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Efficacy of Propofol Combination with either Ketamine, Dexmedetomidine or Midazolam for Sedation during Upper Gastrointestinal Endoscopic Procedures: A Prospective, Randomized, Comparative Study

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What is already known on this subject? What does this study add?

Upper gastrointestinal (UGI) endoscopic procedures are uncomfortable and stressful for most patients; therefore, they are better performed under sedation to decrease pain, anxiety, discomfort and increase patient satisfaction. The ideal drug for procedural sedation should have a rapid onset, short duration of action, short recovery time, maintain cardiovascular stability and with the least adverse effects. However, this is difficult to fulfill in a single agent, so we will compare the efficacy of Propofol in combination with either ketamine, dexmedetomidine, or midazolam as sedative agents in adult patients undergoing elective UGI endoscopic procedures.

1. INTRODUCTION/ REVIEW

Gastrointestinal endoscopy can be categorized as upper or lower endoscopy depending on whether the upper GI tract (esophagus, stomach, duodenum, jejunum) or lower GI tract (rectum, colon, and terminal ileum) is examined ***(Kim, 2023).***

Upper Gastrointestinal (UGI) disorders vary from esophagitis, barrett's esophagus, peptic ulcer, esophageal and/or gastric varices, gastro-duodenal erosions to gastrointestinal tumors which include esophageal and gastric tumors ***(Niimi et al., 2017).*** Such disorders may be asymptomatic or associated with symptoms such as indigestion, abdominal pain, hematemesis, acute or chronic anemia, dysphagia and excessive vomiting ***(Akdamar et al., 1986).*** Sometimes, unexpected symptoms appear suddenly with life-threatening complications ***(Stewart et al., 2014).*** These disorders require upper gastrointestinal endoscopy as a diagnostic and therapeutic procedure that allows doctors to image, assess, and treat GI illnesses ***(Kim, 2023).***

Gastrointestinal endoscopic procedures are a high resource utilization practice with persistent need for their increase in the future. As such, Control of our practice and implementation of measures to continue to provide high quality and safe endoscopic services to our patients is mandatory ***(De Melo et al., 2021).***

However, anxiety, pain, fear, and digestive tract reactions are challenging and may cause compliance problems, adverse cardiovascular and respiratory events with increased risk of unwanted injuries during endoscopy ***(Mogahd et al., 2017).*** Accordingly, several different sedatives and analgesics can be used either singly or combined in gastrointestinal endoscopic procedures to achieve appropriate procedural sedation levels with the fewest side effects ***(Tekeli et al., 2020).***

Dexmedetomidine is a highly selective alpha-2 agonist sedative drug that reduces endogenous norepinephrine release in the brain and spinal cord ***(Ryu et al., 2012).*** It has analgesic, sedative, and anxiolytic effects while causing minimal respiratory depression than other sedatives ***(Afonso and Reis, 2012).*** Yet, it can cause bradycardia, hypotension and has prolonged onset time with a variable recovery time ***(Dhir and Jain, 2023).***

Propofol is another phenolic derivative drug that has both sedative and hypnotic effects mediated by the gamma amino butyric acid (GABA) receptor. Its lipophilicity allows it to cross the blood-brain barrier quickly providing rapid onset and recovery time. Moreover, it has amnestic and anti-emetic properties with limited short-lasting analgesic effects. The main disadvantage of propofol is the occurrence of dose-dependent respiratory and cardiovascular depression ***(Raman et al., 2022).***

Ketamine is N-methyl-D-aspartate (NMDA) receptor antagonist sedative drug; a unique dissociative anesthetic with analgesic and amnestic properties. It maintains airway muscle tone and spontaneous breathing. The main drawbacks of its use are vomiting, excessive salivation, sympathomimetic effects and significant psychotic emergent reactions ***(Bhavani, 2016).***

Midazolam is a positive allosteric modulator of γ-aminobutyric acid (GABA) type A receptors which suppresses neuronal excitability. It is a fast-acting benzodiazepine with a short duration of action ***(Rogawski et al., 2004).*** It has strong ataraxia, potent amnestic, and sedation effect. However, these sedative and amnestic effects sometimes do not provide adequate patient comfort during more sophisticated interventional procedures, Also it induces respiratory depression and has slow patient recovery time ***(Reimann et al., 2000).***

