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EDITORIAL

Dexmedetomidine as an adjuvant during general anesthesia

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Introduction

Newly introduced anesthetic agents are sometimes clinically used in cases of unapproved indication when the drug's mechanisms of action are considered to be reasonable.

Dexmedetomidine, a highly selective α-2-adrenoceptor agonist, has sedative and analgesic effects without respiratory depression. In Japan, dexmedetomidine was approved in 2004 as a sedative in patients during and after mechanical ventilation in the intensive care setting. The frequency of dexmedetomidine use was low immediately after its introduction into clinical practice,[1] which may partly be because its use was limited to up to 24 h; however, this time limitation was removed in 2010. Then, in 2013, a new indication was approved for the sedation of non-intubated patients undergoing surgery or other procedures under local anesthesia. Furthermore, because of the low risk of respiratory depression, dexmedetomidine is used for sedation when performing semi-awake intubation in patients, who are expected to have difficulties with intubation and whose spontaneous breathing should be maintained to avoid a cannot intubate, cannot ventilate situation.

Thus, the indications of dexmedetomidine by drug manufacturers are focused only on sedation, in spite of the concomitant analgesic effect via α-2-adrenoceptor on the dorsal horn of the spine, which is widely observed in the clinical setting. In addition, the existence of synergistic effects between α-2-adrenoceptor agonists (e.g., dexmedetomidine and clonidine) and anesthetics with different mechanisms of action have been shown in animal and human studies [2]. Taking advantage of the characteristics of this drug, the usefulness of dexmedetomidine as an adjuvant to conventional general anesthesia using propofol or inhaled anesthetics and opioids has been investigated [3, 4]. With the anesthetic-sparing property of dexmedetomidine, a reduction in individual doses of anesthetics is also expected to reduce side effects.

In the recent issues of the *Journal of Anesthesia*, a variety of applications of dexmedetomidine that may possibly be clinical workable alternatives have been reported.

Pretreatment with dexmedetomidine before general anesthesia

Yoo et al. [5] prospectively investigated the effect of dexmedetomidine pretreatment on propofol requirement for the laryngeal mask airway (LMA) insertion in a randomized controlled trial. They found that 1 μg/kg of dexmedetomidine administration 10 min before anesthesia induction could reduce the propofol requirement by 38% without prolonged respiratory depression or hemodynamic instability. The median effective dose of propofol for smooth insertion of LMA was lower in the study group than that in the control group who received normal saline (mean of 1.9 vs 3.1 mg/kg). Yang et al. [6] commented that the timing of pretreatment (i.e., 10 min before propofol infusion) probably should have been an additional 5 min earlier to allow for the onset of dexmedetomidine.

Intraoperative dexmedetomidine for intra and postoperative pain management

In terms of postoperative surgical pain, the efficacy of intraoperative dexmedetomidine administration has been shown in meta-analyses [7, 8]. However, from the viewpoint of perioperative patient satisfaction, the treatment target should

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not be limited to surgical site pain, but also any local uncomfortable sensations.

Many studies which aimed to reduce propofol injection pain have been performed [9], and the preventive effects of dexmedetomidine were reported in some studies [10, 11]. Li et al. [12] performed a randomized controlled study to examine the attenuation effect of dexmedetomidine pretreatment for propofol injection pain in 137 patients who underwent electroconvulsive therapy. The pain scores that they observed were lower in the pretreatment groups (0.2 or 0.5 μg/kg dexmedetomidine administration in 10 min) than in the control group who received normal saline. They reported that pretreatment using dexmedetomidine was able to reduce propofol injection pain without interfering with the seizure duration which is considered to be associated with patient response to electroconvulsive therapy.

Unpleasant sensations associated with bladder catheter placement can be reduced using various medications, including muscarinic antagonists, anesthetics, antiepileptics, paracetamol, or local anesthetics [13, 14]. Kwon et al. [15] evaluated the effect of intraoperative dexmedetomidine (1 μg/kg followed by 0.3–0.5 μg/kg/h until the end of surgery) on the degree of catheter-related bladder discomfort after non-urologic surgery in 70 patients. The incidence and severity of catheter-related bladder discomfort were lower in the study group than in the control group who received normal saline, even 1, 2, and 6 h postoperatively.

Dexmedetomidine administration is sometimes started before the end of surgery for postoperative sedation. Especially, in patients who require temporary trachea intubation after surgery but do not need postoperative mechanical ventilation, optimal sedation is required by which spontaneous respiration and tidal volume are maintained. Ishibashi et al. [16] proposed the usefulness of dexmedetomidine in such cases. They retrospectively evaluated the hemodynamic and respiratory effects of dexmedetomidine in 129 intubated and spontaneously breathing patients who underwent endoscopic submucosal dissection. Dexmedetomidine infusion was started 89.1 ± 66.9 min before entering the ICU without loading dose. Ninety-six per cent of the patients were successfully sedated solely with dexmedetomidine over 16.4 ± 3.3 h. No relevant respiratory depression that required ventilator support occurred. The estimated mean plasma dexmedetomidine concentrations ranged from 0.32 to 1.0 ng/ml.

Pharmacokinetics of dexmedetomidine

To plan a dosing regimen, it is important to consider patient characteristics (e.g., age, body weight, etc) and clinical settings, because they affect pharmacokinetics of sedatives. For the simulation of plasma dexmedetomidine concentrations, an appropriate pharmacokinetic model should be used. Many pharmacokinetic models of dexmedetomidine varying in study setting, patient background, and/or covariates have been reported. Those models were externally evaluated in patients under spinal anesthesia, and the model developed by Hannivoort model [17] was found to be the most effective (i.e., least error in the prediction of drug concentrations) during continuous infusion of dexmedetomidine [18]. A further improved model presented in [19] by Hannivoort et al. also performs well (median performance error = 4.6%, median absolute performance error = 17.6%, wobble as intraindividual variability in performance errors = 6.9%, externally evaluated by the author using the same method used in the ref no. [18]; not published). Cardiac output that affects hepatic blood flow can also be an important covariate [20, 21]. Because dexmedetomidine is primarily metabolized by the liver with a high hepatic extraction ratio (approximately 0.7), a decrease of cardiac output may increase the plasma concentration of dexmedetomidine due to the reduced hepatic blood flow. Besides, because of the multiple metabolic pathways, pharmacokinetics of dexmedetomidine is hardly affected by the metabolic activity of a specific hepatic enzyme.

Recently, because of a worldwide epidemic of obesity, overweight patients frequently undergo anesthesia for surgery. Therefore, information on the pharmacokinetics and pharmacodynamics of anesthetics in obese patients is clinically important. Xu et al. showed that morbidly obese patients (body mass index ≥ 40 kg/m^2) presented much higher peak plasma concentrations and deeper sedation than normal weight patients after the administration of dexmedetomidine 1 μg/kg for 10 min [22]. Their findings potentially support the use of the Cortinez pharmacokinetic model in obese patients [23] which was a recently-established pharmacokinetic simulation model for a more appropriate dosing strategy.

These new findings can be useful for the use of dexmedetomidine in daily practice. As the use of dexmedetomidine as an adjuvant for general anesthesia is off-label, approval by the institutional review board and/or obtaining informed consent from patients may be required depending on the circumstances. In the future, the approval of additional indications can be beneficial in utilizing the characteristics of dexmedetomidine to improve the quality of anesthesia practice.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest regarding the publication of this article.

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