Int J Clin Exp Med 2017;10(2):2016-2025
www.ijcem.com /ISSN:1940-5901/IJCEM0040352

*Review Article*

# Dexmedetomidine: therapeutic efficacy in adult patients of the intensive care unit

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Received September 21, 2016; Accepted September 29, 2016; Epub February 15, 2017; Published February 28, 2017

**Abstract:** Optimal management of sedation, pain, agitation, and delirium in intensive care unit (ICU) involves systematic and multimodal approaches to provide comfort and safety. As one of the most widely used alpha 2-adrenergic receptor agonists, dexmedetomidine has become more and more popular for sedation and agitation in critically ill adult patients. The sedative, analgesic and opioid-sparing effects highlight its use in ICUs. The role of dexmedetomidine for the management of sedation, pain, delirium and agitation in adult patients in ICU is reviewed and updated in this present article. Most recent studies demonstrated that the administration of dexmedetomidine was superior to other commonly used sedative agents in ICUs. With increasing evidences of its organ protection effects, cognitive preservation and inflammatory inhibition, dexmedetomidine has been recommended and accepted to be used in ICU patients. Adverse effects associated with dexmedetomidine mainly comprise bradycardia and hypotension, which still need careful consideration before administration. With multiple beneficial effects on ICU patients and potential better cost-effectiveness, dexmedetomidine is believed to be a unique and admirable option.

**Keywords:** Dexmedetomidine, adult, ICU

## Introduction

Appropriate management of pain, agitation, and delirium (PAD) is a cornerstone in intensive care unit (ICU) especially for the mechanically ventilated patients [1]. Failure to properly settle pain and agitation issues leads to prolonged mechanical ventilation (MV), depraved mental outcomes, increased incidence of delirium, length of ICU stay and self-extubation [2, 3]. Appropriate use of sedative and analgesic agents is a vital part of providing comfort and safety for the patients in ICU. Benzodiazepines and propofol are traditionally used as the standard agents of ICU for sedation. With the newer effective agents for sedation emerging, different regimens should be compared to optimize patients' treatment.

Dexmedetomidine is a potent and highly selective α2-adrenoceptor agonist with an extensive range of pharmacological properties [4]. Besides the various benefits during perioperative period [5-7], the sedative, analgesic and opioid-sparing effects highlight its use in the ICU setting. There are many evidences about its effect of organ protection [8-10], and cognitive preservation in critically ill patients [11, 12], with minimal respiratory depression in ICU patients [13, 14].

The mechanism of dexmedetomidine is different from those of traditionally used drugs in this setting, such as benzodiazepines, propofol (γ-aminobutyric acid (GABA) receptor agonists) and opioids (opioid receptor agonist). Dexmedetomidine is not previously recommended for long-term sedation. The randomized, double-blind, multi-center MIDEX [15] and PRODEX trials [15] indicated that longer-term sedation with dexmedetomidine was non-inferior to midazolam and propofol, which means both short-

