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A Comparative Study between Use of Propofol-Ketamine and Propofol-Fentanyl in Total Intravenous Anesthesia for Laparoscopic Surgeries

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ABSTRACT

Background: Total intravenous anesthesia has advantages over traditional inhalational anesthesia. It has the advantages of hemodynamic stability, ease of titration using targeted control infusion systems, less organ toxicity, preservation of hypoxic pulmonary vasoconstriction, and reduction of intra- cerebral pressure, risk reduction of postoperative nausea and vomiting, less atmospheric pollution and more economic. Propofol as a strong anesthetic but has no property of internal analgesia; so, a quick action opioid like fentanyl is usually used for helping in analgesia. **Aim of the work:** The aim of this study was to compare between propofol-ketamine and propofol-fentanyl as a drug combination used for total intravenous anesthesia in laparoscopic surgeries as regarding hemodynamic state, intraoperative analgesia, recovery time, postoperative analgesia, nausea and vomiting as well as emergence reactions. **Patients and Methods:** This comparative study was conducted between July 2017 and June 2019 at Sayed Galal University Hospital on 40 adult patients with sex and age matched. Their age ranged between 20-50 years old. They were randomly divided into two equal groups depending on drug combination used, Propofol-Ketamine Group (I) and Propofol-Fentanyl Group (II). The study was approved by the medical ethics committee of Al-Azhar University Hospitals and a written informed consent was obtained from all patients.

Results: The mean intraoperative blood pressure in Group (I) was higher than Group (II) with statistically significant difference between both groups $p<0.001$. The comparison between the mean of pain (VAS) score, sedation (Ramsay's score) and recovery time of patients in both groups shows that means were higher in Propofol-Ketamine Group than Propofol-Fentanyl Group and there was statistically significant difference between them $p<0.05$. In this study, nausea/vomiting were more common in Group (I) than Group (II) with statistically significant difference between them ($p<0.05$). Emergence reaction (unpleasant dreams or hallucinations) were more evident in Group (I) with statistically significant difference.

Conclusion: There was no significant difference in the average number of heart beats and peripheral oxygen saturation. The combination of Propofol-Ketamine leads to more hemodynamic stability. The combination of Propofol-Fentanyl leads to faster recovery than the combination of Propofol-Ketamine for procedural sedation and analgesia in patients undergoing laparoscopy. Nausea/vomiting were more common significantly in group (I). Emergence reaction was more evident in group (I) and was statistically significant.

Keywords: Anesthesia, Propofol, Ketamine, Propofol-Fentanyl, Laparoscopic Surgeries.

INTRODUCTION

Total intravenous anesthesia is a method of administration of general anesthesia exclusively by intravenous route [(1)].

It has the advantages over traditional inhalational anesthesia in the form of hemodynamic stability, ease of titration using targeted control infusion systems, less organ toxicity, preservation of hypoxic pulmonary vasoconstriction, and reduction of intra- cerebral pressure, risk reduction of postoperative nausea and vomiting, less atmospheric pollution and more economic [(2)].

Laparoscopic procedures have been traditionally performed under general anesthesia (GA). Controlled ventilation under GA has been proven ideal to combat the respiratory changes induced by pneumoperitoneum. Induction agents involve the use of rapid and short- acting IV agents such as thiopentone and propofol as well as inhalational agents such as sevoflurane and desflurane, especially for day care laparoscopic procedures [(3)].

Propofol as a strong anesthetic but has no property of internal analgesia; so, a quick action opioid like fentanyl is usually used for helping in analgesia. Using opioid with propofol drug reduces the essential dose amount, but it increases the respiratory depression.

Ketamine is a sedative and analgesic drug that can be used for analgesia alone or with other drugs [(4)].

Fentanyl in combination with propofol leads to analgesia and more quick recovery and less side effects. Theoretically, ketamine and propofol combination just like fentanyl and propofol combination can cause dose reduction [(5)].

The combination of ketamine and propofol can reserve the efficacy of these two drugs and can also minimize their adverse effects. Some researchers believe that the reduced side effects of this combination may be attributed to the reduced dosages of the drugs since the observed side effects are dose dependent. Furthermore, since the cardiovascular effects of these drugs are opposite, the drugs seem to

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balance each other out in terms of cardiovascular complications when combined [6].

