, and the duration of the procedure is recorded.After the procedure, the patient is permitted to recuperate from anaesthetic. Following extubation, the events observed were for all patients in the post-anesthesia care unit (PACU) will receive oxygen through a face mask at a rate of 5 L/minute for 30 minutes. ECG, NIBP, and SPO2 are all linked and monitored. As normal analgesia, all patients will receive a fixed dose of oral or parenteral tramadol 50mg every 8 hours or NSAIDs.

Each patient's pain level will be measured using the Visual Analogue Scale (VAS), with intervals ranging from VAS0 to VAS10 (immediate post-operatively). Any patient whose VAS is greater than 3 will be noted, and extra analgesia (I.V. Inj. Tramadol 50mg) will be supplied.

- **Group B ((Ketamine-Fentanyl-Propofol)):**

Patients in this group will get 0.8mg/kg ketamine, 0.2mg/kg fentanyl and 1 mg/kg propofol as part of their induction. If any patients respond to stimuli following induction, they will receive 0.2 mg/kg ketamine, 0.1mg/kg fentanyl 0.3 mg/kg propofol, for a total of 1mg/kg ketamine, 0.3 mg/kg fentanyl and 1.3 mg/kg propofol.

1. Secretions.
2. The occurrence of apnea or laryngospasm.
3. Rest period (time from discontinuation of the anaesthetic to spontaneous eye opening, extubation and to stating name and date of birth correctly).
4. Reactions to emergencies.

**Inclusion Criteria:** 240 ASAstatus I and II patients, aged 20-65 years, will undergo elective general, optholmic, orthopedic, plastic, or gynecologic surgery under general anaesthesia.

**Criteria for Exclusion:**

1. Patients under the age of 20 or over the age of 65.
2. Emergency surgery.
3. Patients undergoing neurosurgical procedures.
4. Clinically significant cardiac/renal disease/liver disease.
5. Pregnant or breast feeding women.
6. Patients with significant hemodynamic instability.
7. Patients having significant respiratory disorders.
8. Patient with psychiatric disorders.
9. Any procedure with adjunctive analgesia.
10. Any known contraindications to ketamine or propofol.

All data were analyzed by SPSS statistical package program (Version 20). Within the groups, the normality of variables was measured using the Shapiro-Wilk test. Differences of numerical data between groups were evaluated using student’s t-test and Mann–Whitney U-test when appropriate. Categorical data were analyzed with the Chi-Square test. A $p$ value of $< 0.05$ with the power of 80% was regarded as statistically significant.

## RESULTS

**Table 1: Demographics of the study participants**

| Parameters | | Group A (P) (n=120) | Group B (KFP) (n=120) | Total (n=240) |
|---|---|---|---|---|
| Gender (P value 0.7743) | Male | 49(40.83%) | 51 (42.51%) | 100 (41.66%) |
| | Female | 71 (59.16%) | 69 (57.5%) | 140 (58.33%) |
| ASA | ASA-I | 46 (38.33%) | 68 (56.66%) | 114 (47.51%) |
| | ASA-II | 74 (61.66%) | 52 (43.33%) | 126 (52.52%) |
| Age | Male | 38.2±1.89 | 41.1±2.47 | - |
| | Female | 29.2±1.89 | 31.1±2.47 | |
| Mean weight (kgs) P value 0.2321 | Male | 60.56±1.9 | 59.67±2.7 | - |
| | Female | 53.56±2.6 | 56.67±1.5 | |
| Duration of surgery P value 0.2174 | | 25.21 | 27.01 | - |

The demographics of the study participants across gender, weight, ASA score, and duration of surgery performed across both groups are delineated in [Table 1]. In our study participants, the mean age was found to be 38.2±1.89 years in males and 29.2±1.89 years in females of Group A whereas the mean age of males was 41.1±2.47 years and 31.1±2.47 years in females of Group B.

In group A and B females were predominant than males with 71 (59.16%), 69 (57.5%) cases respectively. ASA score varies significantly in both gender, more no of individuals fell in ASA score 2 in groups A whereas ASA I subjects were more in group B. The mean weight in male subjects was 60.56±1.9 and 59.67±2.7 in group A and B respectively whereas it was reported as 53.56±2.6 and 56.67±1.5 in females of group A and group B respectively.

