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Dexmedetomidine: A Review of its Use for the Management of Pain, Agitation, and Delirium in the Intensive Care Unit

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Abstract: Management of pain, agitation, and delirium is a complex process requiring a multimodal approach to optimize patient outcomes. Dexmedetomidine is a centrally acting alpha-2 agonist with sedative and analgesic properties that has demonstrated efficacy in managing pain, agitation, and delirium in a variety of critically ill patient populations. Dexmedetomidine has demonstrated the ability to provide a mild to moderate level of sedation in diverse ICU populations compared to conventional sedative regimens. Recent literature has demonstrated improved outcomes with dexmedetomidine based vs. benzodiazepine based sedation therapy in select mechanically ventilated ICU patients. However, dexmedetomidine therapy has also been associated with adverse cardiovascular events including hypotension, bradycardia, and asystole. The clinical pharmacology, therapeutic efficacy, safety considerations, controversies, and future directions of dexmedetomidine therapy in the ICU setting will be discussed.

Keywords: Dexmedetomidine, intensive care unit, sedation, agitation, pain, analgesia, and delirium.

INTRODUCTION

Management of pain, agitation, and delirium in the intensive care unit (ICU) setting remains an important therapeutic modality in care of the critically ill patient. Suboptimal management of pain, agitation, and delirium in the ICU has been associated with worsened outcomes [1-3]. Pharmacotherapy such as analgesics, sedatives, and antipsychotics are the cornerstone of management; however their administration may be associated with adverse drug events, cognitive impairment, and delays in weaning from mechanical ventilation [4, 5].

The expansion of ICU sedation literature over the last 20 years has resulted in a rapid evolution in how we manage pain, agitation, and delirium in the ICU [6]. Implementation of assessment scales and goal directed therapy, protocols/guidelines, daily sedation interruption, analgosedation, and pharmacotherapy agent selection has led to significant improvement in outcomes related to patient comfort, time on mechanical ventilation, time in the ICU, delirium, iatrogenic coma, and health care expenditures [3, 7-10].

Dexmedetomidine is an alpha 2 agonist with pharmacological properties that have potential for the management of pain, agitation, and delirium in the ICU [11]. When given via intravenous infusion, dexmedetomidine provides a mild level of sedation with ease of arousability at lower doses, anxiolysis, sympathiolysis, and analgesia with minimal effects on respiratory function [11]. There is a growing body of evidence suggesting that dexmedetomidine may protect against cardiac, renal, and neurological organ dysfunction in select patient populations [12-14].

Conventional management of sedation therapy in the ICU has consisted primary of γ-aminobutyric acid (GABA) agonists such as benzodiazepines, barbiturates, and propofol [15]. Recent data suggest dexmedetomidine based sedation therapy may be associated with improved outcomes in mechanically ventilated ICU patients compared to benzodiazepine based therapy [9, 12, 16, 17]. While there is debate amongst many clinicians on whether benzodiazepines therapy should be avoided in the ICU in favor of dexmedetomidine, it's important to address the strengths and limitations of the available literature [18, 19]. The objective of this paper is to review the clinical pharmacology, therapeutic efficacy, safety considerations, and future directions of dexmedetomidine therapy in the ICU setting.

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AVAILABILITY, LABELING, AND UTILIZATION DATA

Dexmedetomidine originally gained Food and Drug Administration (FDA) approval for marketing in the United States in 1999 under the trade name Precedex™ [11]. After its United States approval, dexmedetomidine has expanded its availability globally in countries such as Australia, Japan, Brazil, and Canada [20]. Dexmedetomidine recently gained approval by the European Medicines Agency (EMA) for marketing in Europe for sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation under the trade name Dexdor™ [21]. Since its United States approval, utilization has continued to rise as new data has become available and clinicians gained more experience with the agent in the ICU setting [22, 23].

Dexmedetomidine is currently indicated in the United States for sedation of adult mechanically ventilated patients in an intensive care setting with a maximum IV infusion rate of 0.7 mcg/kg/hr for 24 hours [24]. Currently there is no approved indication in the United States for use in pediatric critically ill patients. Maximum dosing and duration of therapy varies amongst countries from 0.7 to 1.4 mcg/kg/hr depending upon respective countries package labeling [20].

CLINICAL PHARMACOLOGY OF DEXMEDETOMIDINE

Dexmedetomidine is the imidazole derivative dextroisomer of the α_2-receptor agonist medetomidine [11]. Similar in structure and pharmacological activity to clonidine, dexmedetomidine is a centrally selective α_2-receptor agonist. Dexmedetomidine and clonidine are highly selective for the α_2-receptor subunit over the α_1-receptor subunit, however dexmedetomidine demonstrates eight times more selectivity than clonidine [11]. Dexmedetomidine has potential for administration via the enteral, intramuscular, transdermal, intranasal, epidural, and intrathecal routes in anesthesia and procedural areas, however its use has been limited to intravenous infusions in the ICU setting [25-27].

Pharmacokinetics

Early studies examining the pharmacokinetics of dexmedetomidine primarily involved healthy volunteers or non-critically ill

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patients [28]. Currently there is minimal pharmacokinetic data in the pediatric patient population [29-31]. Alteration of drug pharmacokinetics parameters relating to clearance and volume of distribution of drugs is common in critically ill patients [32].