AIM OF THE WORK

The aim of this study was to compare propofol-ketamine and propofol-fentanyl as a combination used in total intravenous anesthesia for laparoscopic surgeries as regarding hemodynamic state, intraoperative analgesia, recovery time, postoperative analgesia, nausea, vomiting as well as emergence reactions.

PATIENTS AND METHODS

This comparative study was conducted between July 2017 and June 2019 at Sayed Galal University Hospital on 40 adult patients with sex and age matched. Their age ranged between 20-50 years old, following the American Society of Anesthesiologists grade I or II for patients underwent laparoscopic surgeries. They were randomly divided into two equal groups depending on drug combination Propofol-Ketamine, Group (I) and Propofol-Fentanyl Group (II).

Ethical approval and written informed consent:

The study was approved by the medical ethics committee of Al-Azhar University Hospitals and a written informed consent was obtained from all patients.

They were informed about the procedure and the anesthetic technique used as well as purpose of the study. Any unexpected risk occurring during the study was cleared to the ethical committee in time. All patients were identified by a coded number to ensure privacy.

Exclusion criteria

- Allergy to Propofol, Ketamine or Fentanyl.
- Patients ASA III and IV
- Pregnant Women
- BMI ≥ 35
- Duration of surgery less than 30 minutes or more than 2 hours

All patients were admitted to the hospital at least a day before surgery and went a thorough pre-anesthetic checkup.

Anesthetic technique:

Both groups were anesthetized after insertion of intravenous line and putting on basic monitoring including ECG, pulse oximeter, noninvasive automated blood pressure cuff, Capnography and thermometer.

For all patients, the following parameters were monitored:

- Heart rate.
- Noninvasive blood pressure.
- SpO2 (peripheral oxygen saturation).
- End tidal CO2.
- Temperature.

Midazolam (0.05 mg/kg with maximum dose of 5 mg) was given IV 30 minutes before the induction of anesthesia for both groups. Baseline parameters will be observed and recorded. Preoxygenation with 100% oxygen, induction agent and muscle relaxation were done in both groups with Atracurium 0.5 mg/kg, then patients were ventilated with 100% oxygen via a facemask for 60–90 seconds, and intubation was done with an appropriate size of cuffed endotracheal tube. Hemodynamic and other monitoring parameters were observed continuously and recorded. Intraoperative relaxation is achieved with Atracurium infusion of 5–10 mcg/kg/min.

Patients were randomly classified into two groups:

Group (I): Propofol-Ketamine group (n= 20)

Induction of anesthesia was done by propofol 1.5 mg/kg and ketamine 1.0 mg/kg IV bolus doses, then maintenance using propofol intravenous infusion 2.0 mg/kg/hour and ketamine infusion 1.0 mg/kg/hour for the remaining time.

Group (II): Propofol-Fentanyl group (n= 20)

Induction of anesthesia was done by propofol 1.5 mg/kg and fentanyl 1.0 µg/kg IV bolus doses then maintenance using propofol intravenous infusion 2.0 mg/kg/hour and fentanyl 2.0 µg/kg/hour for the remaining time.

Fentanyl and ketamine were diluted with normal saline to make a volume of 10 ml. The drugs were then mixed with diluted propofol in weight-appropriate dosages to make a final volume of 50 ml. The drugs were infused by syringe pump. All the drugs were prepared by an anesthesiology.

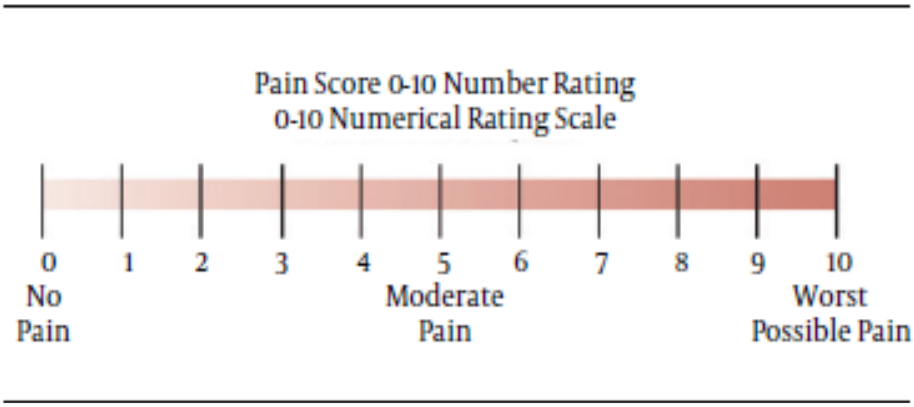
In both groups;