**Table 2: Comparison of hemodynamics parameters in both groups**

| Parameter | Timing | Group A (P) | Group B(KFP) | p-value** | t value |
|---|---|---|---|---|---|
| Systolic Blood Pressure (SBP) | At Baseline | 130.17±5.94 | 131.58±5.53 | 0.446 | 8.883 |
| | At 10 Minutes | 120.26±3.07 | 126.92±2.04 | <0.001 | 8.821 |
| | p-value* | <0.001 | 0.672 | - | 10.21 |
| Diastolic Bloodpressure (DBP) | At Baseline | 89.68±5.76 | 90.01±2.31 | 0.688 | 11.26 |
| | At 10 Minutes | 76.34±6.35 | 93.38±6.08 | <0.001 | 12.32 |
| | p-value* | <0.001 | 0.107 | - | 12.72 |
| Mean arterial pressure(MAP) | At Baseline | 103.17±4.29 | 103.80±4.57 | 0.96 | 11.85 |
| | At 10 Minutes | 92.97±4.58 | 102.22±4.62 | <0.001 | 10.93 |

| | | | | | |
|---|---|---|---|---|---|
| | p-value* | <0.001 | 0.097 | - | 12.54 |
| Heart rate (HR) | At Baseline | 79.95±6.10 | 79.62±2.24 | 0.827 | 6.871 |
| | At 10 Minutes | 80.53±6.88 | 89.83±5.86 | <0.001 | 10.27 |
| | p-value* | 0.498 | <0.001 | | 7.98 |
| Comparison of recovery time for (sec) | Spontaneous eye opening | 193.6 ±2.433 | 219.6 ±0.6405 | < 0.0001 | 8.525 |
| | Extubation | 201.3 ±2.444 | 225.5 ±0.6955 | < 0.0001 | 10.32 |
| | Orientation | 308.4 ±3.020 | 401.8 ±.1.650 | < 0.001 | 9.525 |
| Comparison of ETCO2 | At Baseline | 32.64 ± 0.3409 | 32.12 ± 3.340 | 0.4512 | 0.8326 |
| | At 10 Minutes | 29.84 ± 0.3772 | 31.50 ± 0.25 | 0.0165 | 2.276 |
| | p-value* | <0.001 | 0.001 | | 2.294 |
| Comparison of Vas Scores | (V0) | 3.234 ± 0.1023 | 2.550 ± 0.10 | < 0.0001 | 5.922 |

[Table 2] elucidates the comparison of hemodynamic parameters of SBP, DBP, MAP, HR, changes among the study groups. A paired t-test was used to compare the mean values at baseline and after 10 minutes within each group. An independent sample t-test was applied to compare means between the two groups.

There is a significant rise in heart rate in the group B and a fall in the group A. The peak effect of rise in heart rate in Group A was 80.53±2.88 (79.95±6.10 at base line) and group B was 89.83±6.86 (89.83±5.86 at base line) seen in the $10^{th}$ minute. The peak fall in the systolic BP was in the $10^{th}$ minute in groups, group a 120.26±3.07, (130.17±5.94 of baseline) and Group B 126.92±2.04 (131.58±5.53of baseline). The peak rise in diastolic BP observed in group B was 93.38±6.08 (90.01±2.31 base line) and significant fall noted in group A was 76.34±6.35 (89.68±3.76 base line). MAP in both the groups was compared at baseline and at various intervals. There are statistically significant lower values of MAP in Group a 92.97±4.58 (103.17±4.29 at base line) as compared to Group B 102.22±4.62 (103.80±4.57 at base line) at $10^{th}$ minute of induction. There was a significant difference (P value < 0.0001) between the two groups in the time for recovery for Spontaneous eye opening, orientation and extubation There was a significantly lower (P value 0.0165) ETCO2 recorded at $10^{th}$ minute in Group A was 29.84 ± 0.3772 (32.64 ± 0.3409 at base line) as compared to Group B 31.50 ± 0.25 (32.12 ± 3.340 at base line). The comparison of vas scores also denoted in [Table 2].

