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Research Article

Proven Safety of Alternative Sedation Regimens for Esophagogastroduedonoscopy: A Retrospective Comparative Study

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Abstract

Objectives: In this retrospective study, we aimed to compare cardiopulmonary side effects, sedation characteristics, and patient satisfaction of propofol–meperidine and propofol–ketamine sedation for esophagogastroduodenoscopy (EGD).

Methods: Data were extracted from the anesthesia and endoscopy records of the patients. Patients aged >18 years who underwent elective diagnostic EGD under sedation between January 2015 and December 2016 were enrolled in the study. Depending on the sedation procedure, the patients were divided into two groups: propofol–meperidine group (Group PM) and propofol–ketamine group (Group PK). Cardiopulmonary side effects (hypotension, bradycardia, apnea and hypoxemia), procedure times, and patient satisfaction were compared between the groups.

Results: In total, 154 consecutive patients who underwent elective diagnostic EGD between January 2015 and December 2016 under sedation with propofol–meperidine and propofol–ketamine were included in the study. The overall incidence of side effects did not differ between the groups, but the incidence of hypotension was significantly higher in Group PM compared with Group PK (7.8% vs. 0%, p=0.028). There was no significant difference in hypoxemia (p=0.597) and apnea (p>0.999) between the two groups. Awake time (time interval between the removal of the endoscope and responds readily to name spoken in normal tone) was significantly shorter in Group PM compared with Group PK (7.21±3.70 vs. 8.91±4.10 min, p=0.008). Patient satisfaction for the two groups were similar (p=0.245).

Conclusion: The propofol–ketamine sedation regimen seems to be superior compared with the propofol–meperidine sedation regimen in terms of hemodynamic stability. Both sedation regimens have similar respiratory safety profile. Propofol–meperidine sedation provided faster recovery times than propofol–ketamine sedation for EGD. Furthermore, high patient satisfaction levels were obtained with both sedation regimens.

Keywords: Cardiopulmonaryside effects, gastrointestinal endoscopy, ketamine, meperidine, propofol

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Esophagogastroduodenoscopy (EGD) is a commonly used invasive outpatient procedure for the diagnosis, treatment, and screening of upper gastrointestinal diseases.[1, 2] Sedation and analgesia improve the satisfaction of the patient and endoscopist, as well as the quality of the procedure, by relieving discomfort and pain and providing memory loss of procedure.[3, 4]

In recent years, propofol use has significantly increased for gastrointestinal endoscopy because of its rapid action onset, short recovery profile, and higher satisfaction levels

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as compared with other traditional sedative agents.[5] In spite of these advantages, unlike traditional sedatives, propofol has no analgesic activity and pharmacological antagonist. Furthermore, propofol sedation for EGD is associated with increased incidence of cardiopulmonary events in a dose-dependent manner.[6, 7]

The combination of propofol and ketamine or an opioid reduces the side effects, improves the quality of the cardiopulmonary sedation and analgesia, and decreases the propofol requirement for procedural sedation compared with propofol alone.[8, 9] Pethidine is an opioid receptor antagonist that is widely used as an adjunct for endoscopic sedation.[10] Ketamine is an N-methyl-D-aspartate receptor antagonist that possesses analgesic and sedative properties.[11] Ketamine is not frequently used for sedation in digestive endoscopy.[5-7] The use of ketamine combined with propofol has been studied mainly for procedural sedations in emergency department and pediatric settings, and there are limited data concerning sedation in upper gastrointestinalendoscopy.[8, 12]

In our endoscopy unit, EGD is not routinely performed under sedation; it is only performed for patients who request sedation. In addition, gagging and/or retching are also considered as reasons for sedation during EGD. In our daily practice, we use meperidine or ketamine as an analgesic along with propofol as a sedative for gastrointestinal endoscopy. Moreover, ketamine may be useful to reduce gagging and/or retching during EGD.[11] In this retrospective study, we aimed to compare cardiopulmonary side effects, sedation characteristics, and patient satisfaction with propofol–meperidine and propofol–ketamine sedation for UGE.

Materials and Methods

This was a retrospective study that compares propofol–meperidine and propofol–ketamine sedation for UGE. This study was approved by the ethics committee of the local hospital (Number/Date: 447/April 26, 2017), and written informed consents were obtained from the patients for sedation.