Dexmedetomdine demonstrates a linear pharmacokinetic profile [28]. It is primarily metabolized in the liver by glucuronidation with small amount hydroxylated by the cytochrome P-450 (CYP-450) enzyme system via the 2A6 pathway [28]. Minimal amounts of unchanged drug have been detected in the urine or feces [11]. Dexmedetomidine's α distribution half-life 6-8 minutes with a β elimination half life of 2-3 hours, but can be prolonged in the presence of reduced clearance mechanisms and prolonged therapy [28, 33, 34]. Due to its extensive liver metabolism, patients with severe hepatic insufficiency may require lower dosing [11]. Pharmacokinetics studies have also demonstrated reduced clearance in elderly patients and the presence of reduced cardiac output [35, 36]. Immature uridine diphosphate glucuronosyl transferase (UGT) pathways in neonates result in two thirds reduction in clearance [30]. Maturation of glucuronidation pathways results in matching of adult clearance by one year of age [30].

Currently there is no evidence of clinically relevant CYP-450 mediated drug interactions observed in humans, however drug interaction data when using higher doses and longer duration of therapy has not been tested [28]. No change in clearance amongst patients with different degrees of CYP2A6 metabolism reinforce glucuronidation as the primary route of metabolism [37]. Therapeutic hypothermia has shown to reduce many pharmacokinetic and dynamic properties of drugs, including suppression of CYP P450 activity [38, 39]. The pharmacokinetic parameters of dexmedetomidine in patients undergoing therapeutic hypothermia have not been established. Elimination of inactive dexmedetomidine metabolites occurs predominately via the kidneys (95%), however pharmacokinetic studies do not indicate a need for dose adjustment in patients with renal dysfunction [40].

Dexmedetomidine is highly protein bound (94%) with steady state plasma concentrations that range from 0.27 to 1.37 ng/ml depending upon use of a bolus, maintenance infusion rate, and duration of therapy [28]. Patients undergoing extracorporeal membrane oxygenation (ECMO) therapy can often have reduced plasma concentrations and loss of drug due to circuit polyvinyl chloride (PVC) tubing and to the membrane oxygenator adherence. Dexmedetomidine may have reduced plasma concentrations in the setting of ECMO therapy due to binding to PVC tubing [41].

The steady state volume of distribution (Vdss) of dexmedetomidine ranges is around 1.33 L/kg in adults. The volume of distribution may increase in the presence of hypoalbuminemia and in children less than 2 years of age [36, 42]. The impact on the volume of distribution in bariatrics and patients with extensive vasodilatory physiology has yet to be evaluated.

Pharmacodynamics

Dexmedetomidine exerts its sedative, analgesic, and sympatholytic effects via agonism of α_2-receptor subunits. There are three known α_2 isoreceptors; α_2A, α_2B, α_2C that are agonized by dexmedetomidine resulting in decreased norepinephrine activity both centrally and peripherally [28, 43]. The α_2A receptor is responsible for the sedative and antinociceptive actions as well as the vasodilatory effects of dexmedetomidine. The α_2B receptor is responsible for the vasoconstrictive effects and the α_2C modulates dopaminergic neurotransmission, hypothermia, and a variety of behavioral responses [28].

Dexmedetomidine contains an imidazole ring in its structure enabling it to bind to imidazoline receptors, this may explain some of the dexmedetomidine's non α_2 agonist effects. Imidazoline-1 receptors have been implicated in blood pressure regulation and have anti-arrhythmic effects, while imidazoline-2 receptors may help with generation of memory and neuroprotection [43]. Dexmedetomidine's α_2 isoreceptor effects are dose dependent in nature. At lower concentration, the dominant action of dexmedetomidine is sympatholysis, which is mediated by the α_2A receptor subtype. At higher concentrations, its effects are dominated by activity at the α_2B receptor subtype.

Dexmedetomidine exhibits dose/concentration dependent sedative and analgesic effects [44]. Dexmedetomidine's sedative effects are mediated by α_2A and mimic that of natural sleep when examined by electroencephalogram (EEG) [45-47]. The time to achieve peak effect onset of sedative action is about 15 minutes depending upon use of a bolus [48]. A recent small study examining sleep in patients on dexmedetomidine with daily sedative interruption in the ICU found the majority of sleep architecture to be non- rapid eye movement sleep (REM) sleep stage 1 and stage 2 with no slow wave sleep detected [49]. More data is needed to illicit the mechanism of dexmedetomidine's effect on sleep architecture in the ICU setting.

Basic science models have eluded towards at potential neuroprotective effect of dexmedetomidine through several mechanisms. Improvement in cerebral oxygen demand during cerebral ischemia, reduction in astrocytic glutamate release, increase in anti-apoptotic factors, and blocking of pro apopotic pathways may evoke a neuroprotective effect [50, 51].

In small and large studies dexmedetomidine induces a dose dependent effect on blood pressure, heart rate, and circulating norepinephrine levels [28]refs. The cardiovascular effects of dexmedetomidine demonstrate a biphasic presentation in which low doses produce reduced blood pressure and heart rate, while increased concentrations producing elevated blood pressure through vasconstrictive mechanisms. Increases in myocardial vascular resistance and reduction in myocardial perfusion in healthy volunteers were noted; however they did not appear to differ between plasma concentrations seen in clinical practice (0.5 ng/ml) and supertherapeutic concentrations (5 ng/ml) [52]. The effect of dexmedetomidine on myocardial perfusion in patients with coronary artery disease and heart failure has not been determined.

