Abstract

The safe sedation of patients for diagnostic or therapeutic procedures requires a combination of properly trained physicians and suitable facilities. Additionally, appropriate selection and preparation of patients, suitable sedative technique, application of drugs, adequate monitoring, and proper recovery of patients is essential. The goal of procedural sedation is the safe and effective control of pain and anxiety as well as to provide an appropriate degree of memory loss or decreased awareness. Sedation practices for gastrointestinal endoscopy (GIE) vary widely. The majority of GIE patients are ambulatory cases. Most of this procedure requires a short time. So, short acting, rapid onset drugs with little adverse effects and improved safety profiles are commonly used. The present review focuses on commonly used regimens and monitoring practices in GIE sedation. This article is to discuss the decision making process used to determine appropriate pre-sedation assessment, monitoring, drug selection, dose of sedative agents, sedation endpoint and post-sedation care. It also reviews the current status of sedation and monitoring for GIE procedures in Thailand.

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Key words: Sedation; Monitoring; Gastrointestinal endoscopy; Sedatives; Analgesics

INTRODUCTION

Sedation always has been a critical component of performing gastrointestinal endoscopy (GIE) procedures. The aim of sedation for these procedures is to increase patient’s comfort, to improve endoscopic performance and to increase patient and endoscopist satisfaction. The need for sedation is decided by the type of endoscopy, duration of procedure, degree of endoscopic difficulty, patient physical status and physicians’ preferences. The sedation regimen for GIE procedures is still varied. The guidelines established by the American Society of Anesthesiologists (ASA) and the American Academy of Pediatrics serve as the standard for institutional policy development in the area of procedural sedation.

The guideline defines terms throughout and in particular: (1) Minimal sedation: a drug-induced state which patients respond normally to verbal commands; (2) Moderate sedation (conscious sedation): a drug-induced depression of consciousness which patients respond purposefully to verbal commands. Spontaneous ventilation is adequate. Cardiovascular function is usually maintained; (3) Deep sedation: a drug-induced depression of consciousness which patients can not be easily aroused but respond purposefully after repeated verbal or painful stimulation. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained; and (4) General anesthesia: a drug-induced loss of consciousness which patients are not arousable, even by painful stimulation. Patients often require assistance in maintaining a patent airway. Cardiovascular function may be impaired.

The important component of these guidelines is that the endoscopy team must have the ability to rescue the patient.
Proper breathing is monitored by observing the rate and depth of chest, abdominal movements, and pattern of respiration. Respiratory depression is the main risk of sedation-related adverse events especially in the elderly or in comorbidity patients. The level of sedation and consciousness especially in the elderly or in comorbidity patients. Depression is the main risk of sedation-related adverse effects. It is important to point out that pulse oximetry does not measure alveolar hypoventilation. Oxygen administration may prevent hypoxemia and its deleterious effects, but it will not detect the development of hypercapnea. Additionally, there was a poor correlation between clinical observation and objective measures of ventilation. Capnography is based on the principle that carbon dioxide absorbs light in the infrared region of the electromagnetic spectrum. In the literature, capnography was found to be more sensitive than pulse oximetry or visual assessment in the detection of apneaic episodes. It has also been utilized to allow the safe titration of propofol by a qualified gastroenterologist during endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS).

**Cardiovascular monitoring**

**Noninvasive blood pressure:** Blood pressure and heart rate are important parameters of cardiovascular monitoring. Mean arterial pressure can be an indirect parameter to estimate hypnotic effects. Changes in arterial blood pressure are mediated by cardiodepressive side effects of sedative agents. Baseline hemodynamic parameters also provide useful information of the effects of various medical conditions. Continuous pulse oximetry,
blood pressure, heart rate, respiratory rate and level of consciousness will be documented before the sedation, and at least 5 min for deep sedation and every 15 min for moderate sedation. Blood pressure was therefore far more likely to predict increasing and decreasing doses of sedative agents. Importantly, they provide important feedback throughout the GIE procedure. Additionally, these parameters may influence the selection of the sedative agents.