When used individually, sedatives have known specific limitations and multiple adverse effects, especially when used at high doses to achieve deep sedation ***(Devlin et al., 2010).*** Accordingly, their use in combination may reduce the need for dose escalation of a single agent and subsequently the risk of dose-related adverse events, such as propofol respiratory and cardiovascular depression, emergent reactions with ketamine or severe bradycardia and hypotension with dexmedetomidine ***(Hemphill et al., 2019).***

Low-dose midazolam in combination with propofol is an effective and economical alternative to benzodiazepine-based analgosedation. It is associated with a high degree of patient comfort and rapid recovery times and has a potential cost benefit concerning nursing care and bed facilities ***(Reimann et al., 2000).***

Moreover, studies showed that the combined use of ketamine and propofol (Ketofol) reduced the required amount of propofol and consequently induced hypotension and respiratory depression due to Ketamine`s sympathomimetic effect. Additionally, propofol relieved hallucinations and vomiting associated with ketamine due to its anxiolytic and antiemetic properties. Therefore, employing this combination has many advantages such as favorable recovery time, preserving airway patency, keeping the patient spontaneously breathing, stabilizing the hemodynamic profile, and importantly reducing the adverse effects associated with both drugs ***(Amer et al., 2020).***

Similarly, combining propofol with dexmedetomidine allows for deeper sedation levels**,** despite the sympatholytic effects of both agents, it showed favorable effects with better stable hemodynamics, better sedation level, preservation of saturation, better recovery, and fewer side effects ***(Tekeli et al., 2020).***

2. AIM/OBJECTIVES

To compare the efficacy of ketamine-propofol, dexmedetomidine-propofol and midazolam-propofol combinations as procedural sedative agents for adult patients undergoing elective upper gastrointestinal endoscopic procedures.

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:** A prospective, randomized, comparative, single-center, double-blinded, interventional clinical trial study.
- **Study Setting:** Internal medicine endoscopy unit in Ain Shams University Hospitals, Cairo, Egypt.
- **Study Period:** 1 year after approval of the ethical committee of the faculty of medicine, Ain Shams University.
- **Study Population:** 75 patients will be endorsed as follows:

Inclusion Criteria:

- Both male and female patients aged between 18 and 65 years
- Patients who are scheduled for elective upper gastrointestinal endoscopic procedures with sedation.
- Patients who are classified as ASA (American Society of Anesthesiologists) I and II

Exclusion Criteria:

- Patient refusal to participate
- Respiratory compromise as patients with respiratory failure or with active chest condition e.g. bronchial asthma or pneumonia
- Cardiovascular compromise including heart failure and shocked patients
- Severe uncontrolled hematemesis with shock or risk of aspiration.
- Patients who are allergic or have any contraindications to any of the used drugs.
- Patients who have a chronic neuropsychiatric disorder or on a neuropsychiatric drug.
- Patients on long-term sedative medication, have a history of drug or alcohol abuse.
- Pregnancy and lactation

- **Sampling Method:** Simple random sampling

- **Blinding:**

  Both the patient and the endoscopist will be blinded to the intervention.

  The anesthesiologist who will be the primary investigator will not be blinded to the groups to allow professional case management throughout the procedure, however, an expert anesthesiologist who will also be blinded to the study will be assigned to document all the data outcomes of the procedure to prevent bias.

- **Sample Size:** Using G power software for sample size calculation: setting power at 80% and α error at 5%, it is estimated that a sample size of 66 patients undergoing elective upper gastrointestinal endoscopic procedures (22 patients receiving ketamine-propofol, 22 patients receiving dexmedetomidine-propofol, and 22 patients receiving midazolam-propofol combinations) will be needed to detect a statistically significant difference between the three groups as regards the recovery time in minutes, assuming a large effect size (f=0.40) regarding ***(Tekeli et al., 2020)*** using F test (ANOVA: fixed effects, omnibus, one-way).

Assuming that the dropout is of 10%, **a sample size of at least 75 patients undergoing elective upper gastrointestinal endoscopic procedures (25 patients per group)** will be needed.

Ethical Considerations: The procedure will be done under the supervision of the main supervisor and by an expert. The study will be performed after approval from the Research Ethical Committee (REC), Faculty of Medicine, Ain Shams University. Informed and written consent will be obtained from all participants before starting the study. The study protocol will be explained to the participants before taking their consent to participate in the study.