- Reversal of muscle relaxant was done by using Neostigmine 0.04 mg/kg and Atropine 0.01 mg /kg then extubation of the all patients.
- Follow-up of pulse, blood pressure and SpO2 and pain score were recorded before induction, one minute after induction, every 5 minutes during the operation and 5 minutes after extubation then every 15 minutes in the Recovery room for 2 hours. Sedation was assessed in postoperative period using Modified Ramsay sedation score.

Modified Ramsay sedation score

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

- The quality of analgesia based on a VAS scale of zero = no pain and 10 = the worst pain was evaluated before discharge [7].



VAS scale of pain

- Follow-up of emergence reaction (unpleasant dreams or hallucinations when emerging from the dissociative state).
- **Side effects** such as respiratory depression (respiratory rate <8 breaths per minute, apnea longer than 15 seconds or SpO2<92%), hypotension (more than 20% decrease from the initial value), and bradycardia (heart rate <60 beats per minute), increased secretions, nausea, vomiting, pruritis and any other side effect were recorded.

Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number and percentages of cases) when appropriate. Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples when comparing 2 groups and Kruskal Wallis test with posthoc multiple 2-group comparisons when comparing more than 2 groups.

To compare categorical data, Pearson Chi square (χ^2) test was performed. Fisher's exact two-tailed probability test was used instead when the expected frequency is less than 5 (i.e. when a Pearson Chi-Square test could not be calculated due to small number of observations).

Correlation between various variables was done using Spearman rank correlation equation for non-normal variables.

P values <0.05 was considered significant. All calculations were done using SPSS computer programs (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 23.

RESULTS

The demographic data of all patients was presented in **Table 1**.

Table (1): Demographic data

Variable		Group I (n=20)	Group II (n=20)	*p*-value
Age, years **(Mean ± SD)**		25.24±6.28	26.45±3.72	0.89
Gender n%	**Male**	6(30%)	7(35%)	0.74
	Female	14(70%)	13(65%)	
BMI, kg/m^2 **(Mean ± SD)**		27.48±1.69	27.38±1.90	0.86

This table shows that mean **age** in group (I) was 25.24±6.28 years and in group (II) was 26.45±3.72 years. **Males** were 6(30%) in group (I) and 7(35%) in group (II). **Females** were 14(70%) in Group (I) group and 13(65%) in Group (II). Mean **BMI** in group (I) was 27.48±1.69 kg/m^2 and in group (II) was 27.38±1.90 kg/m^2. No significant statically difference between both groups regarding demographic characteristics.

Table 2 shows that the mean preoperative hemodynamic variables (SBP, DBP, MAP, HR and temperature) were higher in group (I) than group (II) but without any statistically significant difference. Also, ETCO2 just after induction had no statistically significant difference between both groups.

Table (2): Preoperative hemodynamic variables

Variable	Group I (n=20)	Group II (n=20)	*p*-value
SBP, mmHg	127.50±6.15	126.20±10.73	0.64
DBP, mmHg	81.10±5.06	78.95±5.44	0.20
MAP, mmHg	98.25±4.07	96.07±5.89	0.18
HR, bpm	84.80±5.59	82.25±3.46	0.09
SpO2, %	99.1±0.64	99.21±0.61	0.61
ETCO2%	36.35±2.47	37.55±2.37	0.126
Temperature C°	36.79±0.22	36.38±0.15	0.46

BMI: Body mass index, MAP: Mean arterial blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SpO2: Arterial oxygen saturation, ETCO2: End tidal carbon dioxide.

The comparison between the mean perioperative hemodynamic variables in both groups showed non-significant statistically difference except the mean intraoperative MAP in Group (I) which was higher than group (II) (97.40±3.18 versus 92.05±2.56) with statistically significant difference p**<0.001 Table 3**.

