Anesthesia Innovations for Endoscopy of Gastrointestinal Tract

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Additional information is available at the end of the chapter

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Abstract

Gastrointestinal endoscopy (GIE) is a procedure for diagnosis and treatment of gastrointestinal tract abnormalities. This procedure requires some forms of anesthesia. The goal of procedural anesthesia is safe, effective control of pain and anxiety, as well as an appropriate degree of memory loss or reduced awareness. Generally, the majority of GIE procedures are performed by using topical anesthesia and intravenous sedation. General anesthesia is carried out in long and invasive procedures such as endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, and small bowel enteroscopy, as well in patients with history of failed sedation or drug and substance abuse, uncooperative or pediatric patients, and patients with cardiorespiratory system instabilities. The appropriate anesthetic agents for GIE procedures could be short acting, rapid onset with little adverse effects and also improved safety profiles. To date, the new anesthetic drugs and monitoring equipments for safety and efficacy are available. The present review focuses on pre-anesthetic assessment, anesthetic drugs used, monitoring practices, and post-anesthesia care for anesthesia innovations in GIE procedures.

Keywords: Anesthesia, Innovation, Gastrointestinal endoscopy, Safety, Efficacy

1. Introduction

Anesthesia is one of the important components of gastrointestinal endoscopic (GIE) procedures. The aim of anesthesia for these procedures is to improve patient's comfort and endo-

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scopic practice as well as patient and endoscopist satisfaction. The requirement for anesthesia is dependent on the type and duration of endoscopy, experience of endoscopist, and patient's physical status. The anesthetic regimens for GIE procedures are quite different. Several guidelines from American Society of Anesthesiologists (ASA) [1] and American Academy of Pediatrics [2] are established. Appropriate pre-anesthetic assessment, anesthetic drugs used, monitoring practices and post-anesthesia care for anesthesia in GIE procedures are essential.

1.1. Pre-procedure assessment

All patients scheduled to receive anesthesia/sedation should have a history and appropriate physical examination. Several risk factors including history of obstructive sleep apnea, alcohol or drug abuse, and history of adverse reaction to previous anesthesia/sedation are investigated. The patient physical status should be classified according to the ASA. The pregnancy test is recommended in women of childbearing age [3]. Consequently, written consent should be obtained. An anesthesia consultation should be done in high-risk patients including patients with respiratory or hemodynamic instability, obstructive sleep apnea, and high-risk airway management, as well as patients with ASA physical status >III and history of anesthesia-related adverse events.

2. Monitoring

Cardiorespiratory-related adverse events are a leading cause of morbidity and mortality associated with GIE procedures. Continuous monitoring of anesthetized patients is very important for safety. The physicians need to monitor the patients' status throughout the procedure. Clinical observations including pattern of respiration, skin or mucosa color, and level or depth of anesthesia are continuously observed.

2.1. Pulse oximetry

Pulse oximetry is a noninvasive device for continuous measurement of arterial oxygen saturation. Because clinical observation alone is inaccurate in the detection of hypoxemia, pulse oximetry has become a standard of care during GIE procedures. Oxygen saturation levels under 90% must be treated. However, pulse oximetry and oxygen supplementation do not diminish the severity or incidence of cardiorespiratory complications. In addition, oxygen desaturation is relatively a late sign [4].

2.2. Capnography

Moreover, pulse oximetry and clinical observation cannot detect the development of hyper-capnea. Capnography has been utilized to permit the safe titration of propofol by a qualified gastroenterologist during invasive procedures such as endoscopic retrograde cholangiopan-creatography (ERCP) and endoscopic ultrasonography (EUS).

2.3. Noninvasive blood pressure

Blood pressure and heart rate are important parameters of cardiovascular monitoring. The alterations of blood pressure are mediated by the depressive effects of anesthetic agents. Baseline hemodynamic parameters also provide useful information of the effects of various medical conditions. Generally, blood pressure and heart rate will be documented before anesthesia, and at least 5 min for deep sedation and general anesthesia, as well as every 15 min for mild and moderate sedation. Blood pressure is more likely to predict increasing and decreasing doses of anesthetic drugs.

2.4. Electrocardiography

The use of electrocardiography (ECG) was aimed to detect cardiac arrhythmias in high-risk patients undergoing anesthesia. However, the use of ECG during GIE procedure remains controversial [6]. American Society for Gastrointestinal Endoscopy (ASGE) and ASA practice guidelines recommend the use of ECG during GIE anesthesia in patients with significant cardiovascular diseases or arrhythmias. However, ECG is not recommended for routine use of ECG in patients with ASA physical status I or II [1, 4, 7].

2.5. Other monitors

Other monitors such as invasive arterial blood pressure, central venous pressure (CVP), and pulmonary arterial catheterization (PAC) are infrequently used during GIE anesthesia. However, these invasive monitors should be used in some high-risk patients including patients with severe hemodynamic instabilities and patients with shock.