- **Study Tools:**

All the used interventional medications are approved by the Food and Drug Administration (FDA) and the Pharmacy and Therapeutics Committee (PTC) of Ain Shams University Hospitals.

-**Ketamine**: Ketam^{R} 10mls sterile vial (i.e.50mg/1ml), Egyptian International Pharmaceuticals Industries Company (EPICIO), Egypt.

-**Propofol**: Propofol^{R} 1% 20 mls ampoule (i.e. 10mg/1ml), MCT Fresenius Kabi, Egypt.

-**Dexmedetomidine Hydrochloride**: Precedex^{R} 200 µg/2ml vial (i.e.100 µg/1ml), Pfizer, Egypt.

-**Midazolam:** Midathetic^{R} 5mg/1ml ampoule, Amoun, Egypt.

-**Standard nasal cannula:** Kyoling^{R}, adult size, single patient use nasal cannula.

-**Monitor**: Creative Medical UP-7000Monitor, Shenzhen Creative IndustryCo., Ltd, Shenzhen, China

-**Endoscopy:** Pentax[R] Medical EPK-i5000 High Resolution Video Process.

- **Study Procedures and Intervention:**

Consented and enrolled 75 patients will be randomly assigned to one of the following three groups:

1. **Group (1):** which is Dexmedetomidine-Propofol group (n = 25)
2. **Group (2):** which is Ketamine-Propofol (Ketofol) group (n = 25)
3. **Group (3):** which is Midazolam-Propofol group (n = 25)

A. Preoperative settings:

All patients will be fasting for 8 hours. All patients will have their medical and anesthetic history taken with a full physical examination. Revision of radiological images and routine investigations including CBC, coagulation profile, electrolytes, kidney, and liver profiles will be done.

B. Intraoperative settings:

-Standard ASA monitoring as electrocardiogram (ECG) for heart rate (beats/min), pulse oximetry for (SpO_2 as a percentage) and non-invasive blood pressure (NIBP) (mmHg), to record baseline data and follow up throughout the procedure.

- A nasal prong will be connected to the patient with an oxygen flow rate of 3 liter/min. Then, a 20 G peripheral venous cannula will be inserted and intravenous (iv) Ringer's solution 8 ml/kg/hr will be started.

- Diluted 4mg ondansetron will be given slowly iv as an antiemetic premedication.

-After positioning the patient in the left lateral position, all UGI endoscopic procedures will be performed by an accredited gastroenterologist, neither the endoscopist nor the patient know the study drugs. Anesthetic care will be provided by an accredited specialist anesthesiologist. After confirming the readiness of the endoscopist, all patients will undergo deep sedation under monitored anesthetic care (MAC) according to the assigned group:

➔ **Patients assigned to (Group 1) will be injected as follows:**

Dexmedetomidine infusion syringe (50mls**):** will be filled with 2mls of dexmedetomidine (200µg) diluted in 48 ml of 0.9% normal saline to make a final volume of 50mls and a final dexmedetomidine concentration of 4µg/ml. It will be infused as 1µg /kg/hr iv.

Propofol infusion syringe (50mls**):** will be filled with 20mls of 1% propofol (200mg) diluted in 30mls 0.9% normal saline to make a final volume of 50mls and a final propofol concentration of 4mg/ml. It will be iv administered as 0.5 mg/kg slow iv for 10 minutes, then infused at a rate of 0.5mg/kg/hr.

➔ **Patients assigned to (Group 2) will be injected as follows:**

Ketamine infusion syringe (50mls)**:** will be filled with 2mls of ketamine (100mg) diluted in 48mls 0.9% normal saline to make a final volume of 50mls to reach a final ketamine concentration of 2mg/ml. It will be administered as a bolus dose of 0.25 mg/kg iv then infused at a rate of 0.25mg/kg/hr.

Propofol infusion syringe (50mls)**:** will be filled with 20mls of 1% propofol (200mg) diluted in 30mls 0.9% normal saline to make a final volume of 50mls and a final propofol concentration of 4mg/ml. It will be iv administered as 0.5 mg/kg slow iv for 10 minutes, then infused at a rate of 0.5mg/kg/hr**.**

➔ **Patients assigned to (Group 3) will be injected as follows:**

Midazolam infusion syringe (50mls)**:** will be filled with 10mls of Midazolam (50mg) diluted in 40mls 0.9% normal saline to make a final volume of 50mls to reach a final midazolam concentration of 1mg/ml. It will be administered as a bolus dose of 0.05 mg/kg iv over 2 minutes then infused at a rate of 0.025mg/kg/hr.