Table (3): Comparison between perioperative hemodynamic variables

Variable		Group I (n=20) Mean ± SD	Group II (n=20) Mean ± SD	*p*-value
MAP, mmHg	Preoperative	98.25±4.07	96.07±5.89	0.18
	Intraoperative	97.40±3.18	92.05±2.56	**<0.001***
	Postoperative	97.55±2.01	96.25±2.07	0.051
HR, bpm	Preoperative	84.80±5.59	82.25±3.46	0.09
	Intraoperative	81.76±4.55	78.33±3.25	0.40
	Postoperative	82.50±6.72	84.30±6.76	0.10
SpO2 %	Preoperative	99.10±0.64	99.35±0.61	0.84
	Intraoperative	99.90±1.17	99.89±1.35	0.91
	Postoperative	99.15±0.67	98.85±0.74	0.18
ETCO2%	Preoperative	36.35±2.47	37.55±2.37	0.126
	Intraoperative	38.35±2.47	40.23±3.46	0.18
Temperature C°	Preoperative	36.79±0.22	36.83±0.15	0.46
	Intraoperative	36.80±0.24	36.83±0.15	0.59
	Postoperative	36.77±0.20	36.87±0.19	0.14

MAP: Mean arterial blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SpO2: Arterial oxygen saturation, ETCO2: End tidal carbon dioxide.

In **Table 4**, the comparison between the mean of pain (VAS) score, sedation **(Modified Ramsay's score)** and recovery time of patients in both groups shows that means were higher in group (I) than group (II) and there was statistically significant difference between them p**<0.05**

Table (4): Comparison of pain, sedation and recovery time of patients between both groups

Score	Group I (n=20) mean±SD	Group II (n=20) mean±SD	p-value
Sedation, Ramsay's score	4.82±1.35	4.23±0.91	**0.042***
Pain, VAS scale	5.70±0.80	4.50±0.88	**<0.001***
Recovery (min.)	16.90±1.77	11.05±1.53	**<0.001***

VAS; visual analog scale scoring system

Nausea and vomiting were more common in group (I) than group (II) with statistically significant difference between them ***(p<0.05)***. Emergence reaction (unpleasant dreams or hallucinations) was more evident in group (I) with statistically significant difference ***(p<0.003***) **Table 5.**

Table (5): Frequency of side effects of the used drugs in both groups

Complications	Group I (n=20) Mean ± SD	Group II (n=20) Mean ± SD	p-value
Shivering	3 (15%)	7 (35%)	0.14
Nausea/Vomiting	4 (20%)	1 (5%)	**0.039***
Apnea	1 (5%)	2 (10%)	0.54
Bradycardia	2 (10%)	3 (15%)	0.63
Hypotension	1 (5%)	3 (15%)	0.29
Emergence reaction (hallucinations)	6 (30%)	0	**0.003***

DISCUSSION

The current comparative study was conducted between July 2017 and June 2019 in Sayed Galal University Hospital on 40 adult patients matched with sex and age. Their age ranged between 20-50 years old, following the American Society of Anesthesiologists grade I or II who underwent laparoscopic surgeries. They were randomly divided into two equal groups depending on drug combination used, Propofol-Ketamine Group (ketofol; Group I) and Propofol-Fentanyl (Group II).
The aim of this study was to compare the combination of Propofol-Ketamine and Propofol-Fentanyl as total intravenous anesthesia for laparoscopic surgeries and this comparison was regarding hemodynamic state, intraoperative analgesia, recovery, postoperative analgesia, postoperative nausea and vomiting as well as emergence reactions.

In this study, the mean age in Group (I) was 25±6.28 years and in Group (II) was 26±3.72 years. Males were 6(30%) in group (I) and 7(35%) in group (II). Females were 14(70%) in group (I) and 13(65%) in Group (II). Mean BMI in group (I) was 27.48±1.69 kg/m2 and in group (II) was 27.38±1.90 kg/m2. No significant statically difference between both groups regarding demographic characteristics.

In the current study, comparison between the mean perioperative hemodynamic variables in both groups were without any statistically significant difference except the mean intraoperative MAP in Group (I), it was higher than Group (II) (97.40±3.18 versus 92.05±2.56) with statistically significant difference between both groups $p<0.001$.