**Table 1.** Summary of meta-analysis studies revealing the property of dexmedetomidine used in ICU patients

| Study outcomes | Comparison No. of patients | | Characteristics of patients | performance of Dex | WMD/ RR | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| Jen A. Tan 2010 [21] | Dex | Con | ICU | | | | |
| ICU stay (days) | 694 | 570 | | B | -0.48 | -0.18 to -0.78 | 0.002 |
| Duration of MV (hours) | 1013 | 888 | | NS | -0.51 | -1.75 to 0.73 | 0.42 |
| Bradycardia (n/N) | 44/651 | 26/513 | | NS | 1.82 | 0.66 to 5.03 | 0.25 |
| Hypotension (n/N) | 128/843 | 70/702 | | NS | 1.43 | 0.78 to 2.60 | 0.25 |
| Delirium (n/N) | 216/923 | 209/831 | | NS | 0.79 | 0.56 to 1.11 | 0.18 |
| Mortality (n/N) | 89/972 | 75/867 | | NS | 0.85 | 0.64 to 1.13 | 0.26 |
| Laura Pasin 2013 [22] | Dex | Con | Receive MV in ICU | | | | |
| ICU stay | 1274 | 1150 | | B | -0.79 | -1.17 to -0.40 | <0.001 |
| Time to extubation (hours) | 1804 | 1674 | | B | -2.74 | -3.08 to -1.65 | <0.001 |
| Bradycardia (n/N) | 220/1374 | 64/1246 | | W | 2.43 | 1.88 to 3.14 | <0.001 |
| Hypotension (n/N) | 424/1389 | 279/1266 | | W | 1.27 | 1.00 to 1.61 | <0.001 |
| Mortality (n/N) | 200/1499 | 173/1409 | | NS | 1.00 | 0.84 to 1.21 | 0.9 |
| Zhi-Qiu Xia 2013 [23] | Dex | Pro | ICU | | | | |
| ICU stay (days) | 330 | 325 | | B | -0.81 | -1.48 to -0.15 | 0.017 |
| Duration of MV (hours) | 444 | 451 | | NS | 0.53 | -2.66 to 3.72 | 0.744 |
| Bradycardia (n/N) | 37/394 | 27/394 | | NS | 1.36 | 0.85 to 2.18 | 0.203 |
| Hypotension (n/N) | 119/502 | 115/513 | | NS | 1.12 | 0.86 to 1.47 | 0.402 |
| Delirium (n/N) | 17/329 | 41/329 | | B | 0.40 | 0.22 to 0.74 | 0.003 |
| Hypertension (n/N) | 84/419 | 56/427 | | W | 1.56 | 1.11 to 2.20 | 0.010 |
| Mortality (n/N) | 7/133 | 9/134 | | NS | 0.83 | 0.32 to 2.12 | 0.659 |
| Laura Pasin 2014 [24] | Dex | Con | ICU | | | | |
| Delirium (n/N) | 298/1565 | 337/1464 | | B | 0.68 | 0.49 to 0.96 | 0.03 |
| Bo Li 2015 [25] | Dex | Con | Medical/surgical ICU | | | | |
| NAT (n/N) | 87/235 | 142/265 | | B | -0.17 | -0.03 to -0.04 | 0.008 |
| Ken Chen 2015 [26] | Dex | sedatives | Receive MV in ICU | | | | |
| Duration of MV | 562 | 558 | | B | -0.25 | -0.40 to -0.10 | 0.001 |
| ICU stay | 614 | 609 | | B | -0.15 | -0.28 to -0.01 | 0.036 |
| Delirium (n/N) | 226/871 | 200/753 | | NS | 0.85 | 0.63 to 1.14 | 0.27 |
| Bradycardia (n/N) | 186/850 | 66/737 | | W | 2.11 | 1.39 to 3.20 | 0.00043 |
| Hypotension (n/N) | 226/850 | 132/734 | | NS | 1.22 | 0.86 to 1.73 | 0.27 |
| Mortality (n/N) | 177/851 | 137/730 | | NS | 0.99 | 0.78 to 1.24 | 0.9 |
| Moira Cruickshank 2016 [27] | Dex | Con | Receive MV in ICU | | | | |
| ICU stay (days) | 893 | 769 | | B | -1.26 | -1.96 to -0.55 | 0.0004 |
| Time to extubation (days) | 744 | 620 | | B | -1.85 | -2.61 to -1.09 | <0.001 |
| Ventilator-free days | 73 | 67 | | NS | 3.28 | 0.06 to 6.49 | 0.05 |
| Target sedation range | 784 | 661 | | NS | 2.53 | -0.82 to 5.87 | 0.14 |
| Duration of MV (hours) | 560 | 560 | | NS | -0.30 | -1.70 to 1.11 | 0.68 |
| Bradycardia (n/N) | 189/841 | 70/726 | | W | 1.88 | 1.28 to 2.77 | 0.001 |
| Mortality (n/N) | 196/909 | 162/783 | | NS | 1.03 | 0.85 to 1.24 | 0.78 |
| Tachycardia (n/N) | 187/800 | 178/682 | | NS | 0.93 | 0.63 to 1.39 | 0.73 |
| Hypotension (n/N) | 232/789 | 137/675 | | NS | 1.28 | 0.93 to 1.75 | 0.12 |
| Self-extubation (n/N) | 12/566 | 3/564 | | NS | 2.95 | 0.96 to 9.06 | 0.06 |
| Jean-Michel Constantin 2016 [28] | Dex | Pro+BZD | ICU | | | | |
| ICU stay | / | / | | B | -0.304 | -0.477 to -0.132 | 0.001 |
| Duration of MV | / | / | | B | -0.313 | -0.523 to -0.104 | 0.003 |
| Delirium | / | / | | W | 0.812 | 0.68 to 0.968 | 0.02 |
| Bradycardia | / | / | | W | 1.947 | 1.387 to 2.733 | 0.001 |
| Hypotension | / | / | | W | 1.264 | 1.013 to 1.576 | 0.038 |
| Georgia G. Tsaousi 2016 [29] | Dex | Con | NCC | | | | |
| Bradycardia (n/N) | 19/155 | 17/287 | | NS | 3.84 | 0.18 to 83.18 | 0.39 |
| Hypotension (n/N) | 30/185 | 74/317 | | NS | 1.19 | 0.42 to 3.42 | 0.74 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mohammad Mahdi Zamani 2016 [30] | Dex | Con | sepsis | | | | |
| 28-day mortality (n/N) | 9/71 | 19/72 | | B | 0.49 | 0.24 to 0.99 | 0.05 |
| ICU stay | / | / | | NS | 1.54 | -1.73 to 4.81 | 0.36 |
| MV-free day | / | / | | NS | 1.40 | -4.44 to 7.24 | 0.64 |
| TNF-α | / | / | | B | -5.31 | -8.00 to -2.63 | 0.0001 |
| IL-1β | / | / | | B | -1.24 | -1.88 to -0.6 | 0.0001 |
| IL-6 | / | / | | B | -250.77 | -371.78 to -129.75 | <0.0001 |

