



Mini Review

Use of a combination of ketamine and dexmedetomidine (Ketodex) in different clinical cases

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Abstract

Ketodex is a combination of ketamine and dexmedetomidine. Ketamine, an old intravenous anesthetic, is a non-narcotic and non-barbiturate drug. It has several properties of the ideal anesthetic agent. However, ketamine can produce the psychological adverse effects. Dexmedetomidine has analgesic, amnesic, sedative and anxiolytic properties. A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency. It converges on a natural sleep pathway, activating pathways that promote endogenous non-rapid eye movement sleep to exert its sedative effect. However, dexmedetomidine can produce bradycardia and hypotension. A combination of ketamine and dexmedetomidine has several benefits in the terms of hemodynamic stability, absence of respiratory depression, post-operative analgesia and recovery. Several previous studies have been demonstrated the therapeutic utility of the combination of ketamine and dexmedetomidine.

Introduction

Sedoanalgesic drugs are commonly used for sedation and analgesia in several medical procedures. Generally, physicians utilized these agents by the titration technique. Midazolam and fentanyl are the most common sedoanalgesic drugs. Midazolam has the shortest half-life and duration of action, making it an ideal agent when prolonged sedation is not compulsory. Midazolam could be reversed with flumazenil. Fentanyl is a potent synthetic opioid with rapid onset, short duration of action, and lack of direct myocardial depressant effects. Ketamine is a neuroleptic anesthetic agent. It produces analgesia, a dissociative anesthetic state, and unpleasant psychomimetic effects. Dexmedetomidine is a specific central alpha 2-adrenergic agonist that decreases central presynaptic catecholamine release. Its properties of sedation, anxiolysis and analgesia make it a valuable adjunct for procedural and intensive care sedation.

Dexmedetomidine does not appear to be the ideal agent for painful procedures. When used together with ketamine, dexmedetomidine may limit the tachycardia, hypertension,

salivation, and emergence phenomena from ketamine, whereas ketamine may prevent the bradycardia and hypotension from dexmedetomidine. A combination of ketamine and dexmedetomidine has low incidence of adverse effects, good analgesic, predictable recovery and no cardiorespiratory depression [1]. To date, there is substantial interest in ketodex as an agent for procedural sedation and analgesia. This present review focuses on the clinical uses of a combination of ketamine and dexmedetomidine.

Ketodex

Ketamine is a dissociative anesthetic agent and is stable at room temperature. It works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors [2]. Ketamine stimulates the cardiorespiratory systems. It causes an increase in cerebral blood flow, intracranial pressure and cerebral metabolic rate. It should be avoided in the patients with ischemic heart disease, hypertension and raised intraocular pressures. However, ketamine produces unpleasant psychological effects including hallucinations, nightmares and emergence reactions. Ketamine could use by several administration routes.



Dexmedetomidine is a specific central alpha 2-adrenergic agonist primarily in the locus coeruleus. Its favorable properties are sedation, anxiolysis and analgesia as well as no respiratory depression. Furthermore, it provides a more wakeful sedation than other sedatives. Patients are more arousable and alert when stimulated. The most common adverse effects associated with its use for procedural sedation are hypotension and bradycardia. However, dexmedetomidine as the sole agent has not been similarly successful for some invasive procedures [3]. Dexmedetomidine is generally used by intravenous injection. However, it could be used by intramuscular injection or by oral premedication. Dexmedetomidine seemed to show complete bioavailability after intramuscular injection. It seemed to be well absorbed systemically through oral mucosa, the buccal bioavailability being as high as 82% [4]. A combination of ketamine and dexmedetomidine is used. Currently, there is a rising number of reports regarding to this combination (ketodex).

Clinical uses

Tobias presented a descriptive study of the several reports about the use of a combination of ketamine and dexmedetomidine for procedural sedation [5]. His study showed that ketamine could prevent the decrease of blood pressure and heart rate which had been observed with dexmedetomidine. In addition, dexmedetomidine could prevent the increase of blood pressure and heart rate, salivation and psychological emergence reactions from ketamine. Moreover, ketamine initiated the onset of sedation when evaluated with the use of dexmedetomidine alone. The most effective ketodex regimen was the use of a bolus dose of ketamine 1-2 mg/kg and a bolus dose of dexmedetomidine 1 mcg/kg. This regimen might be followed by an infusion of dexmedetomidine 1-2 mcg/kg/h and a supplemental bolus dose of ketamine 0.5-1 mg/kg as needed [5].

Gunduz and coworkers compared the sedoanalgesic effects of the combination of ketamine and dexmedetomidine with the combination of ketamine and midazolam for dressing changes in burn patients. They concluded that both the combination of ketamine and dexmedetomidine and the combination of ketamine and midazolam for burn patients underwent dressing changes were safe and effective. No serious adverse effects were observed. However, ketodex presented in higher sedation and hemodynamic stability [6]. In addition, the combination of ketamine and dexmedetomidine would help to increase pain relief without over sedation in pediatric patients [7].