The results obtained in this study are consistent with those obtained by **Messenger *et al.*** [8]. Also, **Kamalipour *et al.*** [9] found the same results with post-operative blood pressure changes.

In our findings, intra operatively there was an increase in mean arterial blood pressure in Group (I) and a decrease in Group (II). Post operatively the values were near preoperative values in Group (I), whereas in Group (II) the values increased but remained near the pre-operative values. These results were consistent with those obtained by **Pierre *et al.*** [10]. In a study by **Kb *et al.*** [11] which was performed on 60 candidates, they concluded that mixture of Propofol-Ketamine is safer and healthier substitution from hemodynamic stability condition rather than Propofol-Fentanyl. Similarly. Also, **Bahrami *et al.*** [12] found that the MAP was higher in the Propofol-Ketamine group than in the Propofol-Fentanyl group only at the eighth minute during ERCP.

Pawar *et al.* [13] observed that the changes in the mean systolic blood pressure among Propofol-Ketamine and Propofol-Fentanyl groups at 3- and 5-minutes intervals after induction were statistically significant ($p<0.0027$ and $p<0.045$ respectively). Same findings were similar in studies done by **Tan *et al.*** [14] and **Saha *et al.*** [15].

In this study, heart rate changes in Group (II) was slightly higher than the other group but without statistical significance. Conversely, the study of **Mayer *et al.*** [16] as there was a slight decrease in heart rate (9%) in propofol–fentanyl group as compared to propofol–ketamine combination. Also, **Mi *et al.*** [17], in 1998 showed that after induction, the heart rate did not alter significantly when propofol was used alone but decreased between 5% and 35% in patients who were given fentanyl prior to the induction of anesthesia.

Our results were not in agreement with several studies as **Pawar *et al.*** [13] and **Saha *et al.*** [15] who found statistically significant changes in pulse rate in propofol–ketamine and propofol–fentanyl groups but no episodes of bradycardia or tachycardia. Although the increase in pulse rate in Group (I) may be due to the sympathetic stimulation by ketamine and the decrease in pulse rate in Group (II) can be attributed to action of fentanyl on CVS. This is thought to be related to the balancing of propofol's CVS-depressing effect by ketamine's sympathomimetic effect, maintaining hemodynamic stability [18].

The current study shows no significant difference observed in SpO2 in both groups, when compared with respective base line values. As per the respiratory system stability was concerned, both ketamine and fentanyl along with the propofol in the doses used in study showed no respiratory depressant action. Similarly, **Saha *et al.*** [15] did not find significant changes in SpO2 during procedure.

In this study, the comparison between the mean of pain (VAS) score, sedation (Modified Ramsay's score) and recovery time of patients in both groups showed that means were higher in Propofol-Ketamine group than Propofol-Fentanyl group and there was statistically significant difference between them $p<0.05$.

As regard mean of pain (VAS) score, higher scores in Propofol-Ketamine Group with high statistically significance. This means post-procedural pain was less in Propofol-Fentanyl Group. The current findings are in consistent with **Bahrami *et al.*** [12] **and Nazemroaya *et al.*** [19], who reported that post-procedure pain in the Propofol-Fentanyl group was less than in the Propofol-Ketamine group.

In accordance with **Mofidi *et al.*** [20] where they compared the combination of Propofol-Fentanyl, and Propofol-Ketamine; they reported that with Propofol-Fentanyl combination further reduced pain was achieved. In line with **Singh *et al.*** [21], they

found that patients' satisfaction was with the Propofol–Fentanyl group was superior.

As regard sedation score, higher scores in Group (I) with high statistically significance. This means post-procedural pain was less in Propofol-Fentanyl group. Our findings agreed with **Hasanein and El-Sayed** [22] that showed the combination of Propofol-Ketamine resulted in better sedation quality than that of Propofol-Fentanyl, as well as fewer complications, in a study of obese patients undergoing ERCP. The results in the study of **Nazemroaya *et al.*** [19], were parallel our findings.