2.6. Bispectral index monitoring

The depth of anesthesia cannot be reliably judged by clinical assessments alone. Currently, the Bispectral (BIS) index has been reported to be more accurate in measurement of the depth of anesthesia. The BIS scale ranges from 0 to 100 (0, no cortical activity or coma; 40-60, unconscious; 70-90, varying levels of conscious sedation; 100, fully awake). In the past, BIS monitor was used to assess the patient consciousness during general anesthesia [4, 8]. To date, its use has subsequently expanded into the procedural sedation technique. However, the use of BIS during GIE procedures remains a controversial issue.

The usefulness of BIS monitoring for GIE procedure was confirmed by the study of Bower and colleagues. This study showed the correlation of BIS index and the Observer's Assessment of Alertness/Sedation (OAA/S) scale for sedation during GIE procedures. It also suggested that a bispectral index near 82 corresponded with acceptable sedation level for GIE procedure [9]. Al-Sammak and coworkers compared BIS with clinical assessment for sedation during ERCP procedure in pediatric patients. The duration of sedation, recovery period, patient satisfaction, and total dose of sedative agents in the BIS group were better than in the clinical assessment group. This study demonstrated that BIS might be a valuable monitor for safe level of sedation and endoscopist's satisfaction during ERCP [10]. Another study also showed that BIS moni-

toring guided to a decrease in the propofol dose for sedation in ERCP procedures. Mean BIS values throughout the procedure and during the maintenance period of sedation were 61.68 ± 7.5 and 53.73 ± 8.67, respectively [11].

In contrast, several reports demonstrated that BIS index had low accuracy for detecting deep sedation and it was not helpful for titrating propofol to an adequate depth of sedation level. For example, Chen and Rex evaluated the utility of BIS as a monitoring device for nurse-administered propofol sedation (NAPS) during colonoscopic procedure. The study showed the mean time required to accomplish BIS values ≤60 was significantly longer than the mean time required to achieve an Observer's Assessment of Alertness/Sedation score of 1 (deep sedation). Additionally, there was also a lag time between the time required from the last dose of propofol and the time returned to baseline. The authors concluded that BIS index was not a useful device in titrating propofol to an adequate depth of sedation level [12].

Drake and coworkers also confirmed that BIS did not lead to the reduction in mean propofol dose or recovery time when used for sedation in colonoscopy [13]. Moreover, an observational study also showed that BIS index had a low accuracy for detecting deep sedation because of an overlap of scores across the sedation levels. Further improvements in BIS are needed to differentiate deep from moderate sedation for GIE procedures [14].

2.7. Narcotrend™

Narcotrend™ accomplishes a computerized analysis of the raw EEG. A statistical algorithm is used for analysis, resulting in a six-stage classification from A (awake) to F (general anesthesia/coma) and 14 substages [4, 15]. Wehrmann and colleagues evaluated 80 patients who underwent ERCP procedures by using EEG monitoring and clinical assessment for sedation. Their study demonstrated that mean propofol dose, decrease in blood pressure, and recovery time in the EEG monitoring group were significantly lower than in the clinical assessment group. The authors confirmed that EEG monitoring permitted more effective titration of propofol dosage for sedation during ERCP procedures and was associated with more rapidly patient recovery [16].

My previous study used the Narcotrend™ to guide the depth of sedation for ERCP procedure. Narcotrend™ monitoring was an effective tool for maintenance of the depth of sedation level in this procedure [17]. The other study compared the clinical efficacy of Narcotrend™ monitoring and clinical assessment used to provide deep sedation in patients who underwent ERCP procedure. In the study, Modified Observer's Assessment of Alertness/Sedation scale 1 or 2 and the Narcotrend™ index 47-56 to 57-64 were maintained during the procedure. All endoscopies were completed successfully. Both Narcotrend™ and clinical-assessment-guided propofol deep sedation were equally safe and effective as well as demonstrated comparable propofol dose and recovery time. However, the Narcotrend™-guided sedation showed lower hemodynamic changes and fewer complications compared with the clinical-assessment-guided sedation [18].

3. Anesthetic technique

3.1. Topical anesthesia

Esophagogastroduodenoscopy (EGD) is commonly performed by using topical pharyngeal anesthesia. Topical lidocaine is normally used as pretreatment for pharyngeal anesthesia. My previous study evaluated the clinical efficacy of topical viscous lidocaine solution and lidocaine spray when each was used as a single agent for unsedated EGD [19]. All patients were randomized into the viscous lidocaine (V) group (n = 930) or the lidocaine spray (S) group (n = 934). The results showed the procedure was successfully completed in 868 patients from group V and 931 patients from group S. Patient's and endoscopist's satisfaction, pain score, patient tolerance, and ease of intubation in group S were significantly better than those in group V. Additionally, adverse events in group S also occurred significantly lower than group V. This study demonstrated that the use of topical lidocaine spray was shown to be a better form of pharyngeal anesthesia than viscous lidocaine solution in unsedated EGD procedure [19].

Consequently, the use of posterior lingual lidocaine swab can apply for EGD procedure. Soweid and colleagues evaluated the effect of posterior lingual lidocaine swab in 80 patients who underwent diagnostic EGD procedures on patient tolerance, the ease of performance of EGD procedure, and to determine if such use would decrease the need for intravenous sedation [20]. The result of their study demonstrated that patients in the lidocaine swab group tolerated the procedure better than those in the lidocaine spray group. The procedural difficulty and the need of intravenous sedation in the lidocaine swab group were lower than in the lidocaine spray group. Additionally, the patients and the endoscopists in the lidocaine swab group were more satisfied than in the lidocaine spray group. They suggested the use of posterior lingual lidocaine swab for EGD procedure because of patient comfort and tolerance, endoscopist satisfaction, and reduction of the need for intravenous sedation.