Data were extracted from the anesthesia and endoscopy records of the enrolled patients aged >18 years who underwent elective diagnostic UGE under sedation between January 2015 and December 2015. Depending on the sedation used, patients were separated into the propofol–meperidine group (Group PM) and propofol–ketamine group (Group PK). All procedures were performed by the same surgeon who had more than 5 years of experience in gastrointestinal endoscopy. Sedation protocol was performed by the same resident anesthesiologist.

All patients were fasted for solid foods for at least 6 h before UGE. No premedication was administered. In the endoscopy room, after the establishment of intravenous access, 0.9% NaCl infusion had been started at the rate of 10 mL/kg/h. The patients received 3 L/min supplementary oxygen via nasal cannula during the procedure. Three puffs of lidocaine spray were applied on the pharynx as topical anesthesia before the procedure, and patients with a history of allergy to local anesthetics were excluded. Electrocardiography (ECG), heart rate (HR), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) was monitored and recorded during the procedure until discharge from the hospital.

The patients who received the same sedation protocols were selected. In Group PM, 0.4 mg/kg meperidine was administered, followed by 0.5 mg/kg propofol 3 min later. In Group PK, a mixture of 0.5 mg/kg propofol and 0.5 mg/kg ketamine was administered. In both groups, repeated doses of 10–20 mg propofol were used to maintain sedation to achieve moderate level of sedation as described below.

The Observer's Assessment of Alertness/Sedation Scale (OAA/S) was used to assess the sedation level every minute, and moderate sedation (OAA/S 2-4) was provided throughout the endoscopic procedure as per the sedation protocol of the hospital (Table 1).

HR, NIBP, RR, and SpO_2 values were recorded before the sedation induction and every 2 min after the commencement of the sedation throughout the procedure. Thereafter, NIBP was measured every 5 min until hospital discharge and HR, RR, and SpO_2 were continuously evaluated.

The patients were transferred into the recovery room after the procedure. Thereafter, the patients with the following criteria were considered for discharged from the hospital as per the anesthesia protocol of the hospital: 1) mean arterial pressure ≥70 mmHg, 2) HR≥60 bpm 3) SpO_2≥95% in room air, 4) sitting in bed without help, and 5) fully conscious (OAA/S score 5). Before hospital discharge, patients' satisfaction was evaluated using a four-point Likert Scale (1=unsatisfied, 2=somewhat satisfied, 3=satisfied, and 4=very satisfied). Moreover, the recollection of the procedure was specified by the patients as "Yes" or "No."

Table 1. Observer's assessment of alertness/sedation scale (OAA/S)

Observation	Score level
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Table 2. Characteristics of the patients

Characteristics	PM (n=77)	PK (n=77)	P
Age (y)	49±17	47±14	0.409
Gender, M/F	26/51	26/51	>0.999
BMI (kg/cm²)	27.77±4.81	28.25±4.95	0.540
ASA classification I/II	57/20	61/16	0.568
Tobacco/alcohol use	14 (18.2%)	16 (20.8%)	0.272
Co-existing disease	26 (33.8%)	20 (26%)	0.291
Cardiovascular disorders	11 (14.3%)	13 (16.9%)	0.657
Diabetes mellitus	9 (11.7%)	5 (6.5%)	>0.999
COPD	3 (3.9%)	4 (5.2%)	0.834
Others	7 (9.1%)	2 (2.6%)	0.167
Medical treatment	25 (32.5%)	20 (26%)	0.376
Cardiovascular drugs	15 (19.5%)	14 (18.2%)	0.837
Oral antidiabetics	11 (14.3%)	5 (6.5%)	0.113
Bronchodilators	2 (2.6%)	6 (7.8%)	0.276
Others	6 (7.8%)	1 (1.3%)	0.116
Operation history	31 (40.3%)	32 (41.6%)	0.186
Gastrointestinal surgery	6 (7.8%)	7 (9.1%)	0.772
Others	28 (36.4%)	25 (32.5%)	0.611
Additional dose			0.683
No additional dose	72 (80.9%)	58 (75.3%)	
1 additional dose	16 (18%)	18 (23.4%)	
2 additional dose	1 (1.1%)	1 (1.3%)	

Data given as mean ± SD or number and percent of cases.

