

Sedation-related complications in gastrointestinal endoscopy

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Abstract

Sedation practices for gastrointestinal endoscopic (GIE) procedures vary widely in different countries depending on health system regulations and local circumstances. 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-related complications in gastrointestinal endoscopy, once occurred, can lead to significant morbidity and occasional mortality in patients. The risk factors of these complications include the type, dose and mode of administration of sedative agents, as well as the patient's age and underlying medical diseases. Complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. However, sedation-related complications during GIE procedures are commonly transient and of a mild degree. The risk for these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support, as well as post-procedure management. Additionally, physicians must be prepared to manage these complications. This article will review sedation-related complications during

moderate and deep sedation for GIE procedures and also address their appropriate management.

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Key words: Sedation; Complication; Gastrointestinal; Endoscopy

Core tip: Gastrointestinal endoscopic (GIE) procedures are relatively safe. However, these procedures have been shown to cause various effects on cardiorespiratory systems. Sedation-related complications while providing any level of sedation can occur. Fortunately, these complications during GIE procedures are commonly transient and of a mild degree. In addition, significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Standardized discharge criteria should be used to determine the patient's readiness for discharge.

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INTRODUCTION

Gastrointestinal endoscopic (GIE) procedures are relatively safe and now performed routinely because of their minimal invasiveness and diagnostic and therapeutic capabilities. These procedures have been shown to cause various effects on cardiorespiratory systems, which can increase the risks of the procedure in patients with underlying cardiorespiratory diseases^[1,2]. Additionally,

complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. Most predictors of sedation-related complications are patient-centered factors and do not vary significantly from procedure to procedure, although the procedure is complex^[3].

Providing sedation has been the most effective strategy employed, with most patients preferring the use of sedation during endoscopy. The use of sedative agents has been found to improve the performance of the endoscopy, enhancing the successful completion of the procedure. The incidence of sedation-related complications associated with a GIE procedure is relatively low. Risk factors for these complications are age > 60 years, high American Society of Anesthesiologists (ASA) physical status, inpatient status and the involvement of a trainee in the procedure^[4,5]. Sedation-related complications during GIE procedures are usually transient and of a mild degree. The risk of these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-sedation assessment and preparation, appropriate monitoring and support, as well as post-sedation management.

PRE-SEDATION ASSESSMENT

All patients scheduled to receive sedation should have an up-to-date history and relevant physical examination. Many risk factors to be aware of are a history of sleep apnea, alcohol or substance abuse, adverse reaction to sedative drugs, and prolonged duration of procedure. Patients should be classified using the criteria of the ASA^[6]. Cardiorespiratory problems which could occur during the GIE procedure should be carefully evaluated.

Before undertaking any GIE procedure, endoscopists should obtain informed consent from the patient, be familiar with the latest guidelines on sedation, be aware of any medical, surgical and drug history elicited in the pre-admission process, and risk factors should be identified in both out-patients and in-patients^[7,8]. Additionally, physicians must be prepared to manage sedation-related complications. Respiratory depression and oxygen desaturation from the sedative agents used to achieve sedation are thought to be important risk factors for these complications. So, safety and monitoring should be part of a quality assurance program for endoscopy units. This article will review sedation-related complications during GIE procedures and also address their appropriate management.

POST-SEDATION PERIOD

Most sedation-related complications occur during the GIE procedure. Standard monitoring, including non-invasive blood pressure, heart rate, pulse oximetry and ECG, is also routinely used in the post-sedation period. Post-procedural nausea/vomiting and pain need to be

resolved, especially in ambulatory patients. Fortunately, a lower incidence of procedural nausea/vomiting and pain after the GIE procedure is observed even in a therapeutic endoscopy^[9]. Opioid and cyclo-oxygenase-2-inhibitors can be safely and effectively used for procedural pain in GIE patients^[10].

Sedated patients are discharged from the recovery area when the discharge criteria are met. My previous study showed that periodic objective evaluation of home-readiness revealed that the majority of patients would achieve a satisfactory score on or before 1 h after the GIE procedure^[11]. So, patients that have undergone GIE procedures should be admitted to the recovery room unit for at least 30-60 min before discharge. The time to home-readiness by objective evaluation correlates with the type of procedure. Most delays after satisfactory home-readiness scores were reached were due to non-medical reasons.

