

The Use of Esketamine in Clinical Anesthesia Practice

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Abstract: Esketamine, a new noncompetitive antagonist of the N-Methyl-D-Aspartate (NMDA) receptor, has been approved by Food and Drug Administration of the United States of America and recently permitted to apply in Chinese medical institutions. By binding to NMDA receptor, esketamine exerts analgesic, sedative and antidepressant effects with no suppression of respiratory and circulatory system, which is similar to ketamine. However, as the right hand enantiomer of ketamine, esketamine shows higher efficiency, which means that a lower dose can exert comparable effects of ketamine. Meanwhile, the security of esketamine is higher due to less severe adverse events observed in preliminary clinical trials. With more advantages and less disadvantages, anesthesiologists have attached much attention to esketamine. Previous studies have explored the applications of esketamine in clinical practice, such as pediatric anesthesia, painless endoscopy, intubation or non-intubation surgery. These studies focused on the dosage, effectiveness, merits and demerits under different circumstances. In this review, we retrospectively analyzed recent clinical trials, summarized the efficiency and safety of esketamine by classification of applying scenarios. Either anesthetic or subanesthetic dosage, bolus or continuous infusion made a significance in perioperative management. We also promoted some promising applications of esketamine in anesthesia. However, these novel ideas need more high-quality trials to reconfirm. Anyway, esketamine is a superior choice for anesthesiologists.

Keywords: Esketamine, Analgesic, Sedative, Antidepressant, Anesthesia

1. Introduction

Ketamine has been widely used in clinical anesthesia for its properties that provide both anaesthetic and analgesic effects. However, there are apparent side effects including hallucination, dysphoria, oneirodynia and increased secretion and so on. Esketamine is the right hand enantiomer of ketamine. Similarly, esketamine binds to the N-Methyl-D-Aspartate (NMDA) receptor to exert biologic effects [1]. But, its affinity for the NMDA receptor is larger than that of ketamine, which means the administration dosage is less [2]. Esketamine does not inhibit spontaneous breathing and can slightly excite the circulatory system, which has a unique advantage in clinical anesthesia for some specific perioperative patients [3, 4]. More importantly, studies have reported that esketamine has obvious advantages on onset time, recovery time and adverse events during anesthesia recovery [5-8]. Thus, anesthesiologists should attach importance to the use of esketamine. In this review, we

promoted the promising applications of esketamine in anesthetic practice.

2. Esketamine in Basic Anesthesia or Pediatric General Anesthesia

For children who cry before surgery or patients who are difficult to cooperate with opening venous access, esketamine can be administered by intramuscular injection to provide a rapid sedation without disturbing the patient's spontaneous breathing. Furtherly, nasal spray is a noninvasive access to reduce the preoperative separation anxiety [9]. In first aid, esketamine also performs well in analgesia. In a 12-year observation on pediatric trauma rescue, esketamine were often applied to relieve pain and anxiety and rare severe adverse effects were noted [10]. Esketamine can also provide sufficient analgesia and sedation for some particular examinations, such as endoscopy, magnetic resonance imaging and dentistry surgery, with less

security events [11-13].

Emergency agitation is a common postoperative complication in pediatric patients after general anesthesia. Previous studies suggested that nasal spray and subanesthetic dose of esketamine intravenous injection could decrease postoperative agitation of children [9, 14]. However, low dose of esketamine did not prolong the extubation time and recovery time [14].

3. Esketamine in Cesarean Section

In most situations, intraspinal anesthesia facilitates cesarean section, followed by patient-controlled intravenous analgesia (PCIA) with opioids. Recently, esketamine has been used for postoperative analgesia in obstetrics. A single usage of esketamine could alleviate exercise pain during 24 postoperative hours, but could not improve the incidence of depression after partum [15]. But, Wang et al. got positive results that intraoperative esketamine decreased the rate of post-partum [16-18]. There may be two factors to explain the difference, namely diagnostic standards of post-partum depression (PPD) and postoperative analgesics in the two studies were different. Wang et al. furtherly investigated that esketamine in PCIA reduced opioid consumption and inhibited incidence of PPD [19]. Nevertheless the efficiency and safety of esketamine in relieving pain of cesarean section have been well established, more high-quality clinical trails are needed to identify the role of esketamine in PPD, as well as the dosage and usage.