Dexmedetomidine has reduced shivering alone and synergistically with agents such as meperidine and buspirone suggesting an independent mechanism for α_2 agonists, potentially related to vasoconstriction and reduction in shivering thresholds [53-55]. Dexmedetomidine has demonstrated a dose dependent reduction in cerebral blood flow and metabolic rate in healthy volunteers [56, 57]. Dexmedetomidine appears to have no effect on blood glucose concentrations; however increased incidence of hyperglycemia has been noted in larger studies [9, 58]. Gastrointestinal emptying and transit times may be reduced as well [59]. Dose escalation studies examining dexmedetomidine plasma levels up to 8.0 ng/mL have demonstrated no clinically significant respiratory depression [44]. Early clinical trials examining the respiratory effects of dexmedetomidine yielded no negative effects on respiratory function [60, 61]. Similar to etomidate, dexmedetomidine is an imidazole derivative. Etomidate is known to cause inhibition of cortisol synthesis and potentially cause acute relative adrenal insufficiency in the ICU. Animal models suggested dexmedetomidine suppressed cortisol synthesis at higher concentrations, however human studies have not shown significant effect at doses tested in humans [58, 62, 63].

THERAPEUTIC APPLICATION OF DEXMEDETOMIDINE IN THE ICU SETTING

Dexmedetomidine's pharmacological mechanisms lend itself to variety of clinical scenarios in the ICU setting. Dexmedetomidine's pharmacodynamics properties and potential to reduce consumption of opioids and benzodiazepines make it an attractive agent for the management of pain, agitation, and delirium in a variety of patient populations. Early studies with dexmedetomidine in the ICU setting focused on its use as a sedative in surgical patients at lower doses

and for shorter duration of infusions [60, 61, 63-65]. Recent studies have examined its use at higher doses and for prolonged courses in a variety of medical and surgical ICU patients [9, 12, 16, 66]. Table **1** summarizes the findings of select studies examining the use of dexmedetomidine in the ICU setting.

Pain and Agitation

Dexmedetomidine has been studied in a variety of critically ill surgical patients at low doses and shorter courses of therapy. Placebo controlled studies in predominantly cardiac surgery aimed to assess the sedative and analgesic effects of dexmedetomidine [60, 65]. These studies demonstrated low dose dexmedetomidine's ability to provide adequate sedation and analgesia with opioid dose reductions up to 40% in critically ill post-surgical patients [60, 65].

Randomized controlled trials have demonstrated dexmedetomidine's ability to provide adequate analgesia and sedation compared to conventional regimens in a surgical patient population [17, 64, 67]. In a study by Herr *et al*., dexmedetomidine was compared to propofol in an open label fashion in critically ill cardiac surgical patients. Dexmedetomidine provided similar sedation capacity to propofol and was associated with lower opioid requirement; however no differences in extubation times or length of stay were seen.

Maldonado *et al*. performed a single center study in critically ill post-valvular cardiac surgery patients comparing open label dexmedetomidine, propofol, and midazolam based therapy [17]. Sedation was assessed utilizing the Ramsay Sedation Score (RSS) and was targeted to a score of 3 while intubated and 2 after extubation, however time in target and mean sedation scores were not reported. Analgesic consumption was similar in the dexmedetomidine and propofol cohorts, but higher in the midazolam cohort. No difference in extubation times and length of stay were seen amongst study cohorts.

In a multicenter study, dexmedetomidine compared to morphine (DEXCOM) by Shehabi *et al*., low dose dexmedetomidine was compared to analgosedation with continuous infusion morphine in an elderly cardiac surgical population [67]. Time at goal sedation was similar amongst both groups with a 1 hour difference in time to extubation. Consumption of as needed sedatives and analgesics was similar in the two cohorts.

Observational studies from the clinical practice setting have produced mixed results on dexmedetomidine's ability to improve outcomes. A database study of over 10,000 patients by Dasta *et al* reported reductions in length of mechanical ventilation, length of stay, healthcare costs, and mortality with the addition of dexmedetomidine to standard sedative and analgesic regimens in a cardiac surgical population [68]. Two single center observational studies in post cardiac surgical patients demonstrated no improvement in ventilation times or length of stay with low dose dexmedetomidine compared to propofol based therapy [69, 70]. Additionally, dexmedetomidine has not resulted in improved patient satisfaction compared to propofol in a critically ill cardiac surgical population [71].

Early studies examining the use of dexmedetomidine for longer durations and in medical ICU patients indicated that higher dosing would be needed as gauged by time in target sedation scores and increased need for rescue sedatives [72, 73]. There are no head to head trials examining high vs. low dose dexmedetomidine in a prospective fashion, however in a single center retrospective study by Jones *et al*., the efficacy and safety of low-dose ($\leq$ 0.7 mcg/kg/hr; n = 90) and high-dose (> 0.7 mcg/kg/hr; n = 43) dexmedetomidine was evaluated in a single center, mixed medical surgical patient population [74]. Patients in the low dose group had a significantly higher percentage of RASS scores at goal. Patients in the high dose also had more RASS scores classified as under-sedated according to their goal sedation level [74].

Four recent randomized controlled trials examined the effect of higher dosing and prolonged dexmedetomidine therapy compared to GABA agonists in a mixed medical-surgical population [9, 12, 16, 75]. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial evaluated high dose dexmedetomidine vs. lorazepam infusion in mixed medical (70%) surgical (30%) ICU populations that were expected to require more than 24 hours of mechanical ventilation [12]. Dexmedetomidine demonstrated a higher percentage of time within one Richmond Agitation Sedation Scale (RASS) point of the target nurse and physician target sedation level. Almost five times more fentanyl was consumed by the dexmedetomidine group compared to lorazepam, with the difference being more pronounced in patients with deeper sedation goals. Non-significant differences in outcomes such as ventilator free days and mortality were noted between the groups. In a subgroup analysis of patients with sepsis, dexmedetomidine was shown to decrease days with brain dysfunction (delirium and coma) duration of mechanical ventilation, and morality [76]. Favorable outcomes in the ability to meet target sedation level was seen with dexmedetomidine, however utilization of lorazepam as blinded infusion without daily sedation interruption resulted in a median dose of 3mg/hr which is not representative of typical dosing at most institutions. Avoidance of continuous infusion lorazepam, dose reductions, and use of bolus therapy has been associated with improved outcomes [77, 78].

The Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study evaluated high dose dexmedetomidine vs. midazolam infusion in mixed medical (85%) surgical (15%) ICU populations that were expected to require more than 24 hours of mechanical ventilation [9]. Agents were titrated to a lighter target sedation goal of RASS -2 to +1 with daily sedation interruption [9]. No difference was noted in the percentage of time spent at target sedation score. Use of open label midazolam was more common in the dexmedetomidine group. Dexmedetomidine had a 2 day shorter duration of mechanical ventilation compared to midazolam which correlated with a potential pharmacoeconomic savings [79]. Dexmedetomidine patients had similar median duration of infusion and mechanical ventilation compared to midazolam patients which had a 1.5 day longer duration of ventilation after infusion discontinuation, suggesting accumulation of midazolam occurred despite use of daily sedation interruption. Similar to the MENDS trial, a blinded infusion resulted in a median midazolam dose of 0.056 mg/kg/hr. In a 70 kg patient, this would result in almost 4 mg/hr which may not be representative of typical dosing at most institutions that have implemented best practice protocols [80, 81].

Ruokenen *et al*. conducted a randomized trial to compare high dose dexmedetomidine with institutional-specific standard care of either midazolam or propofol based therapy in a mixed medical-surgical cohort [75]. Both treatment arms included titration to goal RASS with daily sedation interruptions. The trial was discontinued early, however time at target sedation and length of ICU stay were similar between the cohorts. Patients with deeper sedation goals (ie. RASS of -4), had less time at target sedation with dexmedetomidine compared to propofol or midazolam (42% vs 62%, respectively; p = 0.006). The findings of this study were used as a pilot for the Dexmedetomidine vs Midazolam or Propofol for Sedation during Prolonged Mechanical Ventilation (PRODEX/MIDEX) study [16].

Similar to the study by Ruokenen *et al*., the PRODEX/MIDEX randomized trial compared high dose dexmedetomidine to either propofol (PRODEX) or midazolam (MIDEX) based therapy, however patients with a mild to moderate sedation target (RASS 0 to -3) were included in the analysis [16]. The study was powered to show non-inferiority of dexmedetomidine in achieving mild to moderate sedation compared to standard therapies with, defined as a RASS of 0 to -3. Patients received a blinded infusion or high dose dexmedetomidine with up to a 72 hour enrollment time. No differences were

Table 1. Select Trials of Dexmedetomidine in the ICU

Study	Population and Design	Treatment	Outcomes
Venn *et al*. 1999[65]	Adult cardiac surgery requiring sedation and MV for at least 6 hours n = 119 Prospective, randomized, double-blind, multicenter, placebo controlled	DEX bolus 1mcg/kg over 10 mins within 1 hour after surgery, then 0.2 – 0.7 mcg/kg/hr CIVI for 6 to 24 hours vs placebo Titration to Ramsay > 2 while intubated Rescue sedation with PROP; analgesia with MSO4	Reduced rescue PROP with DEX† Reduced opioid use with DEX† Increased bradycardia and hypotension with DEX
Venn *et al*. 2001[61]	Adult surgical patients requiring MV and sedation in an ICU for at least 8 hours n = 20 Prospective, randomized, single center	DEX bolus 2.5mcg/kg over 10 mins within 1 hour after surgery, then 0.2 – 0.5 mcg/kg/hr CIVI for 6 to 24 hour vs PROP 1mg/kg bolus and 1-3 mg/kg/hr CIVI Titration to Ramsay > 2 Analgesia with PRN alfentanil	Reduced alfentanil use with DEX†
Martin *et al*. 2003[60]	Adult surgical patients requiring MV and sedation in an ICU for at least 6 hours n = 401 Prospective, randomized, double-blind, multicenter, placebo controlled	DEX bolus 1mcg/kg over 10 mins within 1 hour after surgery, then 0.2 – 0.7 mcg/kg/hr CIVI for 6 to 24 hours vs placebo Titration to Ramsay ≥ 3 while intubated and ≥ 2 after extubation Rescue sedation with PROP and analgesia MSO4	Reduced rescue PROP with DEX† Reduced opioid use with DEX† Increased bradycardia and hypotension with DEX†
Herr *et al*.[64]	Adult CABG patients n = 295 Prospective, multicenter, randomized, open label trial	Intravenous Dexmedetomidine 1mcg/kg over 20 mins within 1 hour after sternal closure, then 0.2 – 0.7 mcg/kg/hr CIVI for for 6 to 24 hours vs PROP infusion Morphine and NSAID's were allowed for pain relief in both groups	Reduced opioid use with DEX†
MENDS[12, 76]	Adult medical and surgical requiring MV for ≥ 24 and up to 120 hours (n = 106) Prospective, randomized, double-blind, two centers	Blinded CIVI DEX 0.15 - 1.5 µg/kg/hr vs LZPM 1 mg/hr - 10 mg/hr Titration per team Rescue sedation with PROP; analgesia with FEN	Reduction in coma free days with DEX† Increased time at goal sedation with DEX† No difference time on ventilator or ICU stay (NS) Neuropsychological testing, or mortality at 28 days and 12 month survival (NS) Reduced brain dysfunction, mechanical ventilation, and mortality with DEX in sepsis subgroup
SEDCOM[9, 79]	Adult medical and surgical within 96 hours of MV and requiring MV + sedation for ≥ 3 additional days (n = 375) Prospective, randomized, double-blind, multicenter	Blinded CIVI Optional initial bolus: DEX 1mcg/kg or MIDZ 0.05 mg/kg DEX 0.2 - 1.4 µg/kg/hr vs MIDZ 0.02 - 0.1 mg/kg/hr (Titration to RASS+2 to -3 with DSI Rescue sedation with MDZ ; analgesia with FEN	Reduced daily incidence of delirium with DEX† Reduced time to extubation with DEX† Increased bradycardia with DEX† Reduced healthcare costs

(Table 1) Contd….

