



## Dexmedetomidine: present and future directions

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Dexmedetomidine is a potent, highly selective  $\alpha$ -2 adrenoceptor agonist, with sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing properties. Dexmedetomidine induces a unique sedative response, which shows an easy transition from sleep to wakefulness, thus allowing a patient to be cooperative and communicative when stimulated. Dexmedetomidine may produce less delirium than other sedatives or even prevent delirium. The analgesic effect of dexmedetomidine is not strong; however, it can be administered as a useful analgesic adjuvant. As an anesthetic adjuvant, dexmedetomidine decreases the need for opioids, inhalational anesthetics, and intravenous anesthetics. The sympatholytic effect of dexmedetomidine may provide stable hemodynamics during the perioperative period. Dexmedetomidine-induced cooperative sedation with minimal respiratory depression provides safe and acceptable conditions during neurosurgical procedures in awake patients and awake fiberoptic intubation. Despite the lack of pediatric labelling, dexmedetomidine has been widely studied for pediatric use in various applications. Most adverse events associated with dexmedetomidine occur during or shortly after a loading infusion. There are some case reports of dexmedetomidine-related cardiac arrest following severe bradycardia. Some extended applications of dexmedetomidine discussed in this review are promising, but still limited, and further research is required. The pharmacological properties and possible adverse effects of dexmedetomidine should be well understood by the anesthesiologist prior to use. Moreover, it is necessary to select patients carefully and to determine the appropriate dosage of dexmedetomidine to ensure patient safety.

**Keywords:** Adrenergic alpha-agonists; Analgesics; Conscious sedation; Delirium; Dexmedetomidine; Sympatholytics.

### Introduction

Dexmedetomidine, a potent and highly selective  $\alpha$ -2 adrenoceptor agonist, has been described as a unique sedative with analgesic, sympatholytic, and respiratory-preserving properties [1]. It has been approved by the U.S. Food and Drug Administration for short-term sedation (< 24 h) of initially intubated and mechanically ventilated adult patients in the intensive care unit

(ICU) and for sedation of non-intubated patients during surgical and other procedures. Although dexmedetomidine is now widely used for the above indications in the ICU and the operating room [2], its clinical applications have been greatly expanded in recent decades due to many favorable physiological effects [3].

This review aims to summarize the current knowledge of dexmedetomidine and discuss its applications, including off-label use, in various clinical settings.

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## Effects of Dexmedetomidine

### Sedative effects

Dexmedetomidine induces a unique sedative response, known as “arousable sedation” or “cooperative sedation”, which shows an easy transition from sleep to wakefulness, thus allowing a patient to be cooperative and communicative when stimulated [4]. This sedative property of dexmedetomidine is similar to natural sleep. Dexmedetomidine is known to suppress noradrenergic neuronal firing of the locus ceruleus in the brain stem [5], which leads to a loss of wakefulness via activation of an endogenous sleep-promoting pathway [6]. Although patient cooperation can be achieved using other sedatives, with careful dose titration, dexmedetomidine may promote cooperative sedation more easily within the recommended dosage range. Hall et al. [7] demonstrated that healthy volunteers sedated with dexmedetomidine (0.2 or 0.6 µg/kg/h after a bolus dose of 1 µg/kg) could be easily aroused when asked to perform various tests, but then returned to a sedative state when left alone.

Dexmedetomidine shows dose-dependent sedative effects. If a large enough dose is administered, dexmedetomidine produces deep sedation or even general anesthesia, which suggests that dexmedetomidine has the potential to become part of a total intravenous anesthesia strategy. However, the cardiovascular effects of dexmedetomidine may limit this application, especially in less healthy patients [8]. Despite dose-related sedation, memory and cognitive functions are not severely impaired with dexmedetomidine administration [7,8].

Dexmedetomidine may provide adequate sedation in critically ill patients. In early clinical trials, dexmedetomidine showed a similar level of sedation to propofol, and the mean times to extubation were also comparable [9–11]. When compared with the propofol group, mean heart rates were mostly lower, but not less than 60 beats/min, and opioid requirements were significantly lower in the dexmedetomidine group [9–11]. Furthermore, a recent study demonstrated that dexmedetomidine decreases the duration of mechanical ventilation [12].