**Table 3: Comparison of present work with previous literature**

| Author | Year | Sample size | Conclusion |
|---|---|---|---|
| Amir Sabertanha etal,[19] | 2019 | 54 | In the propofol and ketofol groups, propofol infusion (100_g/kg/min) and propofol-ketamine infusion (50_g/kg/min propofol + 25_g/kg/min ketamine) were used for the maintenance of anesthesia, Infusion of hypnotic doses of ketofol leads to increase in diastolic and systolic blood pressure and improves blood pressure stability in addition to inducing more as compared with propofol infusion, but it leads to higher risk of nausea and vomiting. |
| Saeed Jalili1 etal,[20] | 2019 | 87 | propofol 100 μg/kg/min (group p, n=44) or ketofol: ketamine 25 μg/kg/min + propofol 75 μg/kg/min (group k, n= 43). Infusion of ketofol in children undergoing tonsillectomy provides shorter recovery time and lower incidence of EA despite the non-significant difference with propofol. |
| Meron Woubshet etal,[21] | 2020 | 128 | ketofol 1:2 group (n ¼ 64) compared with ketofol 1:3 group (n ¼ 64) had similar sedation level assessed by RSS, hemodynamic and respiratory outcome, as well as general postoperative adverse events profile, but the total intraoperative analgesia consumption was significantly higher in ketofol 1:3 group (29.7%) when compared to ketofol 1:2 group (7.8%) with p ¼ 0.002. Ketofol 1:3 group shows the need for additional analgesia in this combination. Whereas ketofol 1:2 combinations for paediatrics undergoing BMA and biopsy has decreased intraoperative analgesia requirement. |
| Tze Yong Foo etal,[22] | 2020 | 1274 | There is low certainty of evidence that ketofol improves recovery time and moderate certainty of evidence that it reduces the frequency of hypotension. There was no significant difference in terms of other adverse effects when compared to other either single or combined agents. During comparison with combined agents, ketofol was more effective in reducing hypotension (RR: 4.2, 95% CI: 0.2 to 0.85; P = 0.76; I2 = 0%), but no differences |

| | | | |
|---|---|---|---|
| | | | were observed in terms of bradycardia (RR: 0.70, 95% CI: 0.14 to 03.63; P = 0.09;I2 = 53%), desaturation (RR: 1.9, 95% CI: 0.15 to 23.6; P = 0.11; I2 = 61%), and respiratory depression (RR: 1.98, 95% CI: 0.18 to 21.94; P = 0.12; I2 = 59%). |
| Alexander Sartorius et al [23] | 2020 | 52 | To conclude, a S-ketamine: propofol ratio of 1.5 in favour of S- ketamine or a ketamine (racemate): propofol ratio of three in favour of ketamine has been empirically observed. Especially patients with poor seizure quality might benefit from the lower amount of propofol compared with a standard 1:1 mixture). Higher age turned out to correlate inversely with seizure quality and positively with time spent in the recovery room. |
| Mehwish Kaneez etal,[24] | 2021 | 220 | Propofol 1.0 mg/kg body weight and ketamine 1.0 mg/kg body weight provides better hemodynamic stability than fentanyl and propofol. More studies are required to evaluate these changes in patients with cardiovascular comorbidities |
| Seyoum Hailu etal,[25] | 2021 | 62 | We conclude the administration of ketofol (0.75 mg/kg of ketamine and 1.5 mg/kg of propofol) for induction of general anesthesia has better hemodynamic stability than propofol during the first 30 min after induction. |
| Present study | 2022 | 240 | Due to its potent advantages over other surgical anaesthetics and sedatives intravenous Ketofol (0.8mg/kg ketamine and 1 mg/kg propofol) + 0.2mg/kg fentanyl has multiple advantages than relaying propofol (2.5mg/kg) alone is recommended as an effective induction agent in Patients Undergoing Elective Surgical Procedures UnderGeneral Anesthesia |

## DISCUSSION

A decrease in arterial pressure is associated with the use of Propofol for general anaesthesia, which is due to a decrease in myocardial contractility, peripheral vascular resistance, and sympathetic tone.[9,10] Propofol's vagotonic effects cause a reduction in heart rate (HR), which can result in severe bradycardia, total atrioventricular block, and cardiac arrest.[15,16] The