Dex, dexmedetomidine; Con, control (placebo or an alternative sedative agent); Pro, propofol; Mid, midazolam; BZD, benzodiazepines; WMD, weighted mean difference; CI, confidence interval; RR, relative ratio; MV, mechanical ventilation; n/N, proportion; /, no data; NAT, neurocognitive assessment test; NCC, neurocritical care (NCC) patients; B, better; W, worse; NS, not significant.

and longer-term use of this agent are suitable in ICU patients. Moreover, compared with midazolam or propofol, patients receiving dexmedetomidine were also easier to rouse, and more cooperative to communicate. Currently, it has been approved by United States Food and Drug Administration (FDA) for sedation via iv. bolus and continuous infusion for up to 24 h on intubated adults and for adult procedural sedation in areas both outside the ICU and operating room setting. With the increasing definition of its molecular mechanisms, dexmedetomidine appears to have effects on apoptosis and the immune system which might be particularly involved in the pathogenesis of ICU patients [16, 17]. While, the most common adverse effects of dexmedetomidine, hypotension and bradycardia, still need attention, which might impact hemodynamic stability of patients especially septic shock [18, 19].

In addition, dexmedetomidine possesses a promising pharmacokinetic profile for use in ICU adults. It has a short onset of sedation, an elimination half-life of nearly two hours, negligible drug-drug interaction potential, and complete elimination within 10 hours after infusion termination [20].