### Analgesic effects

The analgesic properties of dexmedetomidine are mediated by several mechanisms, including spinal, supraspinal, and peripheral actions [13,14]. However, the analgesic efficacy of dexmedetomidine is controversial. A ceiling effect has been shown in an ischemic pain model in healthy volunteers at doses > 0.5 µg/kg [15]. However, in a cold pressor test, a dose-dependent analgesic effect was noted over a wide range of plasma concentrations from 0.5–8.0 ng/ml [8].

The opioid-sparing effect of dexmedetomidine has been well

documented in several clinical trials [16]. Even as a sole analgesic, a 0.4 µg/kg dose of dexmedetomidine can be effectively used for pain relief after laparoscopic tubal ligation, although accompanying drowsiness and bradycardia may be undesirable side effects during the recovery period [17]. A recent meta-analysis of 21 randomized trials demonstrated that intraoperative dexmedetomidine administration for general anesthesia was superior to remifentanyl administration, with lower pain scores during the first 24 postoperative hours and with less hypotension, shivering, and postoperative nausea and vomiting [18].

Dexmedetomidine has anti-nociceptive effects on both somatic and visceral pain when administered via the neuraxial route [19]. A recent meta-analysis including 16 randomized controlled trials showed that neuraxial dexmedetomidine administration significantly decreases postoperative pain intensity and prolongs analgesic duration but with an increased risk of bradycardia [20].

The potential application of dexmedetomidine for the treatment and prevention of neuropathic pain has also been investigated. Local injection of dexmedetomidine was shown to produce an antiallodynic effect in spinal nerve ligation-induced neuropathic pain in a rat model [21]. Moreover, the use of pre-emptive intravenous dexmedetomidine reduces post-thoracotomy pain syndrome after coronary artery bypass surgery [22].

### Cardiovascular effects

The loading dose of dexmedetomidine results in a transient increase in blood pressure and a reflex drop in heart rate, especially in young, healthy patients. This initial cardiovascular response is most likely due to vasoconstriction induced by the stimulation of peripheral α-2B receptors in vascular smooth muscle; however, subsequent hypotension occurs when the vasodilatory effects of the central α-2A receptors predominate. The dose-dependent bradycardia seen with dexmedetomidine treatment is mediated primarily by a decrease in sympathetic tone and partly by baroreceptor reflex and enhanced vagal activity [23,24].

### Respiratory effects

Unlike other sedatives or anesthetics, dexmedetomidine induces minimal respiratory depression, even when higher doses are used [7,8]. In contrast to the infusion of opioids, benzodiazepines, or propofol, dexmedetomidine can be safely infused through tracheal extubation [25]. This favorable property of dexmedetomidine may provide great protection against adverse respiratory events in specific situations, such as awake craniotomy and awake intubation.

Dexmedetomidine minimizes the discomfort of patients with

spontaneous respiration during awake fiberoptic intubation [26]. Although the risk of bradycardia and hypotension should be considered, those events can be easily managed with atropine and vasoactive agents. Dry mouth is one of the side effects of dexmedetomidine [24], and this antisialagogue effect is helpful for creating a dry field during awake fiberoptic intubation.

## Renal effects

The effects of dexmedetomidine on renal function are complex and include a diuretic effect by inhibiting the antidiuretic action of vasopressin (AVP) at the collecting duct [27,28], enhanced osmolal clearance through non-AVP-dependent pathways, and the preservation of cortical blood flow by decreasing renal cortical release of norepinephrine [29]. There is also evidence that dexmedetomidine attenuates murine ischemia-reperfusion injury. A recent study reported that perioperative infusion of dexmedetomidine decreases the incidence and severity of acute kidney injury following valvular heart surgery [30].

## Clinical Uses of Dexmedetomidine

### Anesthetic adjuvant

Dexmedetomidine can markedly reduce the anesthetic requirements of inhaled [31,32] and intravenous anesthetics [33,34]. It can also decrease the dose of opioids required, perioperatively and postoperatively, in patients undergoing a variety of surgical procedures [35–39]. This opioid-sparing effect of dexmedetomidine decreases opioid use and thereby reduces the risk of opioid-induced respiratory depression in bariatric patients or those with significant respiratory disease [40,41].