Electrocardiography: The use of electrocardiography (ECG) was initially intended to detect cardiac arrhythmias in high risk patients undergoing sedation/anesthesia. However, the role of continuous electrocardiography during GIE sedation remains uncertain[7]. ASA and the American Society for Gastrointestinal Endoscopy (ASGE) practice guidelines indicate that patients with significant cardiovascular diseases or dysrhythmia should have electrocardiographic monitoring during GIE sedation. ECG is not required for low risk patients including patients with ASA physical status I or II[10,18].

Other monitors
Generally, the invasive monitors such as arterial blood pressure, central venous pressure (CVP) and pulmonary arterial catheterization (PAC) are rarely used during sedation for GIE procedures. These monitors may be utilized in some patients. For example, arterial blood pressure is used in patients with severe hemodynamic instabilities or patients with shock, and CVP or PAC is used for fluid resuscitation in patients with severe gastrointestinal bleeding.

Sedation depth monitoring
Bispectral index monitoring: As depth of sedation cannot be reliably judged by clinical assessments alone, a reliable method is needed to measure the hypnotic component of sedation. Recently, processed electroencephalogram (EEG) variable such as the Bispectral (BIS) index is developed to ease EEG interpretation. This tool has been reported to be more precise in measurement of sedation level. BIS monitoring is a noninvasive method of assessing patient’s level of consciousness. 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). BIS monitor is designed to measure patient consciousness during general anesthesia. The onset of action is 30 to 60 s, peak effect is 5 to 15 min, and duration of action is 30 to 45 min. Its dose for moderate sedation. Blood pressure was therefore far more likely to predict increasing and decreasing doses of sedative agents. Importantly, they provide important feedback throughout the GIE procedure. Additionally, these parameters may influence the selection of the sedative agents.

The usefulness of BIS monitoring for GIE procedures remains controversial. The study of Bower et al[8] showed that BIS index correlated moderately well with the level of sedation determined by using the Observer Assessment of Alertness/Sedation scale. Al-Samman et al[11] performed a study to compare BIS with clinical assessment of sedation in patients undergoing ERCP. The results in terms of duration of sedation, recovery rate, patient satisfaction and total dose of sedative agent favored the group monitored with BIS[9]. In contrast, many papers demonstrated that BIS index had low accuracy for detecting deep sedation and it was not useful for titrating propofol to an adequate level of sedation[11,12].

Narcotrend™: Narcotrend™ (MonitorTechnik, Hanover Medical School) performs a computerized analysis of the raw electroencephalogram. It has two recording modes: the one channel mode as the standard for the assessment of the depth of hypnosis during anesthesia and sedation, and the two channel mode for comparison of signals from the two hemispheres of the brain. After accounting for artifact, a multivariate statistical algorithm is used for analysis which results in a six-stage classification from A (awake) to F (general anesthesia/coma) and 14 substages[10].

My previous study showed that the Narcotrend™ system monitoring can be successfully used to provide deep sedation in patients undergoing ERCP procedure[14]. Consequently, the use of Narcotrend™ system for monitoring significantly reduced sedation-related adverse events and hemodynamic alterations[13].

SEDATIVE AND ANALGESIC AGENTS

Midazolam
Midazolam is the drug most commonly used for sedation during GIE procedures. It is a shorting, water soluble benzodiazepine with anxiolytic, amnestic, sedative, muscle relaxant, and anticonvulsant properties. These actions are considered to be the result of binding to gamma-amino butyric acid receptors in the central nervous system. It has a rapid onset (1-3 min), a rapid peak effect (3-5 min) and a short duration of action (20-60 min). Duration of midazolam is greater in the elderly patients. Factors that potentiate effects of midazolam include hypoaalbuminemia, advanced age, diminished liver function and concomitant use of drugs that inhibit cytochrome P450. The usual adult dose is 1 to 5 mg (0.015-0.07 mg/kg)[16]. Midazolam has few side effects. These effects are not serious. Respiratory depression is the most important adverse effect. Other side effects are nasal itching, dizziness, anxiety, rash, irritability, dreams, seizures and involuntary muscle movement. Respiratory depression is synergistic when used in combination with opioids.