Ramirez and coworkers also compared the effect of glossopharyngeal nerve block and topical anesthetic agent for EGD procedure [21]. The aim of the study was to evaluate the sedation, tolerance to the procedure, hemodynamic stability, and the adverse events. They performed a clinical trial in a total of 100 patients who underwent EGD procedures. All patients in both arms also received intravenous midazolam. The procedures were reported without discomfort in 48 patients (88%) in the glossopharyngeal nerve block group and 32 patients (64%) in the topical anesthetic group. There were no significant differences in the incidence of nausea and retching in both groups. The study confirmed that the use of glossopharyngeal nerve block provided greater patient comfort and tolerance as well as also diminished the need for sedation in EGD patients [21].

3.2. Intravenous sedation

Sedation for GIE procedure can be safely and effectively performed with a multidrug regimen utilizing anesthesiologist or nonanesthetic personnel with appropriate monitoring. Currently, sedation practices for GIE procedures vary widely. The need for sedation is decided by the

type of endoscopy, duration of procedure, degree of endoscopic difficulty, patient physical status, and physician's preferences. However, the sedation regimen for GIE procedures is still varied. Benzodiazepines and opioids are commonly used by nonanesthetic personnel. In contrast, propofol in combination with opioids and/or benzodiazepines is usually used by anesthetic personnel.

3.3. General anesthesia

The choice of anesthetic technique for GIE procedure depends on the patient and the type of procedure. General anesthesia is commonly utilized in patients with ASA physical status >III and patients with cardiorespiratory instability, as well as in long duration and complicated procedures. Traditionally, tracheal intubation is also performed when general anesthesia is used. An anesthesiologist usually uses balanced anesthesia technique including opioid, inhalation agent, and neuromuscular blocking drug. The majority of these anesthetic agents have short-acting and short-duration properties.

4. Anesthesia innovative techniques

4.1. Target-controlled infusion

Target-controlled infusion (TCI) is a computer-controlled open-loop administration of anesthetic drugs. A continuous infusion technique uses a pharmacokinetic model to predict the patient plasma and effect site concentrations from the infusion design and allows the anesthesiologist to target a selected concentration. The device computes the appropriate infusion system to accomplish this concentration [22]. The TCI rapidly attains and maintains a predefined plasma or effect site concentration of the anesthetic drug. An appropriate target concentration for achieving the desired clinical endpoint is selected. The TCI delivery system performs better than the manual system. Presently, TCI devices for propofol administration are approved in several countries.

Mazanikov and colleagues compared TCI (initial targeted effect-site concentration 2 mcg/mL) with patient-controlled sedation (PCS) (single bolus 1 mL, lockout time set at zero) in 82 patients who underwent elective ERCP procedures. Alfentanil was supplemented if needed. All procedures were performed successfully. Mean consumption of propofol and the recovery time in the TCI group was significantly greater than in the PCS group. However, mean consumption of alfentanil in both groups was comparable. The authors concluded that there were no benefits of TCI over PCS for propofol administration in ERCP procedures [23].

4.2. Patient-controlled sedation

Because of interindividual variability, new techniques of administration for sedation have been developed. Patient-controlled sedation (PCS) devices deliver a predefined bolus of intravenous drug during a defined time with or without a lockout interval. A prospective, randomized, controlled study compared the use of PCS with propofol and remifentanil and the

anesthesiologist-administered propofol sedation for 80 elective ERCP patients. Sedation level was assessed every 5 min by using Ramsay and Gillham sedation scores. All ERCP patients were completely successful except two patients in the PCS group. Mean level of sedation and total propofol consumption in the PCS group were significantly lower than in the anesthesiologist-administered propofol group. However, patient and endoscopist satisfaction were equally high in both groups. The study confirmed that PCS with propofol and remifentanil was a safe and well-accepted sedation technique for ERCP patients [24].

Moreover, the use of PCS with propofol and remifentanil has been compared with fentanyl and midazolam for sedation in patients who underwent colonoscopy by Mandel and colleagues [25]. Their study demonstrated that time to sedation and the recovery time in the PCS with the propofol and remifentanil group were significantly shorter than in the PCS with the fentanyl and midazolam group. However, the perceptions of patients, nurses and endoscopists were comparable between the two groups.

Procedural sedation in cirrhotic patients is challenged. Titration of sedative and analgesic drugs is needed for an optimal sedation level. The use of PCS for sedation in these patients is an alternative technique. Although, dexmedetomidine is suggested for procedural sedation and reported effective for alcohol withdrawal, the efficacy of dexmedetomidine as a sole anesthetic agent is controversial. Mazanikov and coworkers evaluated 50 patients with chronic alcoholism scheduled for elective ERCP procedures. All patients in the PCS with propofol and alfentanil group were successfully sedated, and in 19 of 25 (76%) patients in the dexmedetomidine group. They also suggested that a loading dose of dexmedetomidine 1 mcg/kg over 10 min, followed by continuous intravenous infusion 0.7 mcg/kg/h was insufficient for the ERCP procedure. In addition, dexmedetomidine was also related with prolonged recovery [26].