As regard mean of recovery time, longer durations were in Group (I) with high statistically significance. The results obtained in this study are consistent with those obtained by **Pierre *et al.*** [10]; they found shorter recovery times with Propofol-Fentanyl group. Mixing these two drugs leads more quick recovery. **Pawar *et al.*** [13] found prolong recovery time in ketamine group as compared to fentanyl group. **Hernandez *et al.*** [23] **and Saha *et al.*** [15] reported that patient in Propofol-Ketamine group might have delayed recovery.

On the other hand, **Bahrami *et al.*** [12] reported that recovery time showed no significant differences between the two groups. This may be due to adding a low dose of midazolam (0.5 - 1 mg) to both groups in their study. Also, **Tosun *et al.*** [24] compared a combination of Propofol-Fentanyl with Propofol-Ketamine, but in 40 adult patients undergoing endometrial biopsy. They observed that there was no difference in the recovery times, but the discharge was delayed in the ketamine group. The longer discharge time with ketamine was caused by the higher frequency of vertigo, nausea, and visual disturbances. Regarding patient satisfaction, the Propofol–Fentanyl group was superior.

In this study, nausea/vomiting were more common in Group (I) than Group (II) with statistically significant difference between them ($p<0.05$). These findings are consistent with those obtained by **Vallejo *et al.*** [25] as nausea/vomiting were more common in Propofol-Ketamine group.

In this study, Emergence reactions (unpleasant dreams or hallucinations) were more evident in Group (I) with statistically significant difference. In line with **Green and Krauss** [26] they stated that emergence reaction and vomiting are considered to be significant side effects with ketamine usage. **Hernandez *et al.*** [23] concluded that neither midazolam nor propofol completely prevented the psychomimetic effects of ketamine but such effects were not so severe that patients rejected the anesthetic technique used. Although there is a higher incidence of emergence reaction and PONV in Propofol-Ketamine group compared with Propofol-Fentanyl group, this incidence was lower than the usual incidence rate of ketamine alone. This can be probably explained by its sedative and emetic properties which reduce the overall incidence rates of both these adverse events of ketamine.

CONCLUSION

The combination of Propofol-Ketamine leads to more hemodynamic stability. The combination of Propofol-Fentanyl leads to faster recovery than the combination of Propofol-Ketamine for procedural sedation and analgesia in patients undergoing laparoscopy. Nausea/vomiting were more common significantly in group (I). Emergence reaction was more evident in group (I) and was statistically significant.

REFERENCES

1. **Hernik E, Johan R (2009):** Total intravenous anesthesia techniques for ambulatory surgery. Current Opinion in Anesthesiology, 22: 725-729.
2. **Sukhminder J, Singh B, Sukhwider K *et al.* (2010):** Comparison of two drug combinations in total intravenous anesthesia: propofol-ketamine and propofol-fentanyl. Saudi J. Anesth., 4:72-79.
3. **Singh R, Mahmood G, Homay V *et al.* (2013):** A randomized controlled trial to compare fentanyl-propofol and ketamine-propofol combination for procedural sedation and analgesia in laparoscopic tubal ligation. Saudi J. Anesth., 7:24-8.
4. **Gelen SA, Sarper N, Demirsoy U *et al.* (2015):** The efficacy and safety of procedural sedo-analgesia with midazolam and ketamine in pediatric hematology. Turk J Hematol., 32:351- 4.
5. **Khutia SK, Mandal MC, Das S *et al.* (2012):** Intravenous infusion of ketamine- propofol can be an alternative to intravenous infusion of fentanyl- propofol for deep sedation and analgesia in pediatric patients undergoing emergency short surgical procedures. Indian J Anesth., 56:145- 50.
6. **Morse Z, Sano K, Kanri T (2003):** Effects of a propofol--ketamine admixture in human volunteers. Pac Health Dialog., 10 (1):51–4.
7. **Imani F (2011):** Postoperative pain management. Anesth Pain Med., 1(1):6– 7.
8. **Messenger DW, Murray HE, Dungey PE *et al.* (2008):** Sub-dissociative dose ketamine versus fentanyl for analgesia during propofol procedure sedation: a randomized clinical trial. Acad emerg Med., 15:877-86.
9. **Kamalipour H, Joghatai P, Kamali K (2009):** Comparing the combination effect of propofol–ketamine and propofol – Alfentanil on hemodynamic stability during Induction of general anesthesia in the Elderly. Iranian Red crescent Medical Journal., 11 (2): 176- 80.
10. **Pierre St M, Kessebohm K, Schmid M *et al.* (2002):** Recovery from anesthesia and incidence and intensity of postoperative nausea and vomiting following a total intravenous anesthesia (TIVA) with S- (+)- Ketamine/ Propofol compared to alfentanil / propofol. Anesthesist, 51: 973-9.