Fentanyl
Fentanyl is a potent synthetic opioid with no intrinsic anxiolytic or amnestic properties. It has a rapid onset, short duration of action, lack of direct of myocardial depressant effects, and absence of histamine release. The onset of action is 30 to 60 s, peak effect is 5 to 15 min, and duration of action is 30 to 45 min. Its dose for GIE procedure is 1 to 2 mcg/kg, with a maximum dose of 100 to 150 mcg in most adult patients. Intravenous fentanyl can be easily and rapidly titrated for painful procedures. The combination of fentanyl and midazolam is a popular regimen, with a safety profile when both drugs
are carefully titrated \( ^{17-19} \). Similar to all opioids, fentanyl can cause respiratory depression including apnea and nausea and vomiting. It can also produce the decrease of heart rate and skeletal muscle rigidity.

**Meperidine (pethidine)**

Meperidine is a synthetic opioid. It has an inferior safety profile and a long duration of action compared with fentanyl. Its onset of action is 1 to 3 min, peak effect is 5 to 20 min, and duration of action is 2 to 4 h. Intravenous dose of meperidine in adult patients is 0.5 to 2 mg/kg with a maximum dose of 100 mg. The metabolites of meperidine are toxic to the central nervous system at high doses and in patients with renal impairment. Fatal reactions have also occurred in patients taking monoamine oxidase inhibitors or in patients with hyperthyroidism \( ^{29} \). Meperidine 0.5-1.0 mg/kg iv combined with midazolam 0.05-0.1 mg/kg iv provides effective sedation for GIE procedure. However, meperidine is not recommended for sedation in the emergency department.

**Ketamine**

Ketamine is a dissociative agent which largely spares upper airway muscular tone and laryngeal reflexes, and may represent an alternative to narcotics and benzodiazepines for sedating children for GIE procedures. It can cause a wide range of effects including analgesia, amnesia, anesthetia and sedation. Routes of administration can be oral or rectal, but are usually intravenous or intramuscular. Ketamine is demethylated to form norketamine that is one fifth to one third as potent as ketamine. Intense analgesia can be achieved with subanesthetic dose of ketamine 0.2 to 0.5 mg/kg intravenously. Return of consciousness usually occurs in 10 to 15 min, but complete recovery is delayed.

An undesirable effect is the triggering of visual and auditory hallucinations, which can lead to the nightmares limiting the clinical usefulness of ketamine in adults. Dreams and hallucinations can occur up to 24 h after administration of ketamine. Factors associated with an increased incidence of emergence delirium include the age greater 16 years, female sex, dose of ketamine intravenously greater than 2 mg/kg, and history of personality problems. These effects can be prevented by the prior administration of benzodiazepine. Ketamine also has been highly associated with a high potential for laryngospasm. The critically ill patients may respond to ketamine with unexpected decreases in blood pressure and cardiac output. Previous studies have been reported with the combination of ketamine and midazolam for sedation in pediatric GIE procedures \( ^{21} \). The importance of ketamine for sedation in adult GIE procedures is still needed for further studies \( ^{22} \).

**Propofol**

Propofol is a phenol derivative with sedative, hypnotic and anesthetic properties. It has antiemetic, anxiolytic, hypnotic, amnestic and anesthetic properties. However, it does not have analgesic effects. Propofol rapidly crosses the blood-brain barrier, and causes a depression in consciousness. The onset of hypnosis is 30-60 s \( ^{23} \). The plasma half-life ranges from 1.30 to 4.13 min. Dose reduction is required in patients with cardiac dysfunction and in the elderly due to decreased clearance of the drug. It is not necessary to reduce the dose of propofol in patients with moderately severe liver disease or renal failure.