M: Male; F: Female; ASA: American Society of Anesthesiologist; BMI: Body mass index; COPD: Chronic Obstructive Pulmonary Disease; PM: Propofol-meperidine; PK: Propofol-ketamine.

Table 3. Side effects and procedure related times

Variable	PM (n=77)	PK (n=77)	P
Overall side effects	11 (14.3%)	12 (15.6%)	0.821
Hypoxemia	7 (9.1%)	9 (11.7%)	0.597
Apnea	2 (2.6%)	3 (3.9%)	>0.999
Hypotension	6 (7.8%)	0 (0%)	**0.028**
Procedure related times (min)			
Endoscopy time	8.19±3.36	7.39±2.90	0.113
Awake time	7.21±3.70	8.91±4.10	**0.008**
Time to hospital discharge	35.01±9.81	36.99±10.62	0.233

PM: Propofol-meperidine; PK: Propofol-ketamine.

For each patient, we recorded the demographic data, American Society of Anesthesiologist (ASA) physical status, presence of concomitant disease, history of medical treatment and surgery, and number of additional sedative dose. Cardiopulmonary side effects including hypotension (>30% decrease in baseline mean arterial pressure or systolic arterial pressure <90 mmHg), bradycardia (HR, <50 bpm), hypoxemia (SpO_2 <90% on oxygen supplementation), apnea (respiratory arrest, >15 s), permanent brain damage and death, and other values (arrhythmia, chest pain, or pulmonary edema) were also recorded. Furthermore, endoscopy time (time interval between endoscope insertion and removal), awake time (time interval between the removal of the endoscope and when the patient had an OAA/S score of 5), time to hospital discharge (time interval between the removal of the endoscope and discharge from the hospital), and patient satisfaction were also evaluated. Statistical analysis was performed using the SPSS Software Package for Windows (Statistical Package for Social Sciences, version 17.0, SPSS Inc., Chicago, IL, USA). Quantitative variables were presented as mean±standard deviation (SD). Sample size was calculated based on the incidence of cardiopulmonary side effects. Based on a previous study, cardiopulmonary side effects were approximately 27% with propofol sedation for UGE.[11] Power analysis with α=0.05 and β=0.2 for detecting 50% reduction in cardiopulmonary side effects after adding meperidine or ketamine to propofol revealed that each group required a minimum of 74 patients. Student's t test was used to compare the quantitative data between the groups (normality of the data distribution were analyzed using the Kolmogorov–Smirnov test). Categorical variables were presented as number and percentage of patients and compared with the chi-square or Fisher's exact tests. The correlation between the additional doses of study drugs and the procedure-related times were analyzed using Spearman's correlation test. A p value of <0.05 was considered to be statistically significant.

Results

In total, 154 consecutive patients who underwent diagnostic UGE between January 2015 and December 2016 under sedation with propofol–meperidine and propofol–ketamine were included in the study. All procedures were successfully performed without any surgical complications. The main indication for UGE was epigastric pain/discomfort (n=102), followed by gastroesophageal reflux (n=23), nausea/vomiting (n=25), anemia (n=13), hematemesis (n=11), dysphagia (n=7), and weight loss (n=6).

We did not find any significant differences between the groups in terms of patients' characteristics including age, gender, body mass index, ASA classification, smoking/alcohol use, presence of coexisting disease, and history of medical treatment and surgery (Table 2). The number of patients who required additional doses of study drugs to maintain the desired level of sedation were 17 in Group PM and 19 in Group PK, and there was no significant difference between the groups (p=0.683, Table 2).

Although the overall incidence of side effects did not dif-

fer between the groups, the incidence of hypotension was significantly higher in Group PM compared with Group PK (p=0.028, Table 3). Hypotension was treated with 250 mL isotonic NaCl infusion in 5 min period, and none of the patients required vasopressor treatment with ephedrine. Hypoxemia was successfully treated by increasing the oxygen flow rate. Apnea was recovered using the chin lift maneuver in five patients. Bradycardia, permanent damage, or death did not occur in any patient (Table 3).