Sedation-related cardiorespiratory complications also occur immediately after the GIE procedure. The types of complications in the post-sedation period are similar to the intra-sedation period. Patients who receive benzodiazepine and/or opioid antagonists should be closely observed in the recovery room unit longer than the other patients. If the patient received a reversal agent, the patient must be in a recovery room for at least 2 h after the last administration of that reversal agent.

REVERSAL DRUGS

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^[12]. Naloxone may be administered intravenously, intramuscularly, subcutaneously and *via* an endotracheal tube. The dosage of intravenous naloxone is 1 mcg/kg to 2 mcg/kg every 2-3 min with a maximum dose of 0.1 mg/kg, up to 2 mg. Because of its rapid removal from the brain, naloxone has a short duration of action and one dose typically only lasts for 30-45 min. The patient should be monitored for at least 2 h after administration of naloxone to ensure that re-sedation does not occur. Potential adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema and cardiac dysrhythmias.

Flumazenil

Flumazenil is a benzodiazepine antagonist that can safely reverse the sedative and respiratory effects caused by benzodiazepines^[1]. It is a highly specific benzodiazepine receptor antagonist. The usual adult dose is 0.01 mg/kg, up to 1 mg. Its clinical duration of action is approximately 1 h^[12]. However, its effects are reversible, so it is not recommended for routine use. Similar to naloxone, patients should be monitored for at least 2 h after administration of flumazenil to ensure that re-sedation does not occur. Potential adverse reactions of flumazenil include sweating, flushing, nausea/vomiting, hiccups, agitation,

abnormal vision, paresthesia and seizures.

CARDIOVASCULAR-RELATED COMPLICATIONS

The autonomic nervous system plays an important role in maintaining normal hemodynamics and an adequate coronary blood flow. The sympathetic nervous system regulates the heart rate and rhythm and increases the excitability of the myocardium. The parasympathetic nervous system regulates the heart rate and rhythm, which when stimulated can lead to sinus bradycardia^[13]. Cardiorespiratory complications account for about 50% of potentially serious morbidity and about 50% of all procedure-related deaths associated with the GIE procedure. In many cases, these complications are a direct or indirect consequence of elderly or at risk patients being given unnecessarily high doses of sedative and analgesic drugs^[1].

Hypotension

A significant decline in blood pressure from baseline should alert clinicians. Hypotension is defined as systolic blood pressure less than 90 mmHg which is due to a fall in either cardiac output or total peripheral resistance, lowering the patient's mean arterial pressure^[14]. Episodes of hypotension in clinical practice are most commonly associated with vasovagal events and are generally transient. However, they may become prolonged in the presence of central nervous system depressants^[1]. Blood pressure is a reflection of cardiac output and total peripheral resistance and a fall in either or both will lower the patient's mean arterial pressure. In general, a systolic blood pressure of 90 mmHg should sustain mean arterial blood pressure sufficiently to perfuse tissues in the recumbent patient. Blood pressure lower than this, combined with evidence of inadequate perfusion, requires intervention.

The evaluation of tissue perfusion is the most significant component of cardiovascular assessment. Hypotension encountered during sedation is usually attributed to either vasovagal episodes or the use of sedative and anesthetic agents that depress sympathetic outflow to the cardiovascular system. Benzodiazepines, such as midazolam and diazepam, have a mild vasodilator effect and usually produce a slight fall in arterial blood pressure, even in normal sedative doses. The combination use of a benzodiazepine and an opioid can profoundly drop blood pressure. Propofol has been shown to be safe and effective for sedation during endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography and small bowel enteroscopy because these procedures require more time and patient co-operation^[15-19].

Cardiovascular effects of propofol include decreases in cardiac output, systemic vascular resistance and arterial pressure. A fall in heart rate and/or cardiac stroke volume will also lower blood pressure. Additionally, more profound falls in blood pressure occur in a hypovolemic patient. Propofol has also been proven to reduce post-procedural hypoxemic events, which may be of signifi-

cance in critically ill elderly patients^[20,21] and sick pediatric patients^[22,23]. Prevention of this complication is to take a relevant medical and drug history before the procedure with particular detail required regarding current antihypertensives, antianginal and antiarrhythmic therapy and the use of systemic corticosteroids. The use of volume supplementation might be beneficial and could therefore be recommended in order to avoid propofol-induced hypotension. Additionally, blood pressure and heart rate should be recorded before, during and after the endoscopic procedure.