11. **Kb N, Cherian A, Balachander H *et al.* (2014):** Comparison of propofol and ketamine versus propofol and fentanyl for puerperal sterilization, A randomized clinical trial. J Clin Diagn Res., 8: GC01- 4.
12. **Bahrami FG, Amri P, Shokri J *et al.* (2016):** Sedative and analgesic effects of propofol-fentanyl versus propofol-ketamine during endoscopic retrograde cholangiopancreatography: A Double-blind randomized clinical trial. Anesth Pain Med., 6 (5):398-405.
13. **Pawar D, Bhople P, Pandey S *et al.* (2015):** Comparative evaluation of propofol-ketamine and propofol-fentanyl for minor surgical procedures. Int J Res Med Sci., 3:3795-801.
14. **Tan CH, Onsiong MK, Kua SW *et al.* (1998):** The effect of ketamine pretreatment on propofol injection in 100 women. Anesthesia, 53:296-307.
15. **Saha K, Kaushik, Saigopal M *et al.* (2001):** Comparative evaluation of propofol-ketamine and propofol-fentanyl in minor surgery. Indian Journal of Anesthesia, 45(2):100-3.
16. **Mayer M, Ochmann O, Doenicke A *et al.* (1990):** The effect of propofol-ketamine anesthesia on hemodynamics and analgesia in comparison with propofol-fentanyl. Anesthesist., 39:609–16.
17. **Mi WD, Sakai T, Takahashi S *et al.* (1998):** Hemodynamic and electroencephalograph responses to intubation during induction with propofol or propofol/fentanyl. Can J Anaesth., 45:19–22.
18. **Botero CA, Smith CE, Holbrook C *et al.* (2000):** Total intravenous anesthesia with a propofol-ketamine combination during coronary artery surgery. J Cardioyhorac Vas Anesth., 14:409–15.
19. **Nazemroaya B, Majedi MA, Shetabi H *et al.* (2018):** Comparison of propofol and ketamine Combination (Ketofol) and propofol and fentanyl combination (Fenofol) on quality of sedation and analgesia in the lumpectomy: A randomized clinical trial. Adv Biomed Res., 7:134-9.
20. **Mofidi M, Rouhi R, Mahshidfar B *et al.* (2018):** Propofol-ketamine vs. propofol-fentanyl combinations in patients undergoing closed reduction: A randomized, double-blind, clinical trial. Adv J Emerg Med., 2(4): 44-9.
21. **Singh Bajwa SJ, Bajwa SK, Kaur J (2010):** Comparison of two drug combinations in total intravenous anesthesia: Propofol- ketamine and propofol- fentanyl. Saudi J Anesth., 4:72- 9.
22. **Hasanein R, El-Sayed W (2013):** Ketamine/propofol versus fentanyl/propofol for sedating obese patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). Egypt J Anesth., 29 (3):207–11.
23. **Hernandez C, Parramon F, Gorcia-Velascop P *et al.* (1999):** Comparative study of 3 techniques for total intravenous anesthesia midazolam-ketamine, propofol-ketamine and propofol-fentanyl. Rev Esp anestesiol Reanium., 46(4):154-8.
24. **Tosun Z, Aksu R, Guler G *et al.* (2007):** Propofol-ketamine vs propofol-fentanyl for sedation during pediatric upper gastrointestinal endoscopy. Paediatr Anesth., 17(10):983–8.
25. **Vallejo MC, Romeo RC, Davis DJ *et al.* (1993):** Propofol- ketamine versus propofol- fentanyl for outpatient laparoscopy: Comparison of postoperative nausea, emesis, analgesia, and recovery. J Clin Anesth., 5:64- 8.
26. **Green SM, Krauss B (2004):** Clinical practice guideline for emergency department ketamine dissociative sedation in children. Ann Emerg Med., 44(5):460-71.