Procedure-related times are shown in Table 3. We did not find any significant differences between the groups in terms of endoscopy time (p=0.113) and time to hospital discharge (p=0.233). The awake time was significantly shorter in Group PM than in Group PK (7.21±3.70 vs. 8.91±4.10 min, p=0.008). Moreover, we found a low-level positive correlation between the additional dose requirement and endoscopy time (Spearman Rho coefficient =0.191, p=0.014) and time to hospital discharge (Spearman rho coefficient =0.168, p=0.031).

Patient satisfaction for the two groups was similar (p=0.245). Satisfaction level was qualified as "very satisfied" in 74 patients and as "satisfied" in three of Group PM. Satisfaction level was qualified as "very satisfied" in all patients of Group PK. None of the patients remembered the endoscopic intervention.

Conclusions

EGD is a widely accepted minimally invasive tool that is used in the diagnosis, treatment, and follow-up for upper gastrointestinal diseases.[13] The use of sedation represents a standard for upper gastrointestinal endoscopies in developed countries.[14] Relieving pain and discomfort, eliminating anxiety, diminishing patient's memory of the procedure, and improving patient satisfaction and quality of examination are the objectives of sedation during endoscopy.[10] On the other hand, most of the cardiopulmonary side effects during the course of the procedure are related to sedation.[7]

Propofol-based sedation is the recommended sedation regimen for EGD. Combination of propofol with other sedative and analgesic agents aim to reduce the propofol dose and minimize the likelihood of dose-related side effects.[6-8-10] Various drugs including midazolam, opioids, and ketamine were combined with propofol to induce sedation for EGD, but the best sedation regimen is still under debate.[15]

Although the use of propofol for endoscopic sedation has significantly increased in recent years because of its superior recovery profile,[16, 17] it has been reported that propofol sedation is associated with a higher incidence of cardiac arrest and death compared with traditional sedation during EGD.[7, 18] When propofol is used alone, higher doses are often required for gastrointestinal endoscopy because of its minimal analgesic activityand thus, deepening of sedation may occur.[9, 17-22] Thus, deepening in sedation may occur related to the propofol dose.[17, 18-20-22] Oversedation resulting in hypoxemia was found to be responsible for most of the cardiac arrests.[7-18-21]

Compared with propofol alone, propofol combined with an opioid or ketamine reduces propofol dose, improves dose-related cardiopulmonary complications and quality of sedation, and increases patients' tolerance during procedural sedation.[8, 22] There are limited studies that have investigated the cardiopulmonary safety profile of propofol combined with the meperidine or ketamine during gastrointestinal endoscopy.

To the best of our knowledge, this is the first study to compare propofol–meperidine and propofol–ketamine sedation in UGE. The primary aim was to investigate the cardiopulmonary side effects of these sedation regimens. The present study showed that propofol–ketamine had a better hemodynamic stability compared with propofol–meperidine. All patients who developed hypotension received propofol–meperidine (six patients, 7.8%), and no patient in the propofol–ketamine group had hypotension (p=0.028). Hypotension was ameliorated by the volume replacement without vasopressor requirement. Hypoxemia was the most common side effect in both groups (9.1% and 11.7%, respectively), but there was no significant difference between the groups (p=0.597). Hypoxemia and apnea were transient and improved by chin lift maneuver and increase in oxygen flow rate. We did not have to use artificial airway and ventilation support.

The incidence of cardiopulmonary complications with the combination of propofol and ketamine or meperidine in our study is comparable to previous studies.[22 ,23-25-28] It has been shown that the addition of ketamine to propofol allowed stable hemodynamics because of sympathomimetic effects of ketamine and reduced risk of hypoxemia even in pediatric patients with cardiac defects during procedural sedations.[8-23, 24] In a prospective randomized study by Nejati et al.,[25] it was reported that hypotension and hypoxemia was not observed in two of 31 patients (6.45%) and apnea was observed in one of 31 patients (3.2%) during sedation for colonoscopy with a 1:1 mixture of ketamine and propofol. Tosun et al.[12] found similar rate of hypoxemia (6.52%) and no hypotension with ketamine and propofol sedation in pediatric patients who underwent UGE.