### Cardiovascular surgery

The sympatholytic activity of dexmedetomidine reduces myocardial oxygen consumption by decreasing metabolism and preventing tachycardia [42], which leads to a decrease in the development of postoperative cardiac complications, including myocardial ischemia [43]. A meta-analysis of data from 23 studies (15 for clonidine, 6 for dexmedetomidine, and 2 for mivazerol) consisting of 3,395 patients demonstrated that  $\alpha$ -2 adrenergic agonists significantly reduce mortality and myocardial ischemia during cardiac, vascular, and nonvascular surgery [44]. In a subgroup analysis,  $\alpha$ -2 adrenergic agonists were found to reduce the incidence of myocardial infarction during vascular surgery. However, it should be kept in mind that vasoconstriction and hypotension, resulting from dexmedetomidine use, are potentially pro-ischemic [23,45].

In a randomized controlled study of 32 patients with pulmo-

nary hypertension undergoing mitral valve replacement surgery [46], preoperative dexmedetomidine administration decreased mean arterial pressure (MAP), pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), and the dose of fentanyl required to treat intraoperative hypertension, in comparison with a placebo. It also attenuated the increase in pulmonary and systemic vascular resistance (PVR and SVR, respectively) at the post-sternotomy period, relative to baseline levels. In this study, a 1  $\mu$ g/kg bolus dose of dexmedetomidine was administered 10 min before the induction of anesthesia, followed by a 0.4  $\mu$ g/kg/h infusion terminated just before surgical incision. In another study of healthy volunteers [8], however, high concentrations of dexmedetomidine (at > 1.9 ng/ml) progressively increased MAP, PCWP, PVR, and SVR, whereas these effects were not seen at low concentrations. It is thought that the activation of peripheral  $\alpha$ -2B receptors, which leads to vasoconstriction, contributed to these effects at higher concentrations.

Jalonen et al. [35] reported that intraoperative dexmedetomidine administration decreased plasma norepinephrine levels by 90%, blunted the blood pressure response to intubation and surgery, and decreased the incidence of intraoperative and postoperative tachycardia. However, it induced hypotension more frequently during cardiopulmonary bypass.

### Neurosurgery

Dexmedetomidine, with or without the addition of remifentanyl, has emerged as the most useful agent in providing safe and acceptable conditions during neurosurgical procedures in awake patients [4]. In particular, in awake craniotomy, which requires sophisticated neurological assessment, several studies have demonstrated that dexmedetomidine has many advantages [4,47,48]. Cooperative sedation by dexmedetomidine may permit neurological assessment, while avoiding tachycardia and hypertension. Furthermore, dexmedetomidine has potential neuroprotective effects, including decreasing intracranial pressure and dose-dependently reducing cerebral blood flow and cerebral metabolic rate [49–54]. A possible explanation for these neuroprotective effects is the modulation of neurotransmitter release in the central and peripheral sympathetic nervous systems.

A recent randomized controlled trial showed that the quality of intraoperative brain mapping and the efficacy of sedation with dexmedetomidine were similar to those of propofol-remifentanyl during awake craniotomy [55]. Moreover, adverse respiratory events were fewer in the dexmedetomidine group. The successful use of dexmedetomidine for awake craniotomy in children has also been reported [56].

## Pediatrics

Tobias and Berkenbosch [57] studied the sedative effects of dexmedetomidine versus midazolam in mechanically ventilated pediatric ICU patients. They found that dexmedetomidine, at a dose of 0.25 µg/kg/h, provided a level of sedation equivalent to midazolam at 0.22 mg/kg/h. At 0.5 µg/kg/h, dexmedetomidine provided superior sedation to midazolam, as evidenced by significantly less morphine use and fewer patients with inadequate sedation. When compared with the midazolam group, heart rates were lower in the dexmedetomidine group ( $122 \pm 31$  beats/min vs.  $142 \pm 36$  beats/min in the midazolam group); however, blood pressure did not differ between the two groups.

Dexmedetomidine has also been studied for its potential use in diagnostic radiological procedures in infants and children. When compared with midazolam or propofol, dexmedetomidine was more likely to achieve an adequate lack of movement [58] and a faster onset and recovery [59] in patients aged 1–7 years undergoing MRI. The successful use of dexmedetomidine for invasive procedures, such as central venous catheterization and bronchoscopy [60,61], has also been reported.