Hypertension

Blood pressure continuously fluctuates due to the cyclic nature of the pumping action of the heart. The highest pressure occurs during ventricular contraction. The lowest pressure occurs during ventricular relaxation^[24]. Generally, hypertension is defined as the systolic blood pressure greater than 160 mmHg. Sudden elevations of systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg are generally regarded as an acute hypertensive episode^[25]. The causes of hypertension are background systemic hypertension, anxiety or pain, and a reflex pressure response from intubation of the esophagus. Generally, asymptomatic patients and patients without acute end-organ symptoms should not receive antihypertensive agents in the endoscopy unit.

Cardiac arrhythmias

Autonomic control of the heart rate will respond to demands placed on the patient and may be initiated *via* several baroreceptor-mediated reflexes^[20]. Electrocardiogram (ECG) is also a useful monitor for heart rate and a better assessment of heart rhythm. Continuous ECG monitoring is recommended for a high risk patient with relevant cardiac history. Cardiac arrhythmias are frequently observed during GIE procedures. Fortunately, most of them are not clinically significant.

In healthy patients, a heart rate of up to 120 beats/min will usually allow adequate filling. Sinus tachycardia can be caused by a patient's anxiety or be related to pain, a compensatory mechanism in patients who are hypotensive as a result of either dehydration or blood loss, and following intravenous anticholinergic drugs such as buscopan. Heart rate < 50 beats/min in healthy patients may allow for more time in diastole, but ventricular filling becomes maximized^[24]. Sinus bradycardia is most frequently seen in patients who are taking beta blockers. It can also be induced by vagal stimulation, which occurs at the time of intubation of the esophagus or the stretching of the sigmoid mesentery during colonoscopy or flexible sigmoidoscopy.

Myocardial ischemia/infarction

Myocardial infarction occurs either during or in the few days after endoscopic procedures with or without sedation. A proportion of these are undoubtedly causally related to the endoscopic procedure. The causes of angina

or myocardial infarction are two factors: increased myocardial oxygen demand and reduced myocardial perfusion^[26].

Increased myocardial oxygen demand is due to an increase in the mean arterial blood pressure and heart rate. This can cause angina in patients with ischemic heart disease or occult symptomless myocardial ischemia. Additionally, marked hypertension and/or tachycardia increase myocardial oxygen consumption. On the other hand, hypotension and/or bradycardia reduce myocardial perfusion. Stress-induced myocardial ischemia can occur even in patients with or without clinically significant coronary disease^[27]. This myocardial ischemia is related to the activation of the sympathetic nervous system, resulting in hemodynamic changes causing an increase in cardiac demand.

Prevention or minimization of myocardial ischemia/infarction during GIE procedure: (1) pre-oxygenation in at risk patients and give continuous supplemental oxygen; (2) give patients their normal anti-hypertensive and/or antianginal therapy right up to the time of the endoscopy; (3) angina developing during an endoscopy is usually best managed by giving sublingual nitroglycerine, oxygen supplementation and discontinuing the examination; and (4) if angina or myocardial infarction is suspected during or following an endoscopy, arrange an ECG to exclude an myocardial infarction.

RESPIRATORY-RELATED COMPLICATIONS

Airway management is the most important aspects of patient care and examination of the patient's airway is an essential component of the preoperative assessment. Mallampati score correlates with increased difficulty in airway management. High oxygen concentration is indicated for patients who are spontaneously breathing, regardless of their level of consciousness during medical urgencies and emergencies. The equipment required to provide supplemental oxygen includes a 100% oxygen source, a regulator, tubing and either a nasal cannula or mask. Every office should be equipped with a portable E-cylinder of oxygen.

Respiratory depression

A higher dose of benzodiazepine and/or opioid and the greater the percentage benzodiazepine and/or opioid receptor occupancy in the central nervous system, the greater is the degree of depression of consciousness. Intravenous benzodiazepines such as midazolam and diazepam can cause respiratory depression. Intravenous opioids, such as meperidine and fentanyl, occupy opioid receptor sites within the brain and brainstem and can similarly cause respiratory depression^[26]. Drug induced hypoventilation may cause both hypoxemia and carbon dioxide retention.