Although ketamine-associated laryngospasm and hypersecretion are uncommon, it can lead to respiratory difficulties.[26] In the present study, laryngospasm and hyper-

secretion were not observed in any patient. Emergence reactions are the most frequently investigated side effects related to ketamine in a dose-dependent manner.[27] Even if combined with propofol, doses of ketamine >1 mg/kg were associated with 29% incidence of emergence reactions after procedural sedation.[25] The use 0.5 mg/kg of ketamine with or without propofol may eliminate emergence reactions.[28-29] We did not observe emergence reactions in any patient after the procedure because of low-dose ketamine combined with propofol.

Unlike ketamine, the incidence of hypoxemia and hypotension were found comparable between propofol alone and propofol–meperidine for sedation during colonoscopy.[22] On the other hand, Lopez et al.[30] found a lower rate of hypoxemia when propofol was used alone compared with propofol–meperidine during gastroscopy. Their observed incidence of hypoxemia in propofol–meperidine group (11.9%) was comparable to our findings (9.1%). Tagle et al.[31] observed desaturation in only one patient (1.1%) during gastroscopy under propofol–meperidine sedation. We found desaturation in 9.1% of the patients because of higher dose of propofol in our study compared with Tagle et al.'s study.

Propofol leads to a decrease in cardiac output and systemic vascular resistance, resulting in hypotension.[6] Although meperidine produces only mild hemodynamic depression, addition of meperidine to propofol may potentiate hypotension due to synergic action.[32] Previous studies have revealed that the use of larger initial bolus doses of propofol was associated with higher incidence of hypotension.[22-30] Hsieh et al.[21] reported hypotension incidence as 23% for an initial bolus of 1 mg/kg propofol, which was then titrated in 10–20 mg increments plus 25 mg of meperidine (dose of propofol, 129.80±37.93 mg). In contrast, Sáenz-López et al.[30] reported no hypotension for an initial bolus of 20 mg of propofol, followed by boluses of 10 mg every 30 s plus 25–50 mg of meperidine (dose of propofol, 66.93 mg).

Procedure-related times were evaluated and compared between the groups. Despite the fact that propofol–meperidine had a significantly shorter awake time compared with propofol–ketamine (p=0.008), the time to hospital discharge was not affected by the type of sedation (p=0.233). The results of the present study are comparable to those of previous studies.[11-21-34-37] These studies indicated that the recovery and discharge times might vary because of multiple factors, such as dose of sedatives, concomitant use of other sedatives or opioids, level of sedation, type of the procedure, and assessing methods of recovery.

The American Society for Gastrointestinal Endoscopy and ASA guidelines recommend blood pressure, HR, RR, and SpO2 monitoring for moderate sedation during gastrointestinal endoscopy.[38,39] Continuous ECG is also suggested by ASA for patients with significant cardiovascular disease or arrhythmia.[39] These parameters were monitored for all patients throughout sedation in the present study.

There are several limitations of the present study. First, the retrospective design of the study is a well-known methodological limitation. Although anesthesia and endoscopy records were considered to be reliable and precise, there may be insufficiency in the records. However, in our study, the incidence of side effects might have been underreported. Second, there was no control group (propofol alone). Therefore, we could not evaluate the benefit of meperidine or ketamine addition to propofol. Third, determining the actual side effect rates was difficult because of the limited number of patients.

In conclusion, the present study demonstrated that although respiratory events were similar in both sedation regimens, propofol–ketamine seems to be superior compared with propofol–meperidine in terms of hemodynamic stability. However, propofol–meperidine sedation had a faster recovery time compared with propofol–ketamine sedation for EGD. Furthermore, high patient satisfaction levels were obtained with both sedation regimens.

Disclosures

Ethics Committee Approval: This study was approved by the ethics committee of the local hospital (Number/Date: 447/April 26, 2017)

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Conflict of Interest: None declared.