Emergence agitation often occurs in children recovering from general anesthesia. A placebo-controlled randomized study in children aged 1–10 years demonstrated that the perioperative infusion of 0.2 µg/kg/h dexmedetomidine decreased the incidence of emergence delirium (26% in the dexmedetomidine group vs. 60.8% in the placebo group;  $P = 0.036$ ) after sevoflurane-based general anesthesia, without prolonging the time to extubate or discharge [62].

## Delirium

Sedatives, such as benzodiazepine or propofol, may potentiate the risk of developing delirium in the ICU [63–66]. Several randomized controlled trials have demonstrated that dexmedetomidine-treated patients experience significantly less delirium in the ICU, compared to patients treated with lorazepam [67,68], midazolam [69], or propofol [70,71]. However, in those studies, dexmedetomidine was compared with modulators of GABA receptors, which are well known to increase the incidence of delirium [72]. Therefore, it is unclear whether dexmedetomidine does not induce delirium, unlike other sedatives, or whether it even prevents delirium. Recently, a study by Su et al. [73] demonstrated that prophylactic low-dose dexmedetomidine (0.1 µg/kg/h) effectively prevents the occurrence of delirium during the first 7 days in the ICU after non-cardiac surgery (9% in the dexmedetomidine group vs. 23% in the placebo group; odds ratio 0.35, 95% CI 0.22–0.54;  $P < 0.0001$ ). In this randomized, double-blind, placebo-controlled trial, dexmedetomidine was administered for less than 24 h (from ICU admission on the day

of surgery until 8 AM on postoperative day 1), and the incidence of bradycardia or hypotension did not significantly increase, but the incidence of hypertension, tachycardia, and hypoxemia significantly decreased. These promising results raise the possibility that dexmedetomidine could be used as a preventive pharmacological strategy for delirium.

A recent retrospective study also showed that intraoperative dexmedetomidine-induced sedation reduces postoperative agitation in elderly patients who underwent orthopedic surgery, when compared to propofol-induced sedation [74].

## Safety

Most of the adverse events associated with dexmedetomidine occur during or shortly after a loading infusion. A loading infusion often results in hypertension, hypotension, or bradycardia, which are closely related to the loading dose and infusion rate [75,76]. The incidence of these adverse events can be prevented by slow bolus loading or by omitting bolus loading [77,78]. In fact, many clinicians tend to avoid the administration of a loading dose, especially in critically ill patients [79]. A slow titration to maintain the infusion rate of dexmedetomidine can also be helpful in preventing adverse events. Gerlach et al. [80] demonstrated that the incidence of hypotension was significantly reduced by increasing the time interval between dosage adjustments in the surgical ICU.

Although the incidence of severe bradycardia is low, there are some case reports of dexmedetomidine-related cardiac arrest. Cardiac conduction disorders, including left anterior fascicular block [81] and first-degree AV block [82], and the co-administration of amiodarone and dexmedetomidine [83,84] are potential factors contributing to the development of asystole, especially during general or regional anesthesia. In addition, caution should be taken when administering dexmedetomidine to patients with volume depletion or vasoconstriction. Adequate selection of patients and dosage is most important for the safe use of dexmedetomidine.

Recently, numerous studies have focused on assessing the influence of anesthetic management on cancer recurrence or metastasis. Lavon et al. [85] reported the impact of clinically relevant doses of dexmedetomidine on the metastatic burden in rodent models of stress and surgery, which are similar to perioperative settings. They found that tumor cell retention and the growth of secondary tumors increased with moderate and high doses of dexmedetomidine. They also reported that these effects were mediated through  $\alpha$ -2 adrenergic receptors, although the specific mechanism of action was not elucidated. These negative findings from animal experiments do not necessarily predict similar results in human trials and, thus, further mechanistic, translational, and clinical studies are warranted.

## Conclusions

Dexmedetomidine is a useful and attractive drug, with great potential in many clinical situations. However, certain extended applications of dexmedetomidine require further evaluation. To ensure the safe use of dexmedetomidine, it is necessary to carefully select patients and to determine the appropriate dosage.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

## Author Contributions

Seongheon Lee (Writing—original draft; Writing—review & editing)

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