4.3. Computer-assisted personalized sedation system

The use of propofol for sedation in GIE procedures may allow for better quality of sedation and faster recovery. Computer-assisted personalized sedation system (CAPS) is based on the patient response to stimulation and physiologic profiles. It presents an attractive means of delivering safe and effective doses of propofol. The closed-loop target-controlled system or continuous EEG recordings are used to assess the degree of sedation. Patient-controlled platforms may also be used. These devices may help physicians titrating propofol administration and controlling the physiological functions [27].

The SEDASYS System is a CAPS integrating propofol delivery with patient monitoring to allow physicians to safely administer propofol. The efficacy and safety of this system for sedation during GIE procedures was evaluated and compared with the combination of benzodiazepine and opioid in 1000 adult patients with ASA physical status class I-III. All patients were sedated in mild to moderate depth of sedation level. The study demonstrated that SEDASYS system was safe and effective for sedation during EGD and colonoscopic procedures. Additionally, patient and physician satisfaction as well as recovery time in the SEDASYS group were significantly better than patients in the combination of benzodiazepine and opioid group [28].

The use of inadequate sedative agents results in over and under depth of sedation. The use of CAPS for administration of propofol by nonanesthetic personnel achieving mild to moderate sedation in patients who underwent GIE procedures was evaluated by Pambianco and coworkers [29]. This study showed that propofol administration in mild or moderate sedation level by nonanesthetic personnel used with CAPS system in patients who underwent EGD and colonoscopic procedures was safe and effective. Moreover, low propofol dosage and short recovery time were noted.

4.4. Closed-loop administration of anesthesia

Closed-loop administration of anesthesia systems can provide anesthesia automatically and its effect feedback controlled. This system contains a central system, a target control device such as syringe pump, vaporizer, and other drug delivery systems [30]. Currently, there are several closed-loop administration systems for neuromuscular blockade, depth of anesthesia, and pain control during decreased levels of consciousness. In addition, McSleepy is also a closed-loop control system that displays the patient's depth of consciousness, muscular movement during surgery, and the level of pain [30].

4.5. Teleanesthesia

Teleanesthesia is the use of telemedicine technology in anesthetic management including preoperative assessment at distance, video consultation, and performing anesthesia in remote locations where experienced anesthesiologists are not always present [30, 31]. The impact of telemedicine pre-anesthesia evaluation on periprocedural processes was confirmed by Applegate II and colleagues. Their study demonstrated that telemedicine pre-anesthesia evaluation offered patients time- and cost-saving benefits without more surgical delay. Moreover, telemedicine and in-person assessments were comparable, with high patient and physician satisfaction [32].

5. Anesthetic agents

5.1. Local anesthetic agents

Generally, lidocaine is the most common local anesthetic agent used for GIE procedure. The viscous lidocaine solution and lidocaine spray are usually performed for upper GIE procedure. In addition, lidocaine gel or jelly is frequently employed for lower GIE procedure. Recently, lidocaine lozenge has been tried to use for EGD procedure. Mogensen and colleagues evaluated the effect and acceptance of a lidocaine lozenge compared with a lidocaine viscous oral solution as pharyngeal anesthesia before EGD [33]. The 110 adult patients were randomized to receive either 100 mg lidocaine as a lozenge or 5 mL lidocaine viscous solution 2%. Supplemental intravenous midazolam was administered if needed. They concluded that the lozenge could reduce gag reflex and patients' discomfort, and improved patients' acceptance during the procedure. In addition, the lozenge form had also a good taste [33]. Another study of the lidocaine lozenge used for pharyngeal anesthesia in EGD procedure has been reported by

Tumminakatte and Nagaraj [34]. The authors compared the efficacy, safety, and patient comfort for the lidocaine lozenge and lidocaine viscous as a single agent before EGD procedure. This study showed that lidocaine lozenge was effective and safe for pharyngeal anesthesia before EGD procedure. It was relatively better than lidocaine viscous in terms of lesser discomfort and procedural difficulty as well as increased tolerability of the EGD procedure [34].

Moreover, topical bupivacaine could be used as pretreatment for pharyngeal anesthesia in unsedated EGD. The effect of a bupivacaine lozenge as pharyngeal anesthesia and a lidocaine spray before EGD was assessed by Salale and coworkers [35]. Ninety-nine adult patients were randomized to receive either a bupivacaine lozenge or lidocaine spray. Patient discomfort and the acceptance of gag reflex during EGD procedures were evaluated. The results showed that patient discomfort and gag reflex during procedure in the bupivacaine lozenge group were significantly lower than the lidocaine spray group. The authors also suggested that bupivacaine lozenge for topical pharyngeal anesthesia before an unsedated EGD procedure verified to be a superior option as compared with lidocaine spray [35].