The advantage of propofol over midazolam and meperidine has been demonstrated for therapeutic GIE procedures and not for diagnostic GIE procedures \( ^{24} \). Propofol potentiates the effects of narcotic analgesics and sedatives such as benzodiazepines, barbiturates, and droperidol and therefore the dose requirements may be reduced. However, propofol associated with hypotension, respiratory depression and airway obstruction. The combination of propofol and opioid or benzodiazepine can cause significant cardiovascular depression. Unfortunately, propofol lacks a reverse agent. It also has a narrow therapeutic window which may result in a deeper than expected depth of sedation. Pain at the injection site is the most frequent local complication. To date, it is a controversial issue that personnel specifically trained in the administration of propofol with expertise in emergency airway management need to be present and constantly monitoring the patient’s parameters. However, this issue varies among the countries.

**Propofol administration techniques**

Many methods for propofol delivery have been used for sedation for GIE procedures. Generally, propofol is administered intravenously as a repeated bolus injection, continuous infusion or a mixture of both. In the bolus technique, the initial bolus dose is adjusted according to the patient’s weight, age, ASA physical status and comorbidities. Continuous propofol infusion is titrated to the desired sedation level and to the patient’s characteristics.

Other administration techniques of propofol delivery such as target controlled infusion (TCI), patient controlled sedation (PCS) or computer assisted personalized sedation (CAPS) have been investigated. Propofol TCI rather than bolus method may be a better choice for the prevention of hemodynamic response during GIE procedure. However, propofol TCI does not confer any benefit over bolus propofol with respect to drug consumption and recovery profile for sedation in colonoscopy \( ^{25} \). PCS with propofol is effective and results in high patient satisfaction and faster discharge \( ^{26} \). PCS has been demonstrated to be the effective technique for pain control during GIE procedure \( ^{27} \). CAPS uses feedback from the real time measures of drug effect and patient reaction to tactile stimuli to control propofol infusion \( ^{28} \).

**Propofol for GIE procedures**

**Esophagogastroduodenoscopy:** In a randomized study, 199 patients underwent esophagogastroduodenoscopy (EGD) procedures received fentanyl 0.5 mcg/kg or remifentanil 0.5 mcg/kg, followed by a bolus injection of 1
mg/kg of propofol. The subsequent doses of propofol were 0.5 mg/kg when the patient was conscious or body movement appeared[29]. Recovery time and total dosage of propofol given in the remifentanil group was significantly less than it was in the fentanyl group. However, the frequency of apnea was significantly higher in the remifentanil group. There were no significant differences in frequency of hypoxemia, bag ventilation, or body movement between the two groups. Sedation with propofol is also safe and effective for use in patients with upper gastrointestinal bleeding undergoing urgent therapeutic gastrointestinal endoscopy[34]. The study from Canada demonstrates that sedation with propofol alone or propofol combined with fentanyl or midazolam in children is safe and effective. Propofol in combination with fentanyl or midazolam gives better sedation and ease of endoscopy than propofol alone[35]. In addition, the reports from developing countries including Thailand are also showed that propofol-based sedation for GIE procedures in pediatric patients is safe and effective. Serious adverse events are rare[17,32,33].

ERCP: A meta-analysis shows that propofol sedation during ERCP leads to shorter recovery time without an increase of cardiopulmonary side effects. Propofol sedation can provide adequate sedation during ERCP[34]. Propofol deep sedation administered by an anesthesiologist with appropriate monitoring seems to be a safe procedure during colonoscopy or ERCP in cirrhotic patients[36]. Our previous study demonstrated that propofol-based deep sedation for ERCP procedure in sick elderly patients by trained anesthetic personnel with appropriate monitoring was safe and effective. The clinical efficacy of this technique in sick elderly patients was different or worse than in non-sick elderly patients. Serious adverse events were rare[37]. In general knowledge, dose requirement and complications of propofol are lower when used in the diluted form than in the undiluted form. However, our previous study in ERCP patients did not show that. Propofol requirement and recovery time in the diluted and undiluted propofol groups were comparable. Sedation-related hypotension was significantly lower in the diluted group than the undiluted group[16].