Pulse oximetry is a very useful indicator of oxygenation but not ventilation. However, when supplemental

oxygen is used, the fall in SpO₂ may be significantly delayed for between 30-90 s, so continuous capnography monitoring is recommended in patients being deeply sedated with propofol^[1]. As for over-sedation, loss of verbal contact due to a reduced conscious level may be the first sign of impending respiratory depression. Reduction in SpO₂ on pulse oximetry is a good indicator but it can be a late sign of respiratory depression. Increased PaCO₂ is the most sensitive early warning of respiratory depression^[28]. However, several controlled randomized studies showed a beneficial effect of capnography regarding some surrogate parameters of patients, such as the occurrence of hypoxemia detected by pulse oximetry, but a clear effect on patient outcome has not been demonstrated. Therefore, most national guidelines do not recommend its routine use currently.

Management of over-sedation is to stimulate the patient, both verbally and/or by light shaking, to wake up and take deep breaths. If the patient is not responding, then a benzodiazepine antagonist such as flumazenil and/or opioid antagonist such as naloxone may be required. The airway may need to be protected with chin lift, jaw thrust and, if necessary, airway or laryngeal mask^[26].

Airway obstruction

Obstruction may result in hypoventilation and hypoxia. However, airway obstruction must be distinguished from respiratory depression. Hypoxia is common in patients undergoing an upper GIE procedure with or without sedation. Sedation significantly increases the incidence of desaturation and hypoxia. Supplementary nasal oxygen at 3 L/min in sedated patients abolishes desaturation and hypoxia. Upper airway obstruction may be attributed to anatomical structures or a foreign body^[29]. Independent predictors of airway modifications include male sex, ASA class of III or higher, and increased body mass index^[1].

Laryngospasm is a reflex closure or spasm of the glottic muscles, including the false and true vocal cords. It is more likely to occur during deep sedation. Laryngospasm occurs more frequently in adults who are smokers. Bronchospasm is a lower airway obstruction due to contraction or spasm of the bronchial smooth muscle. It may be a result of an anaphylactoid reaction or a consequence of a hyper-reactive airway in asthmatic patients^[30]. Management of laryngospasm and bronchospasm depends on the severity and the cause.

Hypoxia

Hypoxia may be a consequence of respiratory depression or airway obstruction. The incidence of hypoxia is 1.5% to 70%, which makes it the most common cardiorespiratory complication during endoscopy^[31]. Hypoxemia can lead to several complications, depending on the severity of hypoxemic attack. The use of supplemental oxygen during a GIE procedure is routinely used by many endoscopists. However, oxygen supplementation will delay the detection of apnea and hypoxia^[5]. Additionally, in patients given supplemental oxygen, saturation may be maintained

in the progression of hypercapnia.

Multivariable logistic regressions revealed that independent risk factors for hypoxemia include high body mass index, hypertension, diabetes, gastrointestinal diseases, heart diseases and procedures that combined esophagogastroduodenoscopy (EGD) and colonoscopy^[32]. Hypoxemia occurs typically within 5 min of medication administration or endoscope intubation and only one third of all apnea and abnormal ventilation events eventually lead to hypoxemia^[31].

Pulmonary aspiration

Aspiration of gastric contents into the lungs during a GIE procedure is relatively common. It may cause pneumonia and may result in death. Risk factors for aspiration are the elderly, over-sedated patients, patients with gastrointestinal bleeding, gastric stasis, gastric outlet obstruction, hepatic encephalopathy and a full stomach. Aspiration can also occur when a local anesthetic spray is used in combination with intravenous sedation^[26].

Aspiration may be suspected when a patient starts coughing violently either during or soon after an endoscopic procedure and cyanosis may occur. The higher incidence of pulmonary aspiration is because of the better sensitivity of 2-[¹⁸F] fluoro-2-deoxy-D-glucose positron tomography. However, the low incidence of clinical events needing intervention may still reflect the safety of sedation used for the GIE procedure^[33]. Treatments of pulmonary aspiration includes suction of fluids from oral cavity and throat, increasing the rate of supplemental oxygen, encouraging the patient to cough, chest film, antibiotics and physiotherapy.

ALLERGIC REACTIONS

Pre-sedation assessment includes a comprehensive evaluation of the patient's allergic history. Generally, it is important not to confuse an increased sensitivity or side effect of a drug. Although rare, severe allergic reactions can occur during anesthesia or sedation. The spectrum of allergic reactions can include a minor local reaction to more severe anaphylactic reactions. The diagnosis of anaphylactic reaction is not always easy to establish.

