EDITORIAL

GI Endoscopy Sedation in Patients with Cirrhosis: Routine or Unpredictable?

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Sedating patients with cirrhosis undergoing gastrointestinal (GI) endoscopy procedures poses unique challenges. While the derangement of synthetic and metabolic functions of the liver affects the pharmacokinetics of the sedative medications, the degree of encephalopathy can influence the pharmacodynamic properties of these drugs. Moreover, since the severity of ascites can compromise respiration, drainage is occasionally needed before the procedure. An increased frequency of abnormal gastroesophageal reflux in patients with cirrhosis is a possible effect of esophageal dysmotility. Impairment of gastric emptying and accommodation results in early satiety [1]. As a result of gastroparesis, patients with cirrhosis experience symptoms such as postprandial abdominal pain, nausea, and vomiting [2]. Cardiac afterload is reduced due to a fall in the peripheral vascular resistance.

Some of the common drugs employed in GI endoscopy sedation are midazolam, fentanyl, and propofol. Dexmedetomidine, ketamine, and etomidate are used infrequently. The majority of these sedatives compromise the circulatory system and decrease myocardial contractility. Etomidate and ketamine, exceptions to this rule, are primarily used in patients with a compromised cardiovascular system. The elimination half-life of midazolam is significantly prolonged in patients with severe cirrhosis along with reduced clearance [3], that is, unrelated to the serum levels of albumin or bilirubin. The psychomotor impairment resulting from midazolam administered for GI endoscopy might persist up to 6 h after administration. Liver transplantation normalizes plasma levels with no prolongation of the action of

midazolam [4]. With appropriate titration, intra-procedure sedation-related complications should be low.

Remimazolam, a newer benzodiazepine that has structural similarity to midazolam, displays a metabolic profile of remifentanil and undergoes organ-independent ester hydrolysis. As a consequence, cirrhotic patients are likely to display wakeup characteristics similar to that of propofol as opposed to midazolam. Consequently, remimazolam could be more useful than other drugs in its class in cirrhotics [5]. Currently, the drug is waiting for FDA approval. Similarly, fentanyl is primarily metabolized by the liver and is excreted through the kidneys, with a small amount also excreted unchanged in the kidneys. Nevertheless, single-dose administration, as frequently required in patients undergoing GI endoscopy, is safe and should not increase the risk of sedation-related complications such as hypoxemia and hypotension. Even though fentanyl pharmacokinetics are not affected in patients with liver failure, all of them can cause hepatic encephalopathy, particularly in patients with severe liver failure [6].

Propofol has many properties that are undesirable in patients with severe cirrhosis. Since sensitivity to the sedative and cardiorespiratory depressant effects of propofol are increased in these patients, it is recommended to decrease the dose. Nevertheless, in a study of 20 patients with liver cirrhosis and 20 control subjects undergoing upper GI endoscopy, Suh et al. [7] did not observe respiratory depression or clinically significant hypotension. Although psychomotor performance was more impaired in cirrhotic patients, there was no post-procedural deterioration of psychomotor function even in cirrhotic patients with minimal hepatic encephalopathy.

Ketamine is mainly metabolized in the liver to several metabolites including an active metabolite norketamine, which retains anesthetic activity at one-third the potency of ketamine [8]. It has both analgesic and sedative properties and increases salivary secretions; there is a small risk of laryngospasm with attendant hypoxemia. Furthermore,

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post-procedural hallucinations are possible. Administration of midazolam to preempt hallucinations will necessarily prolong recovery and delays discharge. Cirrhotics are prone to hypotension; since ketamine increases blood pressure and cardiac output, cirrhotics can benefit from ketamine sedation.

Since patients rarely have cirrhosis in isolation, other related comorbidities such as pulmonary hypertension, portal hypertension, encephalopathy, and those that are cirrhosis-independent such as diabetes and congestive heart failure are frequently present.

In this issue of *Digestive Diseases and Sciences*, Edelson et al. [9] report the findings of their retrospective cohort study of cirrhotic patients undergoing endoscopy with moderate sedation and with propofol sedation. This is probably largest database study involving cirrhotic patients undergoing GI endoscopy under sedation. In view of the above-mentioned advantages and limitations of the sedative medications employed in GI endoscopy, one would expect higher levels of complications, particularly hypoxia, hypotension, and bradypnea with propofol-based monitored anesthesia care (MAC) sedation. In their study, two groups of patients receiving moderate sedation and MAC were comparable except that the group receiving moderate sedation was sicker as reflected by higher American Society of Anesthesiologists (ASA) physical status scores. Complication rates were also comparable. As is well known [10, 11], the incidence of hypoxemia and related complications were higher in patients receiving MAC anesthesia. Moreover, given the above-mentioned sensitivity to the sedative and cardiorespiratory depressant effects of propofol in cirrhotics, it is not surprising that there was a higher incidence of hypoxia in patients receiving propofol. The inverse relationship between albumin levels and adverse events could be the result of protein binding of sedative medications, in this case propofol, fentanyl, and albumin. Low albumin, as an inverse inflammatory marker and component of the Child-Pugh classification, could also identify patients that have advanced cirrhosis and/or chronic inflammatory conditions, both also sedation risk factors as was shown by Edelson et al., who also identified another Child-Pugh score component, PT/INR and the Child-Pugh score itself as risk factors for an adverse sedation event [9].

The issue of hypoxia deserves more discussion. Hypoxia emerged as the most common adverse event in this study. This is not surprising in patients undergoing EGD. Of the 15 adverse events, 7 patients exhibited hypoxia (oxygen saturation < 90%). All the patients exhibiting hypoxia were undergoing upper GI endoscopic procedures: six underwent EGD and one was undergoing ERCP. Transient desaturation is common during upper endoscopy; the authors did not mention the degree and duration of desaturation as an indicator of hypoxia severity which would have been helpful even though in a retrospective study, such data are hard to obtain. Another patient undergoing an EGD suffered laryngospasm that can cause life-threatening hypoxia.

Furthermore, 5 of the 7 patients experiencing hypoxia received monitored anesthesia care. Hypoxemia is a forerunner to cardiac arrest in patients undergoing EGD and ERCP [10]. In our own institution, hypoxia was a major precursor of periprocedural cardiac arrests in patients undergoing GI endoscopy. To an extent, hypoxia is inevitable with propofol sedation, the commonest sedative hypnotic used to provide MAC. The pharmacokinetic and pharmacodynamic variability is unpredictable, and sharing of the airway between those administering MAC and endoscopists poses unique challenges. Anesthesia providers have tried a variety of devices to reduce the incidence of hypoxia events [12]. Some drug combinations such as propofol–dexmedetomidine and propofol–ketamine are known to cause less hypoxia. It is crucial to maintain spontaneous ventilation during upper endoscopies. Hypoxia is less of a concern in patients undergoing colonoscopy as the entire airway is available to the sedation provider.

In conclusion, the study of Edelson et al. facilitates understanding not only of sedation issues in patients with cirrhosis undergoing GI endoscopy, but the relation between the type of procedure and sedation, in relation to the occurrence of hypoxia.

Compliance with Ethical Standards

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