Study	Population and Design	Treatment	Outcomes
Maldonado *et al*.[17]	Adult cardiac valvular surgery requiring MV and sedation (n = 118) Prospective, randomized, open-label	Non blinded CIVI DEX 0.2 – 0.7 μg/kg/hr vs PROP 25 -50 μg/kg/min vs MIDZ 0.5 – 2 mg/hr Titration to Ramsay ≥ 3 while intubated and ≥ 2 after extubation	Reduced incidence of delirium with DEX vs MIDZ and PROP† Reduced overall opioid use with DEX vs MIDZ†, but not PROP
DEXCOM[67]	≥ 60 years of age undergoing on-pump cardiac surgery including: CABG, valve surgery, or both (n = 299) Prospective, randomized, double-blind, multicenter	Blinded CIVI DEX i.v. 0.1 – 0.7 μg/kg/hr vs MSO4 10-70 μg/kg/hr Titration to MAAS score of 2–4 Rescue sedation with PROP, analgesia with PRN MSO4	Reduced time to extubation with DEX† Reduced number of days in delirium with DEX† Increase in rate of hypotension and bradycardia with DEX†
PRODEX/MIDEX[16]	Adult medical and surgical within 72 hours of MV requiring light to moderate sedation (RASS 0 to -3) for ≥ 24 after randomization PRODEX: PROP n = 247, vs DEX n = 251 MIDEX: MIDZ n =251, vs DEX n = 249) Prospective, randomized, double blind, multicenter	Blinded CIVI DEX i.v. 0.2-1.4 μg/kg/hr vs MIDZ 0.03-0.2 mg/kg/hr or PROP 0.3-4.0 mg/kg/hr Titration to RASS of 0 to -3 Rescue sedation per team ; analgesia with FEN	PRODEX: Higher RASS scores with DEX† Median duration of MV (NS) ICU LOS or hospital LOS (NS) Per RN assessment: more arousable, cooperative, and better able to communicate pain† MIDEX: Higher RASS scores with DEX† Reduction in median duration of MV with DEX vs MIDAZ† Per RN assessment: more arousable, cooperative, and better able to communicate pain with DEX† Increased incidence of hypotension and bradycardia with DEX†

CABG = Coronary Artery Bypass Graft; CIVI = continuous intravenous infusion; DEX = dexmedetomidine; DSI = daily sedation interruption; FEN = fentanyl; LOS = length of stay; LZPM = lorazepam; MAAS = Motor Activity Assessment Scale; MIDZ = midazolam; MSO4 = morphine; MV = mechanical ventilation; PL = placebo; PROP= propofol; RASS = Richmond Agitation and Sedation Score
† = p value < 0.05

noted in the ratios of time at target in both studies. Duration of mechanical ventilation was significantly shorter by almost 2 days with patients being more arousable and communicative according to a nursing conducted visual analogue scale with dexmedetomidine therapy compared to midazolam. No difference was seen in the duration of ventilation with when compared to propofol. Discontinuation due to lack of efficacy was two fold higher with dexmedetomidine than midazolam or propofol.

Studies examining dexmedetomidine in the ICU setting primarily employ a cardiothoracic, general surgery, and medical ICU population; however use has expanded to other specialty ICU areas. The neuro ICU represents a mixture of neurosurgical and neurological critically ill patients that have needs need to treat pain and agitation, however some indications involve maintaining adequate cerebral hemodynamics such as cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP). Use of dexmedetomidine in the neuro ICU settings has been evaluated in small randomized and observational studies [66, 82, 83]. In the single center Acute Neurological ICU Sedation Trial (ANIST) trial, dexmedetomidine was compared low dose dexmedetomidine vs. propofol in a mixture of brain and non brain injured neuro ICU patients [66]. In this pilot study, dexmedetomidine demonstrated favorable effects on cognition compared to propofol using the Adapted Cognitive Exam (ACE). Observational studies suggest dexmedetomidine may be helpful in weaning sedatives in the neuro ICU population, however higher dosing may be needed [82, 83].

Managing pain and agitation in the burn and trauma patients becomes difficult due to the presence of surgical/trauma pain, brain injury, and withdrawal states. In randomized controlled trials, trauma patients reflect a small percentage of the cohort, thus conclusions about efficacy and safety are difficult to determine [16, 75]. Devabhakthuni *et al.* retrospectively reviewed 127 adult trauma patients who received either propofol or dexmedetomidine therapy which was broken into two cohorts based upon high or conventional dosing [84]. Hospital and ICU length of stay was significantly longer with both dexmedetomidine groups compared to propofol, and mechanical ventilation duration was significantly longer with high dose dexmedetomidine compared to low dose and propofol therapy. No difference in mortality was noted.

Similar to early studies with propofol, concerns over prolonged use has led to dexmedetomidine being utilized as a “rescue” or “weaning” agent in patients failing to wean from mechanical ventilation due to agitation [85-88]. Limits in the package labeling to a 24 hour duration in many countries has led to several observational studies from clinical practice setting that have shown reduction in

sedative requirements after addition of dexmedetomidine to existing regimens.