Chan and colleagues studied the effectiveness of 10% lidocaine pump spray plus plain Strepsils and Strepsils anesthetic lozenge plus distilled water spray for EGD procedure in terms of patient tolerance, taste of anesthetic agent, intensity of numbness, amount of cough or gag, and the degree of discomfort at esophageal intubation. They concluded that topical lidocaine spray was superior to the flavored anesthetic lozenge as a topical pharyngeal anesthesia in unsedated EGD procedure [36]. Furthermore, the safety and efficacy of a lidocaine lollipop as single-agent anesthesia for EGD has been evaluated by Ayoub and coworkers [37]. The main outcome variables of the study were the success rate and safety of local anesthesia by using lidocaine lollipop in addition to the need for intravenous sedation. Their study showed that lidocaine lollipop, a favorable form of pharyngeal anesthesia, was safe and well tolerated for EGD procedure.

5.2. Benzodiazepines

5.2.1. Midazolam

Midazolam is one of the most common drugs used for sedation during GIE procedures. It is a rapid-onset, short duration of action, and water-soluble benzodiazepine with anxiolytic, amnesic, sedative, muscle relaxant, and anticonvulsant properties. These actions are due to the effect of binding to gamma-amino butyric acid receptors in the central nervous system. Midazolam has few adverse effects. Respiratory depression is the most important adverse effect and is synergistic when used in combination with opioids. The standard dose in adult patients is 0.015-0.06 mg/kg [38].

5.3. Opioids

5.3.1. Fentanyl

Fentanyl is a potent synthetic opioid and also commonly used for GIE procedures. It has a rapid onset, short duration of action, and lack of direct myocardial depressant effects. The

onset of action is 30–60 s, and the duration of action is 30–45 min. Generally, the dose for GIE procedure is usually 1–2 mcg/kg, with a maximum dose of 100–150 mcg in adult healthy patients. Because of its analgesic effect, fentanyl is commonly used for therapeutic GIE procedures. Of late, the combination of fentanyl and midazolam is an accepted regimen with a safety profile [39-41]. However, fentanyl can cause respiratory depression including apnea as well as nausea and vomiting. It can reduce the heart rate.

5.3.2. Remifentanil

Remifentanil is a fentanyl analog with a methyl ester group and is hydrolyzed by plasma and tissue esterases. Its metabolism is not affected by genetics, age, hepatic failure, and renal failure. Its action is rapid. The use of remifentanil for sedation in GIE procedures is not entirely recognized. Remifentanil is generally performed by using the continuous infusion technique. The TCI of remifentanil is another preference. The combination of propofol and remifentanil for sedation in GIE procedures is usually used. The study of Abu-Shahwan and Mack demonstrated the efficacy and safety of a combination of propofol and remifentanil for deep sedation in children who underwent GIE procedures [42]. In their study, anesthesia was induced with sevoflurane and nitrous oxide in oxygen, and was maintained with infusion of propofol and remifentanil. All GIE procedures were successfully completed with no complications. However, this combination of propofol and remifentanil demonstrated the reduction of heart rate, blood pressure, and respiratory rate.

Remifentanil in TCI appears to be a satisfactory drug for sedation in GIE procedures. However, propofol in TCI for GIE procedures demonstrates better sedation than remifentanil in TCI. This issue was confirmed by Munoz and colleagues [43]. They compared remifentanil and propofol in TCI for sedation in 69 patients during GIE procedures. The authors concluded that propofol in TCI for sedation in patients who underwent GIE procedures seemed to be an adequate agent. Additionally, propofol in TCI created less adverse effects and higher patient satisfaction than remifentanil in TCI.

5.4. Remimazolam

Remimazolam is a rapidly acting intravenous sedative drug. It combines the properties of midazolam and remifentanil. Additionally, its tendency to cause apnea is very low. Remimazolam has potential to be used as a sedative drug in the intensive care unit and as a novel agent for procedural sedation [44, 45]. Recently, remimazolam was evaluated for sedation in patients who underwent upper GIE procedures by Rogers and McDowell. This clinical trial demonstrated that the time to recovery from sedation of remimazolam was faster and more reliable than midazolam [46]. Moreover, Worthington and colleagues assessed the feasibility of remimazolam for sedation during colonoscopy and reversing the sedative effects of remimazolam with flumazenil in 15 healthy volunteers. The sedation for colonoscopy was successfully completed in more than 70% of subjects. In addition, all subjects rapidly reversed with flumazenil and also rapidly recovered within 10 min. No serious adverse events were observed [47].

5.5. Propofol

Propofol has sedative, hypnotic, and anesthetic properties. However, it does not have analgesic effects. Propofol rapidly crosses the blood–brain barrier. The onset of action is 30–60 s. Dose reduction is needed in patients with cardiac dysfunction and in elderly patients. However, the dose reduction of propofol in patients with moderately severe liver disease or renal failure is not required. Propofol potentiates the effects of analgesic and sedative drugs. The advantage of propofol has been demonstrated for therapeutic GIE procedures and not for diagnostic GIE procedures.

Propofol in combination with opioid or benzodiazepine can cause significant cardiovascular depression and may result in a deeper than expected depth of sedation because of its narrow therapeutic window. Pain at the injection site is the most frequent local complication. Several methods for propofol delivery have been used for GIE procedures. Generally, propofol is administered intravenously as a repeated bolus injection, continuous infusion, or a mixture of both. Currently, the nonanesthesiologist-administered propofol is a controversial issue and also varies among countries.

