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RESEARCH HIGHLIGHTS

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Esketamine as an adjuvant to propofol sedation for gastrointestinal endoscopy

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Propofol is the most commonly used sedative agent for patients undergoing gastrointestinal endoscopy. While propofol sedation ensures patients' comfort and helps to facilitate the endoscopic procedures, adverse events associated with sedation such as respiratory and hemodynamic depression may often arise, especially in elderly patients and those with significant preprocedural comorbidities. Over the recent years, many studies have investigated the use of different sedatives alone or in combination with analgesics for patients undergoing gastrointestinal endoscopy [1–5]. In a national survey of 2758 hospitals in China, the most preferred drugs used for sedation during gastrointestinal endoscopy were propofol plus an opioid agent (such as fentanyl or sufentanil) [6]. Nevertheless, the optimal sedative regimen for the endoscopic procedures is yet to be determined, and thus more clinical studies are certainly required in this research area.

A multicenter, double-blind, randomized controlled trial conducted by Song et al. was recently published in the journal *JAMA Network Open* [7]. This study assessed the effectiveness and safety of adding low-dose esketamine as an adjuvant to propofol-based sedation in patients who underwent same-visit bidirectional endoscopy [7]. The implementation of this trial was based on a previously published study protocol [8]. Figure 1 shows the graphic summary of this study. A total of 782 patients undergoing bidirectional endoscopic procedures in a same-day visit were screened for eligibility at three tertiary hospitals in eastern China. Of them, 660 eligible patients were randomly assigned to either the esketamine group (receiving an i.v. bolus of esketamine 0.15 mg/kg) or the placebo group (receiving an equivalent volume of normal saline). Both groups of patients were intravenously administered sufentanil 0.1 μg/kg and sedated with propofol. Propofol doses were titrated to the target sedation levels: Modified Observer's Assessment of Alertness/Sedation scale score of 1 at the beginning of the esophagogastroduodenoscopy and 2 during the colonoscopy. The designated primary endpoint of this study was the composite of desaturation and hypotension events (defined as any of these two events or both) during the endoscopic procedures.

The results of this study showed that the low-dose esketamine combined with propofol for sedation significantly decreased the incidence of composite desaturation and hypotension events during these procedures. Specifically, the addition of esketamine reduced the incidence of this composite outcome by approximately 61% compared to the placebo group (i.e., 8.2% vs. 21.0%; an absolute risk reduction of 12.8%). Notably, the beneficial effects of esketamine in combination with propofol on the respiratory and hemodynamic outcomes still remained evident after adjusting for possible confounding baseline factors (such as age, sex, body mass index, and hypertension

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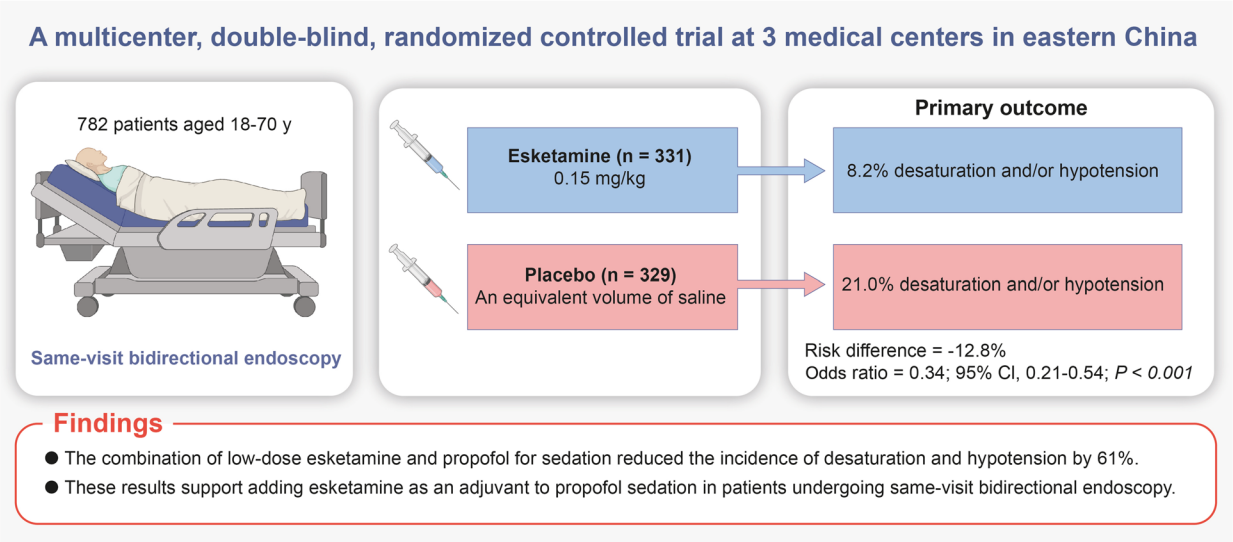