References

1. Sun W, Han X, Wu S, Yang C. Endoscopic Resection Versus Surgical Resection for Early Gastric Cancer: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 2015;94:e1649.
2. Pasechnikov V, Chukov S, Fedorov E, Kikuste I, Leja M. Gastric cancer: prevention, screening and early diagnosis. World J Gastroenterol 2014;20:13842–62. [CrossRef]
3. Obara K, Haruma K, Irisawa A, Kaise M, Gotoda T, Sugiyama M, et al. Guidelines for sedation in gastroenterological endoscopy. Dig Endosc 2015;27:435–49. [CrossRef]
4. Uzman S, Gurbulak B, Gurbulak EK, Donmez T, Hut A, Yildirim D. A comparison of propofol and midazolam/meperidine sedation in upper gastrointestinal endoscopy. Wideochir Inne Tech Maloinwazyjne 2016;11:178–85. [CrossRef]
5. Cohen LB, Ladas SD, Vargo JJ, Paspatis GA, Bjorkman DJ, Van der Linden P, et al. Sedation in digestive endoscopy: the Athens international position statements. Aliment Pharmacol Ther 2010;32:425–42. [CrossRef]
6. Moon SH. Sedation regimens for gastrointestinal endoscopy. Clin Endosc 2014;47:135–40. [CrossRef]

7. Goudra B, Nuzat A, Singh PM, Borle A, Carlin A, Gouda G. Association between Type of Sedation and the Adverse Events Associated with Gastrointestinal Endoscopy: An Analysis of 5 Years' Data from a Tertiary Center in the USA. Clin Endosc 2017;50:161–9. [CrossRef]
8. Yan JW, McLeod SL, Iansavitchene A. Ketamine-Propofol Versus Propofol Alone for Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med 2015;22:1003–13. [CrossRef]
9. Akarsu Ayazoğlu T, Polat E, Bolat C, Yasar NF, Duman U, Akbulut S, et al. Comparison of propofol-based sedation regimens administered during colonoscopy. Rev Med Chil 2013;141:477–85.
10. Igea F, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, Cacho G, et al; Spanish Society of Digestive Endoscopy. Sedation for gastrointestinal endoscopy. Endoscopy 2014;46:720–31. [CrossRef]
11. Tandon M, Pandey VK, Dubey GK, Pandey CK, Wadhwa N. Addition of sub-anaesthetic dose of ketamine reduces gag reflex during propofol based sedation for upper gastrointestinal endoscopy: A prospective randomised double-blind study. Indian J Anaesth 2014;58:436–41. [CrossRef]
12. Tosun Z, Aksu R, Guler G, Esmaoglu A, Akin A, Aslan D, et al. Propofol-ketamine vs propofol-fentanyl for sedation during pediatric upper gastrointestinal endoscopy. Paediatr Anaesth 2007;17:983–8. [CrossRef]
13. Aljebreen AM, Alswat K, Almadi MA. Appropriateness and diagnostic yield of upper gastrointestinal endoscopy in an open-access endoscopy system. Saudi J Gastroenterol 2013;19:219–22. [CrossRef]
14. Benson AA, Cohen LB, Waye JD, Akhavan A, Aisenberg J. Endoscopic sedation in developing and developed countries. Gut Liver 2008;2:105–12. [CrossRef]
15. Dumonceau JM, Riphaus A, Beilenhoff U, Vilmann P, Hornslet P, Aparicio JR, et al. European curriculum for sedation training in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). Endoscopy 2013;45:496–504.
16. Ferreira AO, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? World J Gastrointest Endosc 2015;7:102–9. [CrossRef]
17. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. World J Gastroenterol 2013;19:463–81. [CrossRef]
18. Goudra B, Nuzat A, Singh PM, Gouda GB, Carlin A, Manjunath AK. Cardiac arrests in patients undergoing gastrointestinal endoscopy: A retrospective analysis of 73,029 procedures. Saudi J Gastroenterol 2015;21:400–11. [CrossRef]
19. Bandschapp O, Filitz J, Ihmsen H, Berset A, Urwyler A, Koppert W, et al. Analgesic and antihyperalgesic properties of propofol in a human pain model. Anesthesiology 2010;113:421–8.
20. Uliana GN, Tambara EM, Baretta GA. Use of remifentanil to reduce propofol injection pain and the required propofol dose in upper digestive tract endoscopy diagnostic tests. Braz J Anesthesiol 2015;65:437–44. [CrossRef]
21. Sieg A; bng-Study-Group, Beck S, Scholl SG, Heil FJ, Gotthardt DN, et al. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24 441 patients in German outpatient practices. J Gastroenterol Hepatol 2014;29:517–23. [CrossRef]
22. Hsieh YH, Chou AL, Lai YY, Chen BS, Sia SL, Chen IC, et al. Propofol alone versus propofol in combination with meperidine for sedation during colonoscopy. J Clin Gastroenterol 2009;43:753–7. [CrossRef]
23. Akin A, Esmaoglu A, Guler G, Demircioglu R, Narin N, Boyaci A. Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterization. Pediatr Cardiol 2005;26:553–7.
24. Green SM, Li J. Ketamine in adults: what emergency physicians need to know about patient selection and emergence reactions. Acad Emerg Med 2000;7:278–81. [CrossRef]
25. Nejati A, Moharari RS, Ashraf H, Labaf A, Golshani K. Ketamine/propofol versus midazolam/fentanyl for procedural sedation and analgesia in the emergency department: a randomized, prospective, double-blind trial. Acad Emerg Med 2011;18:800–6. [CrossRef]
26. Krauss B, Green SM. Systemic analgesia and sedation for procedures. In: Chanmugam AS, Chudnofsky CR, Deblieux PMC, Mattu A, Swadron SP, editors. Roberts and Hedges' Clinical Procedures in Emergency Medicine. 6th ed. Philadelphia: Elsevier Inc; 2014. p. 2266–357.
27. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57:449–61.
28. Salen P, Grossman M, Grossman M, Milazzo A, Stoltzfus J. A comparison of ketamine versus etomidate for procedural sedation for the reduction of large joint dislocations. Int J Crit Illn Inj Sci 2016;6:79–84. [CrossRef]
29. Baykal Tutal Z, Gulec H, Derelı N, Babayıgıt M, Kurtay A, Inceoz H, et al. Propofol-ketamine combination: a choice with less complications and better hemodynamic stability compared to propofol? On a prospective study in a group of colonoscopy patients. Ir J Med Sci 2016;185:699–704. [CrossRef]
30. Sáenz-López S, Rodríguez Muñoz S, Rodríguez-Alcalde D, Franco A, Marín JC, de la Cruz J, et al. Endoscopist controlled administration of propofol: an effective and safe method of sedation in endoscopic procedures. Rev Esp Enferm Dig 2006;98:25–35. [CrossRef]
31. Tagle M, Siu H, Ramos M. Propofol in combination with meperidine and midazolam in colonoscopy and upper endoscopy: first prospective study in private practice in Peru. Rev Gastroenterol Peru 2007;27:367–73.
32. Moon SH. Sedation regimens for gastrointestinal endoscopy. Clin Endosc 2014;47:135–40.
33. Angsuwatcharakon P, Rerknimitr R, Ridtitid W, Kongkam P, Poonyathawon S, Ponauthai Y, et al. Cocktail sedation containing propofol versus conventional sedation for ERCP: a prospective, randomized controlled study. BMC Anesthesiol