The potential risk of propofol administration in patients with a known allergy against soy beans and egg should be stated^[34]. In addition, propofol usually produces a burning sensation at the injection site. Some opioids such as meperidine can cause a transient red wheal which is caused by local release of histamine. However, this reaction is a transient phenomenon with no sequelae. Anaphylactic reactions can present with mild dyspnea in mild cases or lead to hypotension and shock in severe cases. When a life threatening anaphylactic reaction does occur, it simulates an acute cardiac, respiratory and metabolic crisis and requires urgent acute critical care. Treatment for anaphylactic reactions includes the discontinuation of the suspected allergen, airway management, fluid resuscitation, anti-histamine drugs, hydrocortisone and epinephrine.

OTHER COMPLICATIONS

Nausea and vomiting

Nausea and vomiting are common side effects of opioids. Additionally, the over distension of the stomach or colonic loop can produce nausea and vomiting after the endoscopic procedure. The prevention of this complication is to reassure the patient and to minimize the opioid dose. In severe cases, anti-emetic agents such as metoclopramide and ondansetron may be required^[35].

Paradoxical reactions

Paradoxical reactions are characterized by combativeness, agitation, talkativeness, disorientation and tachycardia. This reaction frequently occurs with benzodiazepines, in particular midazolam and diazepam, and is more common in children^[36]. Inadequate sedation or cerebral hypoxia may mimic paradoxical reactions. Early recognition of paradoxical reactions is imperative for proper management. The administration of a benzodiazepine antagonist such as flumazenil has been shown to be effective in managing paradoxical reactions with minimal side effects.

PREVENTION OF SEDATION-RELATED COMPLICATIONS

Generally, GIE procedures can be performed by using topical anesthesia, intravenous sedation and general anesthesia^[17,37,38]. Topical anesthesia and intravenous sedation techniques can be effectively done by non-anesthetic personnel. Most national guidelines and several studies from the literature demonstrate that non-anesthetic personnel can safely perform propofol sedation^[39-41]. However, non-anesthetic personnel should sedate patients only to mild and moderate (conscious) sedation levels^[42]. Several previous studies demonstrated the feasibility and safety of computer-assisted personalized sedation (CAPS) to facilitate propofol sedation by non-anesthetic personnel in patients who underwent EGD and colonoscopy procedures^[43-45]. The SEDASYS System is the first CAPS system designed for physicians to provide minimal to moderate sedation levels with propofol. The system continuously monitors and records patient parameters, including oxygen saturation, blood pressure, heart rate, respiratory rate, end tidal carbon dioxide and patient responsiveness.

The risk of GIE procedures can be associated with sedation. The depth of sedation level is one of the risk factors of sedation-related complications. High sedation depth can significantly create sedation-related complications greater than a low sedation depth. Patients with mild hypotension, with co-morbidities and the elderly should be carefully sedated. The titration technique should be used to sedate these patients. Additionally, physicians should continuously monitor the depth of sedation^[46,47].

Prevention of complications in the first place is the best form of management. It is also the professional responsibility of health providers to prevent the avoidable

risks by following national standards for safe sedation. Patients under sedation must have physiological monitoring, including heart rate, blood pressure, oxygen saturation and an expired concentration of carbon dioxide. An anesthesiologist consultation should be done in patients with moderate to severe hypotension (systolic blood pressure < 90 mmHg), patients with severe cardiac and/or respiratory abnormalities, patients with a history of failed sedation, alcoholic or drug addicted patients, phobic or uncooperative patients, such as children, dementia and psychiatric patients, patients being sedated with intravenous propofol, and patients with a high risk of aspiration and requiring endotracheal tube with general anesthesia, including patients with depressed levels of consciousness and patients associated with encephalopathy^[48,49].

CONCLUSION

Sedation-related complications are relatively common. However, the majority of these complications are transient and easily treated. Serious complications are rare for GIE procedural sedation. Sedation-related complications may be severe if physicians do not detect and treat patients earlier. Appropriate pre-sedation assessment and proper patient selection, preparation and optimization of patients, as well as the availability of skilled professionals for sedation administration are key components to provision of quality patient care. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Pulse oximetry and oxygen supplementation are recommended for the reduction of hypoxemia. Capnography monitoring is considered in patients undergoing prolonged endoscopic procedures who are at risk of deep sedation. Additionally, standardized discharge criteria should be used to determine the patient's readiness for discharge. Lastly, physicians should remember that the risk for an unintended deeper level of sedation may be more common after the stimulation of the endoscopic procedure has been removed.

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