stimulation of the sympathetic nervous system by ketamine results in an increase in metabolicand vascular resistance, which leads to an increase in arterial pressure and heart rate, respectively. When ketamine is administered intravenously, increases in plasma concentrations of the neurotransmitters epinephrine and norepinephrine occur as early as 2 minutes after the injection and return to control levels 15 minutes after the administration.[17] Propofol, Fentanyl and ketamine appear to have complementary clinical effects. Combined administration of propofol, ketamine and Fentanyl results in a reduction in the doses of three agents, as well as the reduction of unwanted side effects. An investigation into the effects of subanesthetic ketamine doses on propofol sedation has been conducted by several researchers. A comparison was made between the effects of subanesthetic doses of ketamine and Fentanyl in combination with propofol and the effects of propofol alone on respiration, pain relief (including the use of additional analgesics), and recovery from surgery. Literature has documented the use of a variety of ketamine, and propofol doses [Table 3]. In our investigation, we did not observe any of these negative consequences and confirmed the use of small doses of analgesics as pre- emptive analgesics. This study demonstrated that the use of low- dose of ketamine, fentanyl and propofol in general anaesthetic procedures can delay the onset of the first request for anaesthesia care in the immediate postoperative period by up to 30 minutes. There have been very few studies that have reported similar findings. Because nitrous oxide, like ketamine, has been shown to exert NMDA receptor antagonist properties, it is possible that the use of nitrous oxide in the present anaesthetic technique increased the amount of NMDA receptor inhibition induced by the drugketamine.[18] Nitrous oxide was present in the control group, so it is unlikely that our results were influenced by this factor. Analgesia following surgery was significantly improved by thecombination of Ketamine, fentanyl and Propofol, according to our findings. In comparison to the Group A, the Group B experienced less pain immediately after surgery.

## CONCLUSION

Ketofol (0.8mg/kg ketamine and 1 mg/kg propofol) + 0.2mg/kg fentanyl has multiple advantages than relaying propofol (2.5mg/kg) alone Hemodynamic stability, absence of respiratory depression, rapid recovery, and potent postoperative analgesia. We thus advocate intravenous ketofol as an induction drug, particularly for patients undergoing short surgical operations.

## REFERENCES

1. Pandey S, Pawar D, Bhople P, Khobragade S. Comparative evaluation of propofol-ketamine and propofol-fentanyl for minor surgical procedures. Int J Res Med Sci. 2015; 3(12):3795– 3801. https://doi.org/10.18203/2320-6012.ijrms20151445.
2. Zafar S, Bano F, Sabbar S, Aftab S, Haider S, Sultan ST. Intravenous ketamine alternates injection pain and arterial pressure changes during the induction of anaesthesia with propofol. A comparison with lidocaine. J Coll Physician Surg Pak 2007; 17: 390-3.
3. Ramzan I Turner RJ, Gatt SP, Kam PCA, Daley M. Administration of a crystalloid fluid preload does not prevent the decrease in arterial blood pressure after induction of anaesthesia with propofol and fentanyl. Br J Anaesth 1998; 80: 737-41.