5.5.1. Propofol for GIE procedures

Generally, propofol is usually used for various GIE procedures. A previous study confirmed that sedation with propofol alone or propofol combined with fentanyl or midazolam in children was safe and effective. However, the use of propofol alone provides lesser sedation and ease of endoscopy than the use of propofol in combination with fentanyl or midazolam [48]. In Siriraj GI Endoscopy Center, the combination of propofol, fentanyl, and/or midazolam was usually used for GIE procedures even in pediatric patients. Moreover, our previous studies also demonstrated the clinical effectiveness of an anesthesiologist-administered sedation outside of the operating room for pediatric GIE procedures. Although, all sedation-related complications were relatively high, all of these complications were transient and easily treated [39, 40, 49, 50]. In terms of procedure-related complications, propofol-based sedation does not increase the rate of colonoscopic perforation [51].

For invasive GIE procedures, propofol-based sedation for ERCP and percutaneous endoscopic gastrostomy procedures in sick and elderly patients by anesthetic personnel with appropriate monitoring was also safe and effective without any serious complications [52-54]. The safety of propofol sedation for EUS with fine needle aspiration procedure was confirmed by Pagano and coworkers [55]. The complication rates for propofol deep sedation and meperidine/midazolam administered for moderate sedation were not significantly different. Furthermore, propofol combined with fentanyl and midazolam is frequently used for GIE procedures including EUS and small bowel enteroscopy [56-60].

5.5.2. Nurse-administered propofol

Several guidelines do not recommend the use of propofol for routine GIE procedures. The safety and efficacy of propofol administered by registered nurses has been reported in a case series including 2000 patients undergoing elective EGD and/or colonoscopy [61]. Another

study demonstrated that trained nurse-administered propofol for GIE sedation in patients with ASA class I, II, and III was safe and effective. The anesthetic support was assisted in 11 patients (0.4%) [62].

5.5.3. Gastroenterologist-administered propofol

Similar to qualified nurses, the gastroenterologist can administer propofol effectively. Several guidelines recommend that gastroenterologist-administered propofol should be used to sedate patients only at mild or moderate sedation levels. Additionally, the patients must have ASA physical status not more than III. The study of Vargo and colleagues confirmed that gastro-enterologist-administered propofol for elective ERCP and EUS procedures resulted in the reduction of propofol dosage and the improvement of recovery activity as well as the rapid detection of respiratory depression. This study also demonstrated that gastroenterologist-administered propofol should be a cost-effective sedation technique [63].

5.5.4. Anesthesiologist-administered propofol

Propofol is commonly used by anesthesiologists for anesthesia in GIE procedures. To date, the use of propofol is still controversial. Propofol can be used by well-trained registered nurses or physicians in some countries. However, in developing countries, propofol-based sedation is performed by anesthesiologists or anesthetic nurses. Berzin and coworkers accomplished a cohort study of sedation-related adverse events, patient- and procedure-related risk factors associated with sedation, as well as endoscopist and patient satisfaction with anesthesiologist-administered sedation in 528 patients who underwent ERCP procedures. The study confirmed that anesthesiologist-administered sedation for ERCP patients was safe and effective. Cardiorespiratory-related adverse events were generally minimal [64].

5.6. Fospropofol

Fospropofol is a water-soluble prodrug of propofol that is currently approved for sedation for diagnostic and therapeutic procedures. It is characterized by a smooth and predictable rise and decline rapidly observed following intravenous administration. It does not cause pain on intravenous injection, but it has been associated with paresthesia in the perineal and perianal area. However, fospropofol causes dose-dependent hypotension, respiratory depression, and apnea. Generally, a standard of fospropofol sedation is 6.5 mg/kg. In high-risk and elderly patients, a lower dose should be administered. Bergese and coworkers compared the efficacy and safety of fospropofol in a dose of 4.875 mg/kg and 6.5 mg/kg for sedation in high-risk elderly patients who underwent colonoscopy. This study showed that fospropofol in a dose of 4.875 mg/kg for sedation in high-risk elderly patients who underwent colonoscopy was not a clinically significant advantage. Fospropofol in a dose of 6.5 mg/kg was recommended in the elderly, obese, and high-risk patients when used for moderate sedation [65].

5.7. Ketofol

Ketofol is the combination of ketamine and propofol in various concentrations. It is an agent of choice for a variety of GIE procedures. Ketamine, a neuroleptic anesthetic agent, works on

thalamocortical and limbic N-methyl-D-aspartate receptors. Ketamine stimulates the cardior-espiratory system. A direct effect increases cardiac output, arterial blood pressure, heart rate, and central venous pressures [66]. In contrast, propofol has antiemetic, anxiolytic, hypnotic, and anesthetic properties. Additionally, propofol has a short recovery time without an increase of cardiorespiratory side effects. As a result, the combination of these two drugs has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and post-procedural analgesia. The safety and efficacy of ketofol as a sedoanalgesic agent are dependent on the dose and the ratio of the mixture [67].