Over the last 10 years data on the use of dexmedetomidine has expanded in the pediatric patient population [89]. Several observational studies examining its use in the neonatal ICU, cardiothoracic surgery, general surgery, medical and burns have shown effects similar to adults in providing sedation and analgesia [90-96]. However it's important to note that dexmedetomidine continues to lack labeling for use in pediatrics.

Dexmedetomidine's labeling in the U.S limits its use to mechanically ventilated patients; however it can be continued throughout the extubation process. Dexmedetomidine is typically used in the mechanically ventilated patient population; however its sedative and anxiolytic properties may be helpful in patients in the non-intubated patient and those receiving non-invasive ventilation techniques [28, 97, 98]. It should be noted that dexmedetomidine does not suppress respiratory drive or have known reduction in dyspnea symptoms; therefore it may be applicable in select patient care situations.

Dexmedetomidine used at low doses in surgical patients and higher doses for mixed medical-surgical patients has demonstrated the ability to provide sedation and analgesia therapy in patients with lighter sedation goals. However, increased requirements for opioids, rescue sedatives, discontinuation due to drug failure, and inadequate ability to provide deep sedation limit its ability as the workhorse sedative in many patient care scenarios [12, 75]. The respiratory depressant properties of both opioids and GABA acting sedatives is a predictable and often desired effect in respiratory failure when employing permissive hypercapnea and lung protective ventilation strategies [99].

Consumption of opioids with dexmedetomidine tends to be lower in most surgical cohorts, however increased use has been described when compared to GABA agonists [12, 70]. Potential reasons for increased opioid use with dexmedetomidine includes better ability to communicate pain due to lighter sedation and inability to sedate and suppress respiratory drive in patients receiving lung protective strategies [70]. Utilization of dexmedetomidine in patients receiving permissive hypercapnea and lung protective ventilation strategies in syndromes such as acute respiratory distress syndrome (ARDS) has not been defined. In both medical and surgical studies, requirements for concomitant rescue sedatives such as benzodiazepines and propofol with dexmedetomidine is common, particularly when deeper levels of sedation are needed [9, 70, 74]. The findings of the SEDCOM and MIDEX studies suggest a benefit to ventilation times with dexmedetomidine over midazolam, however no benefit was seen in the PRODEX study against propofol. Requirements for therapeutic neuromuscular blockade is a common exclusion criteria or is not reported as subgroup in most studies examining dexmedetomidine in the ICU setting [9, 12]. The inability to achieve deep sedation in a high percentage of patients should draw caution from clinicians seeking to use dexmedetomidine in patients undergoing therapeutic neuromuscular blockade.

Delirium

Delirium is a common manifestation in up to 80% of critically ill patient populations and has been linked to increased length of stay, healthcare costs, and mortality [100-102]. Failure to treat delirium early in the ICU setting may be associated with worsened outcomes [1]. The pathophysiology of ICU delirium is still poorly understood, but preliminary data points towards a mixture of toxic metabolic, sleep pathway, and drug induced etiologies [103]. Administration of benzodiazepines, in particular lorazepam at high doses, is associated with the development of delirium in the ICU setting [104]. Dexmedetomidine's proposed benefits over conventional sedative and analgesic agents include promotion of sleep, lack of anticholinergic effects, and reduction or cessation of opioids and GABA agonists such as benzodiazepines. Due to its associated morbidity and mortality, pharmacological and non-pharmacological interventions aimed at preventing the incidence and reducing time in delirium remain a focal point of investigation in the ICU setting [105-108].

In the study by Maldonado *et al*., dexmedetomidine started perioperatively demonstrated a significant reduction in the incidence of ICU delirium compared to the propofol and midazolam cohorts [17]. Dexmedetomidine based therapy was associated with a 3% incidence of delirium compared to 50% in the midazolam and propofol groups. In the DEXCOM study there was a trend towards a reduction in the incidence of delirium with dexmedetomidine, however the duration of delirium was three days shorter on average with dexmedetomidine [67]. Sub-group analysis showed a significantly lower incidence of delirium in patients requiring intra-aortic balloon pump therapy receiving dexmedetomidine compared to morphine [67]. Prevention or "prophylaxis" of delirium in the cardiac surgical population with dexmedetomidine remains to be proven.

The higher severity of illness and organ function make the incidence and etiologies of delirium in medical populations more common than most surgical ICU settings. In the MENDS study, dexmedetomidine patients had over twice as many delirium and coma-free days when compared to the lorazepam group [12]. However when examining delirium free days alone, there was no statistical difference between the groups [12]. High dose lorazepam has been associated with 100% risk of transitioning to delirium at doses > 20 mg per day [104]. Median doses of lorazepam in the MENDS study would equal 72 mg/day.

In the SEDCOM study randomization to dexmedetomidine or midazolam therapy occurred up to 96 hours after admission to the ICU. No significant different in baseline delirium was seen in the dexmedetomidine (60.3%) and midazolam (59.3%) groups, however dexmedetomidine had a lower daily prevalence of delirium and more delirium-free days compared to midazolam. The incidence of delirium increased on day one after initiation of the blinded midazolam infusion. The impact of sedative therapy prior to enrollment and high median midazolam dose may be responsible for worsened delirium in the midazolam group after enrollment.

In the pilot study by Ruokonen *et al*., the incidence of delirium was higher in the dexmedetomidine group; however this may have been influenced by a higher number of delirium assessments in the dexmedetomidine group [75]. Delirium metrics in the PRODEX/ MIDEX study have not been reported. The impact of dexmedetomidine on the incidence of delirium in burn, trauma, neuroscience, and pediatric ICU's has not been evaluated.