Colonoscopy: Patient-controlled sedation with propofol/remifentanil yields superior facility in sedation and recovery time compared with midazolam/fentanyl[38] when used in an appropriate care setting[39]. Wang et al[40] compared cardiorespiratory function and sedative and analgesic effects, using combinations of midazolam with either fentanyl or propofol in a non-randomized group of 480 patients undergoing colonoscopy procedures. The combination of midazolam with either fentanyl or propofol allowed patients to undergo colonoscopy under comparable sedative and analgesic conditions. The combination with fentanyl had a significantly lower effect on pulse rate and blood pressure. The combination with propofol produced superior amnestic effects.

The use of sedation for GIE procedures in very elderly patients has been established as a safe and effective technique when carried out by trained anesthetic personnel with appropriate monitoring and dose adjustment[10]. In the past, there was controversy regarding the frequency of sedation-related complications of colonoscopies especially for colonoscopic perforation. Many physicians believed that propofol-based sedation usually tended to deepen the sedation level and mask the earlier signs and symptoms of colonoscopic perforation. To date, we know that colonoscopy under propofol-based sedation does not increase the perforation rate[39].

Percutaneous endoscopic gastrostomy: Garcia-Suarez and colleague evaluated the efficacy and safety of propofol sedation administered by endoscopists, while performing percutaneous endoscopic gastrostomy (PEG). All PEG procedures were carried out successfully, at a median time of 8 min. All sedation-related complications were mild and quickly reversible[40]. Similar to other GIE procedures, low-dose propofol sedation is safe and may be enough for very elderly patients (≥ 90 years of age) undergoing PEG procedures[41]. Consequently, propofol-based sedation does not increase rate of complication during PEG procedure[42,43].

EUS: The safety of balanced propofol sedation in 112 patients underwent EUS with fine needle aspiration (FDA) procedures was assessed by Pagano et al[44]. The study showed that all patients completed the examination. Mean dose of midazolam and propofol was 2.1 mg (range 1-4 mg) and 350 mg (range 180-400 mg) respectively. The mean recovery time after procedure was 25 min (range 18-45 min). No major complications related to sedation were occurred during the procedures. The oxygen saturation never reduced to less than 85%. Furthermore, there does not appear to be a significant difference between complication rates for propofol deep sedation and meperidine/midazolam administered for moderate sedation[45]. Propofol combined with fentanyl and midazolam is commonly used for GIE procedures including EUS[16,18,46,47].

Nurse-administered propofol: ASA guideline on sedation by non-anesthesiologists characterizes propofol as an agent that is frequently associated with deep sedation. It does not preclude the administration of propofol by non-anesthesiologists[41]. In contrast, ASGE guideline on deep sedation restates the opinions of the ASA guideline. The ASGE guideline does not recommend the use of propofol for routine procedures[46]. To date, many studies have documented the safe administration of propofol by non-anesthesiologists. Administration by registered nurses is more cost-effective than administration by anesthesiologists. However, the administration of propofol by a registered nurse supervised only by the endoscopist is controversial because the drug has the potential to produce sudden and severe cardiorespiratory depression.
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. Five episodes of oxygen desaturation to <85%, four of which required temporary mask ventilation, occurred. Four of these episodes occurred during upper endoscopy.

Another study is also showed that nurse-administered propofol sedation (NAPS) provided by properly trained nurses is safe and only associated with a minor risk. The study of 2527 patients undergoing 2656 GIE procedures was assessed. Patients were ASA group I, II and III in 34.7%, 56.0% and 9.3%, respectively. One hundred and nineteen of 2527 patients developed short lasting hypoxia (4.7%), 22 patients (0.9%) required bag-mask ventilation and 8 patients (0.3%) had to be discontinued. In 11 patients (0.4%), anesthetic assistance was called due to short lasting desaturation. However, the national or international structured training programs are at present few or none.

Gastroenterologist-administered propofol: Similar to qualified nurses, the gastroenterologist can administer propofol effectively. The qualified nurses and gastroenterologists must have a thorough knowledge of the pharmacology of the agents used for sedation and the training necessary to recognize and manage oversedation. However, the importance of preprocedural assessment and preparation as well as appropriate monitoring cannot be overlooked. Many guidelines recommend that gastroenterologist and nurse-administered propofol should be sedated the patients only in mild or moderate (conscious) sedation level. Additionally, the patients must have ASA physical status not more than III.