Propofol infusion syringe (50mls)**:** will be filled with 20mls of 1% propofol (200mg) diluted in 30mls 0.9% normal saline to make a final volume of 50mls and a final propofol concentration of 4mg/ml. It will be iv administered as 0.5 mg/kg slow iv for 10 minutes, then infused at a rate of 0.5mg/kg/hr**.**

All patients will be targeted to reach a level of deep sedation defined as Ramsay sedation scale (RSS) score of ≥ 4. RSS will be assessed every 5 minutes throughout the procedure till its end. In the case of RSS score is < 4 or if the patient shows limb movement at any time within the procedure, rescue propofol doses of 20 mg iv increments will be given.

●**Ramsay Sedation Scale:**

Score	Response
1	Awake and anxious, agitated or restless.
2	Awake, cooperative, accepted ventilation, oriented, or tranquil
3	Awake, responds only to commands
4	Asleep, brisk response to light, glabellar tap or loud noise
5	Asleep, sluggish response to light, glabellar tap or loud noise
6	Asleep, no response to light, glabellar tap or loud noise

(Ramsay et al., 1974)

-Upper gastrointestinal diagnostic and therapeutic endoscopy will be performed by Pentax^{R} Medical EPK-i5000 High Resolution Video Process. Therapeutic gastroscopy will include variceal band ligation, and endoscopic haemostasis as injection of bleeding peptic ulcers with adrenaline or bleeders control via either argon plasma coagulation (APC) or heater probe coagulation.

-Any hemodynamic instability will be managed as per the standard guidelines. Any incidence of bradycardia (HR<50 beats/min), tachycardia (HR > 20% of baseline values), or hypotension (MAP < 60 mmHg) will be managed by requesting the endoscopist to cease the procedure till atropine 0.01 mg/kg is given to treat bradycardia, or an extra bolus dose of propofol to increase the depth of sedation and analgesia to treat tachycardia. However, if hypotension is encountered, it will be treated by giving 250 ml of I.V. crystalloids bolus and if no improvement I.V. ephedrine 6 mg will be given.

C. Postoperative settings:

After the procedure is over and the drug infusions are stopped, patient will be transferred to the PACU and connected to Standard monitoring as electrocardiogram (ECG), pulse oximetry and non-invasive blood pressure (NIBP) (mmHg), to record data upon arrival to PACU and to calculate his modified Aldrete score at which patient will be discharged when his score is ≥9.

●Modified Aldrete Score:

Criteria	Characteristics	Points
Activity (Able to move voluntarily or on command)	Able to move 4 extremities	**2**
	Able to move 2 extremities	**1**
	Unable to move extremities	**0**
Respiration	Able to breathe deeply and cough freely	**2**
	Dyspnea or limited breathing	**1**
	Apneic	**0**
Circulation	BP +/- 20% of pre-anesthetic level	**2**
	BP +/- 20-49% of pre-anesthetic level	**1**
	BP +/- 50% of pre-anesthetic level	**0**
Consciousness	Fully awake	**2**
	Arousable on calling	**1**
	Not responding	**0**
Oxygen Saturation	Able to maintain O2 saturation >92% on room air	**2**
	Needs oxygen to maintain O2 saturation >90%	**1**
	O2 saturation>90% even with supplemental oxygen	**0**

(Aldrete, 1995)

♦ Measurements and Data collection:

●Demographic data as:

-Age (years), sex (m/f), body mass index (BMI) derived from body weight and height as (Kg/m^2), ASA (I and II**).**

●**Vital Data:**

Peripheral oxygen saturation (SPO_2) (oxygen %) measured by pulse oximetry during the procedure, Mean arterial pressure (MAP)(mmHg), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), heart rate (HR)(beats/min) will be recorded at the baseline, after the induction of sedation and every 5 min until the end of the procedure. and upon transferal to the PACU till the patient has modified Aldrete score ≥9 and ready for discharge.

●**Outcomes**:

●**The primary outcome**: will be:

1-Induction time (Minutes):

The time to reach a sedation level of ≥ 4 on Ramsay's sedation score.