Fig. 1 Graphic summary of the study by Song et al. [7]

history) and study centers. Hence, all these data and analyses suggest the robustness of the primary study outcome. In addition to the reduction of desaturation and hypotension rates, the propofol requirements were also decreased in patients who received low-dose esketamine. The two study groups did not differ in terms of post-procedure pain, fatigue, and other adverse events (including nausea, vomiting, dizziness, headache, and hallucination), suggesting the safety profile of adding esketamine to the propofol-based sedation for these patients.

Esketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that produces potent analgesic effects. Racemic ketamine is a 1:1 mixture of two enantiomers: esketamine and its stereoisomer arketamine. Esketamine is about 4 times more affine for the NMDA receptors than arketamine, and is approximately twice as potent as an analgesic and anesthetic as ketamine [9]. Thus, esketamine leads to less drowsiness and more analgesia. In addition, it activates the sympathetic nervous system and counters respiratory and hemodynamic depression [10, 11]. Although several recent studies have investigated the use of low-dose esketamine adjunct to propofol sedation in patients undergoing endoscopy [4, 5], Song et al.'s study for the first time demonstrated that esketamine reduced the incidence of two important and common adverse events during sedation for the endoscopic procedures in a statically and clinically significant manner [7].

A subanesthetic dose of esketamine was administered to provide analgesia while reducing its possible psychotomimetic side effects. Zheng et al. showed that the use of esketamine 0.25 mg/kg led to a more stable hemodynamic status and reduced rates of hypotension, bradycardia, hypoxemia, choking, body movement and injection pain in patients undergoing painless gastroscopy [4]. Eberl et al. applied esketamine 0.15 mg/kg to reduce the total requirement of propofol for sedation during endoscopic retrograde cholangiopancreatography [5]. For elderly patients, the combination of esketamine and propofol reduced the median effective concentration of propofol during gastrointestinal endoscopy [12]. A recent study showed that a single low dose of esketamine 0.2 mg/kg infused over 40 min after childbirth reduced major depressive episodes for mothers with symptoms of prenatal depression [13].

Over the recent years, other sedatives have also been applied in gastrointestinal endoscopy. Chen et al. suggested that ciprofol was superior to propofol in terms of hemodynamics and respiratory stability, injection pain, and nausea and vomiting [14]. A recent meta-analysis showed that remimazolam, when compared to propofol, led to similar sedation efficacy and fewer episodes of respiratory depression, hypotension, and bradycardia [15]. Nonetheless, the optimal sedative regimen in gastrointestinal endoscopies is yet to be determined and further studies are still needed.

In summary, Dr. Song and colleagues presented a well-designed and well-conducted multicenter clinical trial that supports the addition of low-dose esketamine to propofol-based sedation to reduce the risk of respiratory and hemodynamic complications during same-visit bidirectional endoscopic procedures. Further studies are encouraged to test the generalizability of the benefits of esketamine in other endoscopic procedures and in different countries.

Authors' contributions
NS drafted the manuscript, KP reviewed and mainly revised the manuscript.

Availability of data and materials
Not applicable.

Declarations

Competing interests
The authors declare no competing interests.

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