4. Djaini G, Ribes-Pasto MP. Propofol auto-co-induction as an alternative to midazolam co-induction for ambulatory surgery. Anaesthesia 1999; 54: 51-8.
5. Amornyotin S. Ketofol: A Combination of Ketamine and Propofol. J Anesth Crit Care. 2014; 1(5):00031. https://doi.org/10.15406/jaccoa.2014.01.00031
6. Dehkordi ME, Razavi SS, Momenzadeh S. A Comparison between Sedative Effect of Propofol- Fentanyl and Propofol-Midazolam Combinations in Microlaryngeal Surgeries. Iran J Pharm Res. 2012; 11(1):287–294. https://doi.org/10.22037/ijpr.2011.1033
7. TrisselLA, Gilbert DL, Martinez JF. Compatibilityofpropofolinjectable emulsion with selected drugs during simulated Y-site administration. Am J Health SystPharm. 1997;54:1287–1292.
8. Andolfatto G, WillmanE. A prospective case series of single-syringeketamine- propofol (ketofol) for emergency department proceduralsedationandanal- gesia inadults. Acad EmergMed. 2011;18:237–245.
9. Weatherall A, Venclovas R. Experiencewithapropofol-ketaminemixturefor sedation during pediatric orthopedic surgery. Paediatr Anaesth. 2010;20:1009–1016.
10. Ding J, Chen Y, Gao Y. Effect of propofol, midazolam and dexmedetomidine on ICU patients with sepsis and on arterial blood gas. Exp Ther Med. 2019, 18(6):4340–4346. https://doi.org/10.3892/etm.2019.8091.
11. Furuya A, Matsukawa T, Ozaki M, Nishiyama T, Kume M, Kumazawa T.Intravenous ketamine attenuates arterial pressure changes during the induction of anaesthesia with propofol. Eur J Anaesthesiol. 2001;18(2): 88–92.
12. Yousef GT, Elsayed KM. A clinical comparison of ketofol (ketamine and propofol admixture) versus propofol as an induction agent on quality of laryngeal mask airway insertion and hemodynamic stability in children. Anesth Essays Res. 2013;7(2):194.
13. Gül R, Hizli Ş, Kocamer B, Koruk S, Şahin L, Kilinçaslan H, et al. The safety and efficacy of remifentanil compared to fentanyl in pediatric endoscopy. Turkish J Med Sci. 2013;43(4):611– 6.
14. Smischney NJ, Beach ML, Dodds TM, Koff MD. Ketofol as a sole induction agent is associated with increased hemodynamic indices in low-risk patients. Anesthesiology. 2011;16:A485.
15. Furuya A, Matsukawa T, Ozaki M, Nishiyama T, kume M, Kumazawa T. Intravenous ketamine attenuates arterial pressure changes during the induction of anaesthesia with propofol. Eur J Anaesthesiol 2001; 18: 88-92.
16. Igarashi M, Nishikawa K, Nakayama M. Circulatory changes at the time of anaesthetic induction and endotracheal intubation. Comparison of thiamylal induction group and propofol induction group. Jap J Anaesthesiology 1998; 47: 1193-99.
17. Okuyama K, Inomata S, Okubo N, Watanabe I. Pretreatment with small-dose ketamine reduces predicted effect-site concentration of Propofol required for loss of consciousness and laryngeal mask airway insertion in women. J Clin Anesth. 2011;23:113–118.
18. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4:460–3.
19. Amir Sabertanha, Bibifatemeh Shakhsemampour, Mina Ekrami and Elahe Allahyari; Comparison of Infusion of Propofol and Ketamine-Propofol Mixture (Ketofol) as

Anesthetic Maintenance Agents on Blood Pressure of Patients Undergoing Orthopedic Leg Surgeries; Anesth Pain Med. 2019 December; 9(6):e96998.

20. Saeed Jalili, Ali Esmaeeili, Koorosh Kamali, Vahideh Rashtchi; Comparison of effects of propofol and ketofol (Ketamine-Propofol mixture) on emergence agitation in children undergoing tonsillectomy; African Health Sciences Vol 19 Issue 1, March, 2019.
21. Meron Woubshet, Eyayalem Melese, Zewetir Ashebir, Lemlem Getachew; Effectiveness of ketamine and propofol (ketofol) in 1:2 versus 1:3 combinations for procedural sedation and analgesia in pediatric patients undergoing bone marrow aspiration and / or biopsy: A prospective cohort study; International Journal of Surgery Open 27 (2020) 64-71.
22. Tze Yong Foo, Norhayati Mohd Noor, Mohd Boniami Yazid, Mohd Hashairi Fauzi, Shaik Farid Abdull Wahab and Mohammad Zikri Ahmad; Ketamine-propofol (Ketofol) for procedural sedation and analgesia in children: a systematic review and meta-analysis; BMC Emergency Medicine (2020) 20:81.
23. Alexander Sartorius, Juliane Beuschlein, Dmitry Remennik, Anna‑Maria Pfeifer, Sebastian Karl,Jan Malte Bumb, Suna Su Aksay, Laura Kranaster, Christoph Janke; Empirical ratio of the combined use of S‑ketamine and propofol in electroconvulsive therapy and its impact on seizure quality; European Archives of Psychiatry and Clinical Neuroscience (2021) 271:457–463.
24. Mehwish Kaneez,Yasmeen Azeem, Fatima Kanwal, Suresh Kumar, Syed Muhammad Jawad Zaidi, Fariha Sardar; Comparison of hemodynamic changes in ketamine versus fentanyl as co- induction agent with propofol in elective surgical procedures; Ann Pak Inst Med Sci.2020; 16(4):161-165.
25. Seyoum Hailu et al; Effectiveness of ketofol versus propofol induction on hemodynamic profiles in adult elective surgical patients: A Randomized Controlled Trial; International Journal of Surgery Open 37 (2021) 100392.