2-Recovery time (Minutes):

The time from the stoppage of the drug infusions till achieving a score of≥9 according to the modified Aldrete score.

●**Secondary outcomes:**

1-Hemodynamic Parameters.

Mean arterial pressure (MAP)(mmHg), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), heart rate (HR)(beats/min). and Peripheral oxygen saturation (SPO_2) (oxygen %).

2-Ramsay Sedation Scale

All patients will be targeted to reach a level of deep sedation defined as Ramsay sedation scale (RSS) score of ≥ 4. RSS will be assessed every 5 minutes throughout the procedure till its end.

3-Endoscopist satisfaction: Endoscopist assessment of the sedation as excellent/good/not bad/bad

4-Endoscopy procedure time (minutes): The duration of time the endoscope entered until exited the oral orifice.

5-Rescue propofol total doses (mg): In the case of RSS<4 or if the patient shows limb movement at any time within the procedure, propofol 20 mg iv increments will be given and total given doses in mg will be recorded

6-Sedation-related adverse effects (SRAEs) and complications:

Any incidence of respiratory (e.g. apnea, desaturation) or hemodynamic compromise (e.g hypotension, bradycardia, tachycardia, arrhythmia, cardiac arrest) or any other adverse effects (e.g. nausea, vomiting, allergy, seizure, recovery agitation, and

delayed recovery) will be managed accordingly and documented.

- **Statistical analysis:** all data will be recorded, analyzed, and statistically compared between the three groups to identify any significant differences between them.
- **Statistical Methods:** The collected data will be revised, coded, tabulated, and introduced to a PC using a reliable software program. Data will be presented, and suitable analysis will be done according to the type of data obtained for each parameter. Data will be tested first for normality.
- **Statistical tests:** The collected data will be revised, coded, tabulated, and introduced to a PC using a reliable software program. Data will be presented and suitable analysis will be done according to the type of data obtained for each parameter.

1-Descriptive Statistics:

-Mean Standard deviation (SD) and range for parametric numerical data.

-Frequency and percentage for non-numerical data.

2-Analytical Statistics:

Analysis of variance (one-way ANOVA) will be conducted to assess the statistical mean difference between the three groups. If the test shows a significant difference between the groups Independent sample t-test will be used to assess the statistical significance of the difference of a parametric variable between two independent means of the two tests and Chi-squared test will be used for categorical data.

Probability (P-value):

P-value ≥ 0.05 will be considered non-significant

P-value <0.05 will be considered significant

P-value <0.001 will be considered highly significant.

4. REFERENCES

Afonso Joana, and Flávio Reis. "Dexmedetomidine: Current Role in Anesthesia and Intensive Care.". Rev Bras Anestesiol.2012; Jan-Feb;62(1):118-33. doi: 10.1016/S0034-7094(12)70110-1. PMID: 22248773.

Akdamar, Kemal, Atilla Ertan, Naurang M. Agrawal, F. G. McMahon, and Jerome Ryan. "Upper Gastrointestinal Endoscopy in Normal Asymptomatic Volunteers.".Gastrointestinal Endoscopy.1986; 32(2):78–80. doi: 10.1016/S0016-5107(86)71760-4.

Aldrete, J A. "The post-anesthesia recovery score revisited.". Journal of clinical anesthesia.1995; vol.7(1): 89-91. doi:10.1016/0952-8180(94)00001-k

Amer Akram M., Azza M. Youssef, Hala S. El-Ozairy, and Ahmed M. El-Hennawy. "Propofol-Ketamine versus Dexmedetomidine-Ketamine for Sedation during Upper Gastrointestinal Endoscopy in Pediatric Patients: A Randomized Clinical Trial.". Brazilian Journal of Anesthesiology (English Edition).2020; 70(6):620–26. doi: 10.1016/j.bjane.2020.09.006.

Bhavani, Sekar. "Non–Operating Room Anesthesia in the Endoscopy Unit.". Gastrointestinal Endoscopy Clinics of North America.2016; 26(3):471–83.

De Melo, Silvio W., Gordon L. Taylor, and John Y. Kao. "Packaging and Waste in the Endoscopy Suite.". Techniques and Innovations in Gastrointestinal Endoscopy.2021;23(4):371–75.doi:10.1016/j.tige.2021.07.004.