2012;12:20. [CrossRef]
34. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. Gastrointest Endosc 2004;59:795–803. [CrossRef]
35. Sipe BW, Scheidler M, Baluyut A, Wright B. A prospective safety study of a low-dose propofol sedation protocol for colonoscopy. Clin Gastroenterol Hepatol 2007;5:563–6. [CrossRef]
36. Türk HŞ, Aydoğmuş M, Ünsal O, Işıl CT, Citgez B, Oba S, et al. Ketamine versus alfentanil combined with propofol for sedation in colonoscopy procedures: a randomized prospective study. Turk J Gastroenterol 2014;25:644–9. [CrossRef]
37. Khajavi M, Emami A, Etezadi F, Safari S, Sharifi A, Shariat Moharari R. Conscious Sedation and Analgesia in Colonoscopy: Ketamine/Propofol Combination has Superior Patient Satisfaction Versus Fentanyl/Propofol. Anesth Pain Med 2013;3:208–13. [CrossRef]
38. ASGE Ensuring Safety in the Gastrointestinal Endoscopy Unit Task Force, Calderwood AH, Chapman FJ, Cohen J, Cohen LB, Collins J, Day LW, et al. Guidelines for safety in the gastrointestinal endoscopy unit. Gastrointest Endosc 2014;79:363–72.
39. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004–17. [CrossRef]