Recent studies have demonstrated reductions in time spent in delirium with pharmacological approaches such as atypical antipsychotics and non-pharmacological approaches such as physical/occupational therapy [105, 106]. There are few studies examining the use of dexmedetomidine as primary therapy for the management of delirium [109]. In a pilot study of 20 patients by Reade *et al*., open label dexmedetomidine (0.2–0.7 mcg/kg/hour) was compared with haloperidol infusion (0.5–2 mg/hour) in a single-center, mixed medical-surgical ICU cohort [109]. Patients needed to be experiencing agitation and high levels of sedatives that prevented them from extubation. At baseline, delirium was present in 30 and 40% of the dexmedetomidine and haloperidol groups respectively. In the delirium diagnosed patients, there was a trend towards the dexmedetomidine group spending less time with delirium than haloperidol; however this did not reach statistical significance due to the small sample size. Dexmedetomidine was associated with reduced duration of supplemental propofol, mechanical ventilation, and length of stay compared to haloperidol infusion after its introduction.

Prevention and treatment of ICU delirium requires a multimodal approach [110]. Antipsychotics, in particular haloperidol, are

recommended by consensus guidelines for the management of ICU delirium [111, 112]. Recent studies have demonstrated typical and atypical antipsychotics potential to reduce the incidence and duration of ICU delirium [105, 107, 113]. The ongoing MIND USA trial which is evaluating haloperidol, ziprasidone, and placebo for the treatment of ICU delirium allows for dexmedetomidine as a rescue therapy for refractory agitation [114].

Addition of dexmedetomidine as a primary or adjunctive therapy has demonstrated reduction in the incidence and prevalence of delirium select ICU patient populations; however study protocols appear to have resulted in excessive dosing of benzodiazepines in the control arms that may not be reflective of clinical practice. Antipsychotics have potential efficacy for both prophylaxis and treatment of ICU delirium. Large scale randomized trials in diverse ICU populations using established best practices for pain, agitation, and delirium are needed to define the efficacy of dexmedetomidine for the prevention and treatment of ICU delirium.

SAFETY CONSIDERATIONS

Despite more central selectively for alpha 2 agonists over clonidine, dexmedetomidine still poses risk of peripheral cardiovascular side effects. The most common adverse events seen with dexmedetomidine are cardiovascular in nature and include hypotension, hypertension, and bradycardia [28, 115]. The incidence of hypotension with dexmedetomidine in the ICU setting ranges from 16 to 98% of patients depending upon the patient population, dosing, bolus utilization, and definition of the endpoint [28, 84, 116]. Risk factors for hypotension include and higher dosing, rapid infusion titration, intravascular volume depletion, and use in hemodynamically unstable patients [116].

Dosing of dexmedetomidine > 0.7 mcg/kg/hr may be associated with more hypotension in different critically ill patient populations. In a retrospective analysis of trauma patients, Devabhakthuni *et al*. found 89% of low dose and 98% of high dose dexmedetomidine patients met the studies criteria for hypotension [84]. However, Jones *et al*. found no difference in the incidence of hypotension with high vs low dose dexmedetomidine in a mixed medical-surgical cohort [74]. Both prospective and observational studies of dexmedetomidine have reported higher rates of hypotension in cardiac surgery, trauma, and medical patients compared to conventional management with GABA agonists and opioids [16, 64, 70, 84]. Hypertension is commonly seen around bolus administration with rates around 12 to 44% depending upon the patient population [9, 60, 64, 65].

The incidence of bradycardia with dexmedetomidine therapy ranges from 3 to 42% in the ICU setting depending upon the patient population, dosing, bolus utilization, and definition of the endpoint [9, 117]. Risk factors for bradycardia include and higher maintenance dosing, heart block, concomitant rate control medications, cardiovascular disease, and use during therapeutic hypothermia [9, 60, 117, 118]. Asystole events have been described with the use of dexmedetomidine, with the majority of cases occurring in the operative setting [117, 119-121]. While many of these events resolved with cessation of therapy and supportive care, some of these cases resulted in patient death [117].

The effects dexmedetomidine on cerebral blood flow raises concerns over its use in select neuro and trauma ICU subpopulations with brain injury. A small observational study by Aryan *et al*. in a neurosurgical patient population demonstrated no significant changes in ICP and CPP, however more studies examining cerebral perfusion, oxygenation, and metabolic status with dexmedetomidine are needed [82].

Treatment of serious cardiovascular side effects involves dose reduction, cessation, and supportive therapies including fluids and vasopressors as clinically indicated. Glycopyrrolate has been described and as potential antidote for bradycardia associated with dexmedetomidine, however hypertension has been reported with its administration in pediatrics [24, 122]. With limited information on how to manage cardiovascular adverse events associated with dexmedetomidine, avoidance through patient selection and administration techniques becomes important to promote its safe use in the ICU setting. Early studies examining dexmedetomidine in the ICU utilized a bolus, lower maintenance infusion rates, and shorter duration of infusion. These studies found the majority of adverse cardiovascular events to be in the window of the bolus administration [60, 64, 65]. Ickergil *et al*, examined efficacy and safety of dexmedetomidine with and without a bolus using low maintenance dosing in a mixed surgical ICU cohort [123]. They found a no difference in ability to provide effective sedation, with reduction in cardiovascular events with cessation of bolus therapy. Recent studies in the ICU have abandoned the bolus due to the high incidence of side effects surrounding its administration [12, 16].

Rebound hypertension, tachycardia, agitation, and neurological sequelae have been described with the prolonged use of dexmedetomidine [124-127]. The majority of events have been described in the pediatric cardiac surgical population. Slow weaning of dexmedetomidine may be warranted in select patient populations with close monitoring for signs of withdrawal hypertension, tachycardia, and agitation [127].