Meta-analysis studies pooling the property of dexmedetomidine used in ICU patients were summarized in the present article (**Table 1**), and we further reviewed the efficacy of dexmedetomidine for sedation, analgesia, delirium and agitation of adult patients in an intensive care setting, as well as summarizing its cost-effectiveness properties to help establish the preferable role of dexmedetomidine in clinical practice.

## Pharmacology

Dexmedetomidine is a highly selective α-2 adrenoceptor agonist, which is chemically described as (+)–4-(S)-[1-(2,3-dimethylphenyl) ethyl]-1 H-imidazole monohydrochloride. It is nearly eight times more specific for α-2 adrenoceptors than clonidine [20]. The receptors are widely distributed and can be found in the central and peripheral nervous systems and several organs [31]. Dexmedetomidine provides dose-dependent sedation which mimics S2 sleep in human [32, 33]. The mechanism of action is also distinct from other sedatives targeting g-aminobutyric acid (GABA) or opioid receptors. Dexmedetomidine can provide sedation through its unique mechanism of action primarily within the locus coeruleus, which is considered the hypnotic or wakefulness modulator area in the brain [34]. Presynaptic stimulation of α-2 adrenoceptors prevents the release of norepinephrine and Postsynaptic action constrains sympathetic activity, which leads to decreased blood pressure and heart rate [35]. Directly simulation of α-2 adrenoceptors in the spinal cord causes analgesic effect. What's more, dexmedetomidine has little effects on ventilation, which highlight its clinical use.

## Sedation with dexmedetomidine in the ICU

Proper sedation plays a key role in care of critically ill patients to diminish the stress and anxiety, which are related to the tracheal intubation and other invasive interventions [36]. The typical goal of sedation in ICUs is to keep the patients calm, cooperative and easy to rouse [37]. The choice of such sedative agent is imperative, as patients in ICU are susceptible to shock and tremendously vulnerable for cardiovascular complications [38].

Increasing evidences suggest that dexmedetomidine is a promising sedative agent used in ICU considering its excellently sedative properties with wide safety margin due to little respiration interruption [39, 40]. Guidelines recommend the use of dexmedetomidine for sedation

in critically ill patients [41]. Meta-analysis showed better outcomes with dexmedetomidine involving shorter length of ICU stay [21-23, 26-28], decreased time to extubation [22, 27] and duration of MV [26, 28] (**Table 1**). A recent meta-analysis [30] still indicated that dexmedetomidine improved short-term mortality of sepsis patients compared with other sedatives without affecting the ICU length of stay. Moreover, propofol [13] and midazolam [35] required to maintain target sedation during ventilation were significantly decreased when dexmedetomidine was used. Compared with clonidine, short-term sedation with dexmedetomidine was more likely to attain target sedation [42]. While, compared with propofol, studies didn't found superior effects of dexmedetomidine for short-term sedation [43, 44]. In term of long-term sedation (>24 h), the time to extubation and duration of MV were significantly shorter in dexmedetomidine recipients than midazolam in the MIDEX trial [15], but no difference was found in the time at target sedation in the SEDCOM trial [45] or duration of study drug treatment in MIDEX [15]. The time to extubation and duration of study drug treatment were significantly shorter in patients with dexmedetomidine than with propofol, but no significant difference in the duration of MV or the length of ICU stay [15].

### Effect of analgesia and opioids sparing

Although commonly used opioids are effective for pain prevention, the major adverse effects including constipation, histamine release, respiratory depression and altered mental status remain cumbersome [46], which may prolong ICU length of stay and produce other negative effects. Dexmedetomidine has been demonstrated to have an analgesic-sparing effect through its ability to reduce opiate consumption in critically ill patients. Dexmedetomidine exerts anti-nociceptive action at both the spinal and supraspinal levels [31, 48, 49]. The major sites of analgesic action are the posterior horns of the spinal cord where the modulation of pain impulses is mediated by the noradrenergic bulbar/spinal pathway. Moreover, the mechanisms inhibiting pain transmission in the peripheral sensory nerves are still involved [31, 48]. A previous study showed 50% reduction of morphine requirements in the patients when dexmedetomidine was used [14]. Recent data also suggest a role of dexmedetomidine in intractable pain for palliative care, but further investigation into this use is warranted [47].