One previous study evaluated a combination of ketamine with two different doses of dexmedetomidine for sedation during muscle biopsy in patients with Duchenne muscular dystrophy. This previous study confirmed that a combination of dexmedetomidine and ketamine is safe and effective for moderately painful procedures with limited cardiorespiratory effects [8]. Additionally, the successful use of a combination of ketamine and dexmedetomidine (ketodex) for sedation in a 21-year-old patient with Duchenne muscular dystrophy undergoing bone marrow aspiration and biopsy was also presented by Rozmiarek and colleagues [9]. Another case

report of the use of ketodex for sedation in a 9-year-old, 45 kg child with Duchenne muscular dystrophy and a history of egg allergy underwent esophagogastroduodenoscopy (EGD) procedure [10]. The utility of ketodex was also demonstrated in management of the elderly patient who experienced airway obstruction during an EGD procedure under anesthesia secondary to previously undiagnosed tracheomalacia [11].

Generally, ketamine induced hemodynamic response and psychological effects including intraoperative hypertension, tachycardia and unpleasant dreams. Premedication with dexmedetomidine should be reduced these responses. Gupta and coworkers compared the clinical efficacy and safety of dexmedetomidine with midazolam for premedication in 80 normotensive adult patients with ASA class I and II. They suggested that dexmedetomidine premedication was safe and effectively reduced the ketamine-induced hemodynamic response and post-operative psychological effects [12]. Furthermore, ketodex offered better analgesia and cardiorespiratory parameters as well as shorter recovery time [13]. Consequently, Sinha and colleagues compared the effectiveness of the combination of ketamine and dexmedetomidine (ketodex) versus dexmedetomidine alone in awaked fiberoptic intubation. The authors concluded that the use of ketodex offered better intubating conditions, sedation and hemodynamic parameters than the use of dexmedetomidine alone in awaked fiberoptic nasotracheal intubation [14].

Ketodex for electroconvulsive therapy (ECT) was reported by Shams and El-Masry [15]. A combination of ketodex and propofol in ECT procedure had an effective antidepressant, less agitation and more patient satisfaction when compared to a combination of ketamine and propofol. Another case report of the use of ketodex for sedation in an elderly patient underwent a painful procedure was published [16]. This case report confirmed ketodex possessed sedative and analgesic properties as well as permitted preservation of airway reflexes and respiratory drive. In addition, it had been reported to lessen the incidence of cognitive dysfunction after the procedure in elderly patients [16] and also could be used to produce additional analgesia in complex regional pain syndrome [17].

Ketodex for various procedures in pediatric patients had been reported. McVey and Tobias utilized a bolus dose of ketamine 2 mg/kg and dexmedetomidine 1 mcg/kg given over 3 min followed by a continuous infusion of dexmedetomidine 2 mcg/kg/h for the first 30 min and followed by 1 mcg/kg/h afterward. Supplemental medication was given by ketamine 0.5 mg/kg as needed. They described that the use of ketodex presented effective procedural sedation in pediatric patients with relatively lower cardiorespiratory adverse effects [18]. The use of ketodex for upper gastrointestinal endoscopies [19] and endoscopic retrograde cholangiopancreatography procedure [20] in pediatric patients was reported.

The use of ketodex for non-cardiac surgery in pediatric patients with cyanotic heart diseases [21,22] and pulmonary embolism with history of pulmonary arterial hypertension with history of PAH and pulmonary embolism were also reported [23]. For cardiac catheterization procedure, ketodex



was tried to utilize in this procedure [24]. Another case report of ketodex infusion used for a 15-year-old girl who underwent scoliosis repair surgery with intraoperative wake-up test was presented [25]. Moreover, Goyal and Islam also reported a young girl patient with xeroderma pigmentosum previously anesthetized with delayed recovery, accomplished successfully with intravenous ketodex for a surgical procedure [26].

Furthermore, ketodex could be used by intramuscular injection or by oral premedication. For example, the study of intramuscular ketamine, dexmedetomidine and a combination of both (ketodex) for MRI [27] and the study of Ravipati for burn procedures [28], were also evaluated. The study of Singh demonstrated that oral dexmedetomidine provided more effective sedation and fewer adverse effects than oral ketamine [29]. However, a previous study indicated that ketodex was not superior to a combination of sevoflurane and sufentanil in pediatric patients with obstructive sleep apnea [30].

Conclusion

Ketodex is a combination of ketamine and dexmedetomidine. It is a sedoanalgesic agent for procedural sedation and analgesia. A combination of ketamine and dexmedetomidine has several benefits in terms of hemodynamic stability, absence of respiratory depression, post-operative analgesia and recovery. The most effective regimen seems to be the use of a bolus dose of a 1 mcg/kg of dexmedetomidine and a 1-2 mg/kg of ketamine. This could be followed by 1-2 mcg/kg/hr of dexmedetomidine infusion with supplemental bolus doses of 0.5-1 mg/kg of ketamine as needed. The clinical uses of ketodex have been established in the various studies. Future studies with direct comparisons to the other regimens need to be performed.

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