Devlin, John W., Stephanie Mallow-Corbett, and Richard R. Riker. "Adverse Drug Events Associated with the Use of Analgesics, Sedatives, and Antipsychotics in the Intensive Care Unit.". Critical Care Medicine.2010; Jun; 38(6 Suppl): S231-43. doi: 10.1097/CCM.0b013e3181de125a.

Dhir, Ankita, and Kajal Jain. "Sedation for Endoscopic Procedures: Treading a Tightrope." Indian Journal of Gastroenterology.2023; 42(2):153–55.doi:10.1007/s12664-023-01375-3.

Hemphill, Scott, Luke McMenamin, Mark C. Bellamy, and Philip M. Hopkins."Propofol Infusion Syndrome: A Structured Literature Review and Analysis of Published Case Reports.". British Journal of Anaesthesia.2019; Apr; 122(4): 448-459. doi: 10.1016/j.bja.2018.12.025.

Kim, Nayoung."Sex/Gender Differences in Gastrointestinal Endoscopy from the Perspective of Patients and Gastroenterologists.". Clinical Endoscopy.2023;May; 56(3):268–82. doi:10.5946/ce.2022.270.

Mogahd, Mona Mohamed, Mohammed ShafikMahran, and GhadaFoadElbaradi. "Safety and Efficacy of Ketamine-Dexmedetomidine versus Ketamine-Propofol Combinations for Sedation in Patients after Coronary Artery Bypass Graft Surgery.". Annals of Cardiac Anaesthesia.2017; 20(2):182–87. doi: 10.4103/aca.ACA_254_16.

Niimi, Keiko, Rei Ishibashi, Takashi Mitsui, Susumu Aikou, Shinya Kodashima, Hiroharu Yamashita, NobutakeYamamichi, Yoshihiro Hirata, Mitsuhiro Fujishiro, YasuyukiSeto, and Kazuhiko Koike "Laparoscopic and Endoscopic Cooperative Surgery for Gastrointestinal Tumor.". Annals of Translational Medicine.2017; Apr; 5(8):187. doi:10.21037/atm.2017.03.35.

Raman, Vikasini, Sivakumar Segaran, T. Ramyavel, SagievKoshy George, and Mamie Zachariah. "Comparison of Haemodynamic Changes between Propofol and Ketofol as Induction Agents in Patients Undergoing Laparoscopic Surgeries under General Anaesthesia.". Journal of Anaesthesiology Clinical Pharmacology.2022; 38(2):215. doi: 10.4103/joacp.joacp_251_20.

Ramsay MA, Savage TM, Simpson B, Goodwin R. "Controlled sedation with alphaxalone-alphadolone.". British Medical Journal.1974; Jun 22; 2(5920):656–59.doi:10.1136/bmj.2.5920.656

Reimann FM, Samson U, Derad I, Fuchs M, Schiefer B, Stange EF. "Synergistic sedation with low-dose midazolam and propofol for colonoscopies.". Endoscopy.2000; Mar;32(3):239-44. doi: 10.1055/s-2000-134. PMID: 10718390.

Rogawski MA, Löscher W. "The neurobiology of antiepileptic drugs.". Nature reviews. Neuroscience.2004; Jul;5(7):553-64. doi: 10.1038/nrn1430.

Ryu, J. H., S. W. Lee, J. H. Lee, E. H. Lee, S. H. Do, and C. S. Kim. "Randomized Double-Blind Study of Remifentanil and Dexmedetomidine for Flexible Bronchoscopy.". British Journal of Anaesthesia .2012; 108(3):503–11. doi: 10.1093/bja/aer400.

Stewart, B., P. Khanduri, C. McCord, M. Ohene-Yeboah, S. Uranues, F. Vega Rivera, and C. Mock "Global Disease Burden of Conditions Requiring Emergency Surgery.". British Journal of Surgery .2014;101(1): e9-22. doi:10.1002/bjs.9329.

Tae Hoon Lee, Chang Kyun Lee."Endoscopic Sedation: From Training to Performance.". Clinical endoscopy.2014; vol. 47(2): 141-50.doi:10.5946/ce.2014.47.2.141.

Tekeli AE, Oğuz AK, Tunçdemir YE, Almali N. "Comparison of dexmedetomidine-propofol and ketamine-propofol administration during sedation-guided upper gastrointestinal system endoscopy.". Medicine (Baltimore) .2020; Dec 4; 99(49):e23317.doi: 10.1097/MD.0000000000023317