Although dexmedetomidine has analgesic properties and displays opioid-sparing propensities when used as a sedative agent [34]. Dexmedetomidine alone does not meet total analgesic requirements for ICU patients; rather, it just decreases the total amount of opioid required, potentially minimizing the adverse effects of those therapies. Data from recent studies remain in opposition on concomitant analgesic use [50-52].

### Prevention and management of delirium

Delirium is an acute fluctuation in mental status which is common in ICU patients. It was reported that 20% to 50% of nonventilated patients and 60% to 80% of mechanically ventilated patients develop delirium [53]. Kinds of adverse clinical outcomes related to delirium in ICU, including long-term cognitive decline, increased morbidity, mortality and hospital costs [54-56]. With various factors influencing the development of delirium, treatment for ICU delirium is a real challenge for clinicians. Current approaches to prevent delirium focus on effective treatment of pain, early mobility of patients, light sedation and exploiting nonpharmacologic interventions. Benzodiazepines are historically used for provision of sedation and treatment of agitation in the ICU; However, they have been recognized as a risk factor of delirium in ICUs [41, 57, 58].

The unique properties of dexmedetominidine including GABA receptor-sparing and opioid-sparing effects, normal sleep-mimicking effect, less respiratory depression and anticholinergic activity make it beneficial in the management of delirium in ICU. Numbers of studies including two meta-analysis (**Table 1**), have proposed that sedation with dexmedetonidine is associated with lower incidence of delirium and improved outcomes when compared to benzodiazepine or opioid-based sedation methods in mechanically ventilated patients [23, 24]. In the SEDCOM trial [45], patients receiving dexmedetomidine had significantly lower incidence of delirium and longer delirium-free days compared with midazolam [45]. Compared to lorazepam in the MENDS trial, patients receiving dexmedetomidine also had significantly more

delirium and coma-free days, and the incidence of delirium/coma or coma was significantly lower, but not delirium [50]. Compared with morphine in the DEXCOM study, the duration of delirium was significantly shorter in patients receiving dexmedetomidine, however, the incidence of delirium did not significantly differ [50]. Moreover, dexmedetomidine recipients were less likely to suffer delirium than remifentanil recipients, but the length of delirium or ICU stay didn't significantly differ between dexmedetomidine and remifentanil in ICU patients [59].

The neuroprotective and anti-inflammatory effects of dexmedetomidine might play a key role in prevention of delirium [38, 60, 61]. In addition, as part of a cascade of events in critically ill patients, extreme norepinephrine release is supposed to contribute to the development of delirium [62]. Reduction of glutamate release and lack of GABA receptor modulation or cholinergic receptor activity may explain the better outcomes in dexmedetomidine recipients [63, 64]. The critical role of GABA receptors in modulation of neurotransmitters responsible for development of delirium has been found in clinical settings [50, 61]. The action pathway of dexmedetomidine is independent of the GABA receptors, thus have intrinsic delirium-sparing effects [65]. Sleep deprivation has been reported to aggravate inflammatory responses, insulin resistance and activation of the hypothalamic-pituitary axis [66, 67]. Non-rapid eye movement sleep with a more natural sleep cycle induced by dexmedetomidine [39, 50, 68] improves sleep quality and thus benefit patients' outcomes such as delirium-free days and mortality [38, 69].

### Prevention and management of agitation

Agitation is quite common in the ICU patients and results in prolonged hospitalizations [70]. Insufficient treatment of agitation enhances patients' stress response leading to tachycardia, hypertension, and hyperglycemia, all of which aggravate mortality and morbidity of critically ill patients. Apprehension of health, type of surgery and anesthesia, postoperative pain and disorientation are all associated with the agitation and anxiety of critically ill patients [71]. Moreover, helplessness feelings, pain, confusion, and memory loss with sleep deprivation exacerbate agitation and anxiety in ICU patients [71].