Vargo et al. completed a randomized, controlled trial of gastroenterologist-administered propofol vs meperidine and midazolam for elective ERCP and EUS. Capnography was used to detect apnea or hypercapnia. This study shows that propofol leads to significantly improved recovery of baseline activity and food intake 24 h after the procedure. The authors suggest that propofol would be more cost-effective than meperidine and midazolam for ERCP and EUS procedures. Additionally, patients undergoing advanced upper endoscopic procedures and monitoring with graphic assessment of respiratory activity, received a propofol infusion under the control of a qualified gastroenterologist can detect early phases of respiratory depression, resulting in a timely decrease in the propofol infusion without significant hypoxemia, hypercapnia, hypotension, or arrhythmias, and the satisfaction scores are extremely high.

Anesthesiologist-administered propofol: Generally, propofol is administered by anesthesiologists for sedation/anesthesia in various surgical procedures including GIE procedures. To date, there are controversial issues about propofol. For example, who, when and how should administer propofol? In Western countries, propofol can be performed by well-trained registered nurses or physicians. So, anesthesiologist-administered propofol compared with nonanesthesiologist-administered propofol is less cost-effectiveness. However, in developing countries like Thailand, propofol-based sedation is performed by anesthesiologists or anesthetic nurses and is usually done in the operating room. In Siriraj GI Endoscopy Center, topical anesthesia is the most common anesthetic technique used for GIE procedure. General anesthesia for this procedure is performed about 2.7%.

Berzin et al. accomplished a prospective 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. The study confirmed that the anesthesiologist-administered sedation for ERCP patients is safe and effective. Cardiac and respiratory events are generally minor. Despite the frequency of minor sedation-related events, procedure interruption or premature termination is rare in the setting of anesthesiologist-administered sedation. However, no randomized, controlled studies comparing anesthesiologist-administered propofol with nonanesthesiologist-administered propofol for GIE procedure are done.

Fospropofol: Fospropofol is a water-soluble prodrug of propofol that currently approved for sedation and analgesia for diagnostic and therapeutic procedures. It is hydrolyzed rapidly to release propofol. Fospropofol 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 paresthesias in the perineal and perianal area. However, the mechanism of this is still unknown. Similar to propofol, fospropofol causes dose dependent hypotension, respiratory depression and apnea. Additionally, the US FDA approval information and product label state that fospropofol should be administered only by persons trained in the administration of general anesthesia.

Dexmedetomidine: Dexmedetomidine is a centrally acting alpha 2-adrenoceptor agonist with sedative and analgesic effects. It also has been considered for sedation for GIE procedure. Because of minimal effects on ventilation, dexmedetomidine may be beneficial in patients with respiratory depression or airway obstruction. One reported advantage is that patients can be sedated but are able to be aroused to full consciousness easily. However, dexmedetomidine can cause hypotension and bradycardia. The other disadvantages of dexmedetomidine include a slow onset and longer duration of action.

To date, the efficacy of dexmedetomidine for GIE procedures remains controversial issues. In the study of Demiraran et al., dexmedetomidine performed as effectively and safely as midazolam when used as a sedative in upper gastroscopy and it was superior to midazolam with regard to retching, rate of side effects and endosco-
monitoring for at least 30 min after the last intravenous drug administration or at least 90 min after the last intramuscular drug administration. In ambulatory cases, prior to discharge from the hospital, patients’ vital signs must remain stable and must be free from active bleeding or excessive pain. Additionally, patients must be able to tolerate fluids. The presence of a driver and an escort must be verified. Consequently, the patients should be reminded not to drive for at least 24 h.

CONCLUSION

Sedation for GIE procedure can be safely and effectively performed with a multi-drug IV regimen utilizing anesthesiologist or non-anesthetic personnel with appropriate monitoring. However, comprehensive pre-sedation assessment and proper patient selection and preparation as well as availability of skilled professionals for sedation administration are key components to provision of quality patient care. Additionally, the physician must always be prepared to rescue patients who move to a deeper level of sedation, and there should be an awareness of complications.

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