In some particular cases, cesarean section should be conducted with general anesthesia. The depth of anesthesia and the influence of anesthetic drugs on the fetus must be considered. According to the consensus of Chinese obstetrical anesthesia experts in 2020 and a published book, esketamine has strong analgesic effect and little impact on neonates, which is especially suitable for anesthesia induction of emergency cesarean section [20]. In addition, the analgesic effect of esketamine can reduce the stress responses caused by endotracheal intubation and skin cutting.

4. Esketamine in Short Non-Intubation Surgery

Non-endotracheal intubation can be performed for short operations with low requirements for muscle relaxation. Non-endotracheal intubation is beneficial to the rapid recovery of patients after surgery, but adequate sedation, analgesia, stability of patients' breathing and circulation should be ensured during the procedure. Esketamine has slight affection on respiration, which can preserve spontaneous breathing safely [3]. The stress responses caused by operative stimulations can be well suppressed owing to adequate anesthesia and analgesia effects of esketamine. All these advantages of esketamine make it a priority in short non-intubation surgery, including gastrointestinal endoscopy, abortion, endoscopic retrograde cholangiopancreatography

(ERCP), hysteroscopic surgery and fiberoptic bronchoscopy [3, 4, 8, 21-24].

5. Esketamine in Anesthesia of Asthmatic Patients

Asthma is a lung disease characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness. Asthma often leads to hypoxia and even hypercapnia, which is of great harm to anesthetic management. Perioperative management for asthmatic patients should lay importance on minimizing airway stimulation. Esketamine has the effect of dilating bronchial smooth muscle, and the use of esketamine in patients with reactive airway diseases or bronchospasm can improve lung compliance and make anesthetic procedure easier [25, 26].

6. Use of Esketamine in Patients with Hypovolemia/Hypotension

At present, anesthetic drugs commonly used in clinical practice have different degrees of inhibition on the cardiovascular system. Owing to its property of sympathomimetic action, studies have indicated that esketamine provide a more stable circulation in general anesthesia [3, 11]. Therefore, we promote esketamine a suitable choice for hypovolemic or hypotensive patients. However, relative studies are urgently needed.

7. Esketamine in Intubation General Anesthesia

Perioperative opioids use is connected with evident adverse effects, including nausea, gastrointestinal paralysis, delirium, hypoxemia, tumour progression, chronic pain and addiction. Thus, methods to reduce opioids consumption were paid much attention, such as nerve block, lidocaine infusion and other non-opioid analgesics. With strong analgesic effect, esketamine has been widely applied to intubation general anesthesia. Previous studies illustrated that anesthetic or subanesthetic dose of esketamine could induce an opioid-reduced anesthesia and improve the quality of postoperative analgesia [27-29]. Dexmedetomidine, lidocaine, and esketamine composed an effective opioid-free intraoperative medication which not only suppressed pain and stress, but reduced postoperative opioids consumption [30]. Ren et al. determined the role of esketamine on rising the mechanical pain threshold, which means that esketamine may alleviate perioperative pain by downregulating pain sensitivity [31].

8. Is There an Optimal Dosage of Esketamine

The dosage of esketamine is mainly influenced by

application situation and drug combination. For painless bronchoscopy, propofol combined with 0.2mg/kg esketamine provided effective sedation and analgesia [24]. For painless abortion, when plus 2mg/kg propofol, esketamine 0.25mg/kg was better than 0.2 or 0.3mg/kg [4]. Wang et al. recommended a bolus dose of 0.5mg/kg for painless gastroscopy [32]. As for painless gastroenteroscopy, 1 mg/kg esketamine combined with remimazolam showed the considerable rapid awakening in comparison with propofol anesthesia [3]. But, when combined with propofol, 0.2mg/kg was proposed for gastroenteroscopy [8]. Su et al. investigated the role of esketamine on percutaneous liver tumor ablation and recommended 0.1mg/kg esketamine [33]. While 0.4mg/kg and 0.2mg/kg may be more beneficial for thyroidectomy and reduction of propofol injection induced pain, respectively [23, 31]. Yuan et al. suggested 0.25mg/kg esketamine in thoracic surgery for the reduction of opioids consumption and promotion of postoperative recovery [28].

There might be an optimal dosage of esketamine in different practice, but more importantly, a subanesthetic dose should be profitable and safe when combined with other sedations and analgesics.

9. Conclusion

Esketamine is a new noncompetitive antagonist of the NMDA receptor as well as the right hand enantiomer of ketamine. With sufficient effectiveness and mild adverse events, esketamine has been increasingly used in perioperative management of diverse anesthesia situations. Anesthesiologists should attach much more importance to the use of esketamine.

Disclosure Statement

All the authors do not have any possible conflicts of interest.

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