Adequate sedation medications can further prevent the secondary behavioral and cognitive responses of agitation and anxiety [72]. Clinical trials have demonstrated that dexmedetomidine benefit sedation in postsurgical patients as well as those who are agitated and excessively anxious and uncooperative patients [50, 73]. It is also a viable adjunctive choice for extubation in patients suffering agitation [74, 75]. Compared with normal treatments, dexmedetomidine was also less likely to suffer from agitation in delirious patients [38, 50, 76, 77]. A recent trial also indicated that with a better efficacy, safety, and cost-benefit profile than haloperidol, dexmedetomidine benefited the management of agitation due to delirium in nonintubated patients in whom haloperidol treatment had failed [78]. However, dexmedetomidine may not be the best agent for management of acute agitation due to the potential adverse events induced by rapid dosage adjustment and bolus therapy [79].

### Other properties

Previous studies have reported the protective effects of dexmedetomidine on several organs including the heart, lung, nervous system, and kidney [8-10]. Dexmedetomidine potentially stabilize the hemodynamic profile by decreasing sympathetically mediated hyperdynamic responses, which may further contribute to myocardial protection [9]. In addition, neuroprotective effects were also found, probably through modulating neurotransmitter release in the central and peripheral sympathetic nervous system and preventing apoptosis of the neurons [80, 81]. Additionally, both absolute and relative $CO_2$ reactivity, as a measure of cerebral blood flow and autoregulation were significantly lower in septic shock patients receiving dexmedetomidine than sedation [82]. Patients receiving dexmedetomidine had lower intra-abdominal pressure (IAP) after 24 hours and IAP 48 hours than those receiving propofol. High IAP not only has undesirable effects on splanchnic, respiratory, cardiovascular, renal, and neurologic function but is also related to high mortality [83, 84].

Mucosal immunity and bacterial clearance effects by facilitating macrophage phagocyto-

sis and bactericidal killing were still found in dexmedetomidine studies. These properties are quite vital in sepsis and septic shock [45, 85]. In SEDCOM trial, critically ill patients receiving dexmedetomidine had less incidences of secondary infections [45, 86]. Dexmedetomidine can decrease levels of TNF-α, IL-1β, and IL-6 in patients with sepsis. This anti-inflammatory effect of dexmedetomidine can suppress the exaggerated production of inflammatory cytokines in septic shock [86].

However, reduction in proinflammatory cytokines appears to offset potential direct hypotensive effect of dexmedetomidine [38]. Bradycardia induced by dexmedetomidine is mainly dose-dependent and can be optimized by slow administration of the bolus loading or skipping bolus loading all together [39].

## Cost-effectiveness

Dexmedetomidine is about $45.21 per vial in 100 mcg/mL in a 2 mL glass vials. Referred to the maximum allowed daily dose, dexmedetomidine is more expensive than midazolam, lorazepam, and propofol. A cost-minimization analysis forecast that total ICU costs would be lower with dexmedetomidine than with midazolam or propofol [87], the savings potential results from shorter time to extubation. Even though numbers of studies indicated that dexmedetomidine cut the total hospital costs and the ICU costs, compared with propofol and midazolam, when the benefits were assessed in terms of length of ICU stay or total hospital stay, the results were not consistent. This revealed limited improvements in terms of quality adjusted life-years.

## Conclusion

With an acceptable tolerability profile and the potential effects of organs protection, the benefits of dexmedetomidine are clinically obvious for sedation, analgesia along with prevention of delirium and agitation in the ICU. So, dexmedetomidine might be a significantly effective and practical agent to manage ICU patients.

## Disclosure of conflict of interest

None.

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