Ketofol is also commonly used for sedation during GIE procedures. My previous study evaluated the clinical efficacy of the ketofol and propofol alone when each regimen is used as sedative agents for colonoscopic procedure. A 194 patients were randomized into two groups; 97 patients in group PK received propofol and ketamine and 97 patients in group P received propofol and normal saline for sedation. All patients were premedicated with 0.02–0.03 mg/kg of midazolam. All colonoscopic procedures were completely successful. There were no significant differences in patient tolerance, hemodynamic parameters, recovery activity, patient and endoscopist satisfaction, as well as the sedation-related adverse events between the two groups. In addition, these adverse events were transient and mild in degree [68].

5.8. Dexmedetomidine

Dexmedetomidine is a specific central alpha-2 adrenoreceptor agonist with sedative and analgesic properties. Dexmedetomidine has no effect at the GABA receptor, and is not associated with significant respiratory depression. The patients can be sedated but are able to be awakened to full consciousness easily. It induces a biphasic blood pressure response: high doses cause hypertension, and lower doses cause hypotension and bradycardia. The other disadvantages of dexmedetomidine include a slow onset and longer duration of action [42].

To date, the role of dexmedetomidine for GIE procedures is not entirely established and remains a controversial issue. Samson and colleagues compared the sedation efficacy and the hemodynamic effects of dexmedetomidine, midazolam, and propofol in 90 patients with ASA physical status I or II, who underwent elective diagnostic upper GIE procedures. The results demonstrated that endoscopist satisfaction level, recovery, and the hemodynamic stability in the dexmedetomidine group were significantly better than in the midazolam and the propofol groups [69]. However, dexmedetomidine alone is less effective than the combination of propofol and fentanyl for moderate sedation during ERCP procedure [70]. Most of the patients needed supplementary analgesic and sedative drugs to accomplish the depth of sedation level. However, these findings do not allow us to conclude that propofol alone is better than dexmedetomidine alone, because the conclusion was established for propofol combined with fentanyl. Moreover, dexmedetomidine was associated with higher hemodynamic instability and a prolonged recovery phase [70].

5.9. Ketodex

Ketamine is a dissociative anesthetic agent and works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors. Its actions are described by catalepsy in which eyes remain

open and there is slow nystagmic gaze while corneal and light reflexes remain intact. Direct effects increase cardiac output, blood pressure, heart rate as well as pulmonary arterial and central venous pressures, which stimulates the cardiorespiratory system. However, ketamine produces unpleasant psychological effects including hallucinations, nightmares, and emergence reactions. Dexmedetomidine is a specific central alpha-2 adrenergic agonist that decreases central presynaptic catecholamine release. It has no effect at the GABA receptor, and is not associated with significant respiratory depression. Its properties of sedation, anxiolysis, and analgesia together with its beneficial pharmacokinetics make it a valuable adjunct for procedural and intensive care sedation [66].

The use of ketodex for GIE procedures was reported by Goyal and colleagues [71]. They used a bolus dose of ketamine 2 mg/kg and dexmedetomidine 1 mcg/kg for upper GIE procedures in pediatric patients. The results of the study showed that blood pressure, heart rate, and oxygen saturation did not change significantly from the baseline. The airway interventions were not used. In addition, there were also no laryngospasm and postprocedural shivering. The delirium score was lower than 4 in all patients except for two cases. This case series supported the use of ketodex was safe and clinically effective for upper GIE procedure in pediatric patients [71].

5.10. Muscle relaxants

5.10.1. Cisatracurium

Cisatracurium, an isomer of atracurium, is about three times more potent than atracurium and less tendency to release histamine than atracurium. It experiences spontaneous degradation at physiological pH and temperature by Hofmann elimination. Liver disease does not appear to have an effect on cisatracurium. Pharmacokinetics and pharmacodynamics of cisatracurium in normal adult and liver transplant patients do not show clinically significant differences in the recovery profiles [72]. Because of its beneficial properties, cisatracurium is a muscle relaxant drug of choice for tracheal intubation and maintenance during general anesthesia in GIE procedures [50, 59].

5.10.2. Rocuronium

Rocuronium is a steroidal nondepolarizing neuromuscular blocking drug and has a rapid onset of action. It is a muscle relaxant drug of choice for tracheal intubation and maintenance during general anesthesia in GIE procedures [50, 59, 73]. Rocuronium has emerged as an alternative to succinylcholine for facilitating rapid tracheal intubation in full stomach patients. It is predominantly useful as a relaxant agent for tracheal intubation in patients at risk of hyperkalemia and patients with known or suspected increased intracranial or intraocular pressure. However, rocuronium may be used cautiously in patients with impaired liver function [74].

5.11. Reversal drugs

5.11.1. Naloxone

Naloxone is a pure mu-opioid antagonist with a high affinity for the receptor. It can reverse both the analgesic and respiratory effects of opioids [4, 42]. The standard dosage of intravenous naloxone is 1–2 mcg/kg with a maximum dose of 0.1 mg/kg and up to 2 mg. However, naloxone has a short duration of action and one dose typically only lasts for 30–45 min. Patients should be monitored for at least 2 h after the last dose of naloxone. The adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema, and cardiac dysrhythmias.