Gerlach and colleagues examined the impact of an institutional dexmedetomidine protocol that removed bolus functionality and titrations of infusions no faster than 30 minutes [116]. They found a substantial reduction in adverse cardiovascular events after protocol implementation. Due to the risk of adverse cardiovascular event associated with rapid titration and bolus therapy, administration of dexmedetomidine for acute agitation or routine ICU care may pose a safety risk. A bolus with opioid, benzodiazepine, or antipsychotic may be needed to avoid adverse cardiovascular events. Institutional guidelines on the management of pain, agitation, and delirium should address the prescribing and administration of dexmedetomidine to promote its safe use in the hospital setting.

Therapeutic neuromuscular blockade in the ICU requires administration of sedatives to general anesthetic dosing to provide amnesia during blockade [128]. Dexmedetomidine has been studied as part of the total anesthetic regimen with neuromuscular blockade in the operating potential inability to provide deeper sedation levels should draw clinicians away from using dexmedetomidine in the presence of therapeutic neuromuscular blockade in the ICU setting [129].

Other rare adverse events reported with dexmedetomidine include rash, drug fever, and rebound agitation events [124, 130, 131]. Familiarity with the use of dexmedetomidine by bedside clinicians, institutional protocols/guidelines that address prescribing and monitoring, and optimization of intravenous smart pump technology are all important factors in promoting safe use of dexmedetomidine in the hospital setting [116, 132].

FUTURE DIRECTIONS

Dexmedetomidine has been extensively studied at lower doses for short term sedation in surgical patients. Recent studies have examined dexmedetomidine's use in a variety of patient conditions using higher dosing and longer durations of therapy [133].

Alpha 2 agonists such as clonidine have been used as adjunctive agents for the management of alcohol and opioid withdrawal in hospital setting [134-137]. While the dysregulation of γ-aminobutyric acid (GABA) and glutamate in the central nervous system are primarily responsible for the manifestation of the alcohol withdrawal syndromes, other neurotransmitters such as dopamine, norepinephrine, and serotonin have been identified as playing a role in symptomotology [134].

While the majority of the literature with alpha 2 agonists in alcohol withdrawal involves the use of clonidine, the use of dexmedetomidine as an adjunctive has been described in the literature

[134, 138-143]. When used adjunctively, alpha 2 agonists have demonstrated a reduction in the consumption of benzodiazepines in patients experiencing withdrawal [135-137]. Two small case series highlight a reduction in benzodiazepine consumption and symptom severity with the addition of dexmedetomidine to benzodiazepine therapy [142, 143]. No seizures occurred in the cohorts, however issues with cardiovascular intolerance were identified, including possible asystole events [143].

To date, no published randomized controlled trials examining adjunctive dexmedetomidine therapy with a symptom driven GABA agonist for alcohol withdrawal syndromes exist in the literature. It's important to note that recent studies examining the use of dexmedetomidine in a mixed medical-surgical patient population excluded or failed to report on the impact of dexmedetomidine in patients at risk of the alcohol withdrawal syndromes [9, 12, 16]. While dexmedetomidine has been used successfully for the management of alcohol withdrawal symptomatology, it's important for clinicians to identify that it has been used as an adjunctive agent therapy with a GABA agonist agent. Dexmedetomidine has no known GABA agonist properties. Thus it will not protect the patient from seizure, despite suppressing alcohol withdrawal symptomotology and providing mild sedation. Limited data on the use of dexmedetomidine in patients at high risk of withdrawal and actively withdrawing should draw caution from clinicians at this time.

The anti-shivering properties of dexmedetomidine make it a potential therapeutic option for the management of shivering associated with therapeutic hypothermia [38]. Prevention and treatment of shivering during therapeutic hypothermia typically involves the use of opioids and neuromuscular blockers [144]. Adjunctive agents such as buspirone have shown efficacy as well in mild cooling conditions [38]. Bradycardia and hypotension are common manifestations of therapeutic hypothermia, its unknown if the potential for bradycardia will be increased with dexmedetomidine therapy. Therapeutic hypothermia could potentially alter dexmedetomidine clearance and volume of distribution making further studies needed to establish the efficacy and safety of dexmedetomidine for shivering during therapeutic hypothermia [38].

The analgesic, anxiolytic, and cardiovascular properties of alpha 2 agonists make them a potential therapeutic option for the management of drug withdrawal states, sedative and anesthetic allergy or sensitivity, psychiatric emergencies, and palliative care situations in the ICU setting [145-151]. Dexmedetomidine's use in special patient populations will continue to rise, prompting further investigation on the efficacy and safety of this agent in both broad and specialized patient populations in the ICU setting.

CONCLUSION

Dexmedetomidine's alpha 2 agonist proprieties lend itself as a potential therapeutic option for the management of pain, agitation, and delirium in the ICU setting. Since its introduction to clinical practice, literature on dexmedetomidine has continued to expand on its use in a variety of indications and critically ill patient populations. The potential improvement in outcomes such as mechanical ventilation and delirium with dexmedetomidine have triggered further research into how we manage our patients pharmacologically and non-pharmacologically in the ICU setting. The mild to moderate sedative properties of dexmedetomidine make it a viable pharmacological option for many critically ill patient populations. Limitations of existing literature on efficacy and safety prevent dexmedetomidine from becoming an all purpose, work horse agent for pain, agitation, and delirium in the ICU. Future research will continue to help define the role of dexmedetomidine in the ICU.

CONFLICT OF INTEREST

The author does not report any affiliation with or financial interest in a commercial organization that poses a conflict of interest with this article.

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