5.11.2. Flumazenil

Flumazenil is a benzodiazepine antagonist. It is a highly specific benzodiazepine receptor antagonist and can safely reverse the sedative and respiratory effects caused by benzodiazepines. The adult dose is 0.01 mg/kg and up to 1 mg. Its duration of action is just about 1 h. However, this effect is reversible. Importantly, the patients should be observed for at least 2 h after the administration of flumazenil [4, 42]. The adverse reactions of flumazenil consist of sweating, flushing, nausea/vomiting, hiccup, agitation, abnormal vision, paresthesia, and seizure.

5.12. Sugammadex

Sugammadex is a selective relaxant binding drug that quickly reverses the effects of aminosteroid neuromuscular blocking agents such as rocuronium and vecuronium. It was successfully used to reverse rocuronium-induced neuromuscular block in patients where neostigmine was insufficient. Dogan and colleagues investigated the efficacy of sugammadex after unsatisfactory decurarization following neostigmine administration. This study was performed on 14 patients who experienced inadequate decurarization (TOF < 0.9) with neostigmine after general anesthesia. A dose of 2 mg/kg of sugammadex was used. The result confirmed that sugammadex was successfully performed to reverse rocuronium-induced neuromuscular block in patients where neostigmine was insufficient [75]. The capability to reverse a rocuronium-induced neuromuscular block at any stage and possibly to improve patients' safety might make sugammadex a very attractive drug for the use in day-case anesthesia.

Another study compared the efficacy of sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in elective surgical patients [76]. All patients, ASA physical status I-III obtained a dose of 0.1 mg/kg vecuronium for tracheal intubation and maintenance dose of 0.02–0.03 mg/kg if needed. Neuromuscular blockade was monitored by using acceleromyography. At the end of surgery, patients were randomized to receive either sugammadex 2 mg/kg or neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg. The study showed that mean recovery times to a TOF ratio of 0.8 and 0.7 in the sugammadex group were significantly shorter than in the neostigmine group. No serious adverse events were noted.

The authors concluded that sugammadex presented significantly quicker reversal of vecuronium-induced neuromuscular blockade compared with neostigmine [76].

5.13. Inhalation agents

5.13.1. Sevoflurane

Sevoflurane is an inhalation agent with ideal properties for deep sedation during GIE procedures in pediatric patients. In addition, it is commonly used for balanced general anesthesia. A retrospective study reviewed data from children receiving sevoflurane inhalation administered by an anesthesiologist via laryngeal insufflation to attain deep sedation for outpatient GIE procedures. All patients were adequately sedated with sevoflurane, and no intravenous line was needed. Time to awakening, discharge, and complication rate in the sevoflurane group were significantly lower than in the combination of midazolam, fentanyl, and ketamine, as well as in the propofol alone groups. This report suggested that deep sedation with sevoflurane insufflation for pediatric outpatient GIE procedure is as safe as conventional sedation techniques [77].

Consequently, Meretoja and colleagues compared anesthesia with sevoflurane or halothane for bronchoscopy or gastroscopy, or both in 120 infants and children. All pediatric patients were assigned to receive either 7% sevoflurane or 3% halothane in 66% nitrous oxide in oxygen for induction of anesthesia. Induction time and psychomotor recovery as well as the incidence of nausea/vomiting and cardiac arrhythmia in the sevoflurane group were significantly lower than in the halothane group. This study confirmed that the use of sevoflurane was better than the use of halothane for bronchoscopy and gastroscopy procedures in pediatric patients [78].

5.13.2. Desflurane

Desflurane is an ether inhalational anesthetic agent. It offers the advantage of precise control over depth of anesthesia along with a rapid, predictable, and clear-headed recovery with minimal postoperative adverse events. It also has advantages when used in extremes of age and in obese patients. Desflurane is generally used for the maintenance of balanced general anesthesia because of its rapid recovery. Currently, the use of desflurane may increase the direct costs of anesthetic care [79]. However, no significant differences were demonstrated between desflurane and sevoflurane in the late recovery period.

6. Post-anesthesia care

Blood pressure, heart rate, respiratory rate, oxygen saturation, and level of consciousness are monitored and documented at least every 15 min or less, for a minimum of 30 min after the last dose of sedation drug. These parameters should be monitored and noted in the recovery period. Moreover, the patients should be monitored for at least 2 h after the last dose of a reversal drug. All patients will be discharged from the recovery room once the discharge criteria are completed. Generally, the majority of sedated patients would complete an acceptable score on or before 1 h after GIE procedure. Most delays after satisfactory scores were due

to nonmedical causes [80]. In ambulatory cases, the presence of an escort must be confirmed, and the patients should not drive for at least 24 h.

7. Conclusion

GIE procedure requires some forms of anesthesia. To date, sedation for GIE procedure can be effectively and safely performed by anesthesiologist or nonanesthetic personnel with appropriate patient selection and monitoring. The new anesthetic drugs and monitoring equipments for safety and efficacy are available. However, pre-anesthetic evaluation and preparation, anesthetic drugs used, monitoring practices and post-anesthesia management are still essential for the anesthesia innovations in GIE procedures.

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