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The Effects of Dexmedetomidine on Preventing/Decreasing Severity of Delirium When Given to Surgical Intensive Care Unit Patients: A Systematic Review of Randomized Control Trials

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Introduction

Dexmedetomidine is a selective a_2-adrenergic receptor agonist. Alpha receptors are mainly found in the central nervous system and within the smooth muscle that composes the majority of blood vessel walls (Giovannitti et al., 2015). There are 3 subtypes of alpha receptors: a-2A, a-2B, and a-2C. The a-2A and a-2C are found in the central nervous system and the a-2B are the receptors found within vascular smooth muscle. More specifically, a_2 receptors are located in the prejunctional area and inhibit neurotransmitter release and provide negative feedback; a_1 receptors are postjunctional and mediate effects on target tissues (Giovannitti et al., 2015). Suppression of neural firing is achieved with all 3 receptors due to the fact that a-2A, a-2B, and a-2C all inhibit adenylyl cyclase, thus inhibiting cyclic adenosine monophosphate, or cAMP (Giovannitti et al., 2015).

The general role of cAMP is to act as a messenger in numerous transduction pathways that control cell processes such as transcription, protein expression, metabolism, regulation of neurotransmitter synthesis and regulation of membrane protein activity by converting extracellular signals to intracellular signals in stimuli received by receptors within the cell (Yan et al., 2016). The role of adenylyl cyclase is to catalyze the reaction of adenosine triphosphate into cAMP; therefore, when adenylyl cyclase is inhibited, so is cAMP (VIVO Pathophysiology). The inhibition of cAMP causes potassium to diffuse into the cell through calcium activated channels, ultimately preventing calcium from entering the axon terminal and leading to suppression of neural firing and inhibition of norepinephrine/ascending noradrenergic pathways (Giovannitti et al., 2015). This change in ions and neurotransmitter pathways leads to sedation and hypnosis experienced by the patient A negative feedback loop is generated when alpha

receptors are stimulated, further decreasing sympathetic response, which in turn decreases heart rate and blood pressure (Giovannitti et al., 2015).

Dexmedetomidine has three main uses: prolonged sedation, procedural sedation/anesthesia, and decrease the incidence of emergence/postoperative delirium (Giovannitti et al., 2015). Postoperative delirium occurs following a surgical procedure and emergence delirium refers to delirium experienced immediately post-anesthesia. Both forms of delirium exhibit symptoms similar to dementia. The difference between the two is that once the cause of the postoperative delirium is found and treated, the symptoms will subside. Symptoms differ between patients, but disorientation, emotional dysregulation, sleep disturbances, and perceptual disturbances may occur (Oh & Park, 2019). The Diagnostic and Statistical Manual or Mental disorders, Fifth Edition, (DSM-5), criteria for delirium can be observed in Table 1 (American Psychiatric Association, 2013). Currently, there is no sole factor that has been identified in the onset of delirium. The two leading hypotheses that attempt to explain the pathophysiology of delirium involve: cytokine interaction on the blood-brain barrier and neurochemical imbalances that affect transmission (Oh & Park, 2019). Upon completion of functional magnetic resonance imaging, it was found that individuals experiencing delirium demonstrated disruption of reciprocity functions within certain brain structures and a dysregulation of mental coordination processing areas by a portion of the hypothalamus (Oh & Park, 2019).

Diagnostic Criteria
A: A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B: The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends t fluctuate in severity during the course of a day
C: An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D: The disturbance in criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E: There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

(Table 1)

Risk factors of postoperative delirium can be broken into 3 categories: preoperative, intraoperative, and postoperative. Preoperative factors include advanced age, comorbidities such as cardiovascular disease/anxiety disorders, preoperative fluid fasting/dehydration, hypo/hypernatremia, and drugs with anticholinergic effects (Oh & Park, 2019). Intraoperative risk factors include site of surgery being abdominal or cardiothoracic, and intraoperative bleeding; postoperative factors include pain (Oh & Park, 2019). Emergency surgery and postoperative complications raise risk for cognitive impairment and duration/severity of delirium. Studies have demonstrated that ICU patients who develop delirium while in the hospital have a higher chance of having a worse prognosis and a lower 6-month survival rate (Oh & Park, 2019).

As aforementioned, dexmedetomidine is a selective a_2-adrenergic receptor agonist and is primarily used for prolonged sedation, procedural sedation/anesthesia, and decrease the incidence of emergence/postoperative delirium (Giovannitti et al., 2015). It has been proposed that dexmedetomidine is associated with lower rates of postoperative delirium when used as

procedural and postoperative sedation compared to midazolam or propofol (Hoy & Keating, 2012).

Purpose

The purpose of this systematic review was to integrate research evidence from studies published from 2010 to 2020 on the relationship between administration of dexmedetomidine and severity/prevalence of postprocedural delirium in patients in the surgical intensive care unit.

Methods

This is a systematic review involving research that involves administration of dexmedetomidine in post-surgical intensive care unit patients and if it's mechanism of action aids in preventing or decreasing instance and severity of delirium. This systematic review follows the guidelines outlined in the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement (Liberati et al., 2009).

Information Sources

Clinical trial studies were recovered by searching the MEDLINE Complete and PubMed databases and utilizing MeSH terminology search. The electronic search was supplemented by a manual search from current issues of periodicals and follow-up of other cited materials.

Search Strategy

The MeSH terms utilized to search for applicable articles on PubMed included: "intensive care units" or "critical care" or "critical care nursing", and "delirium", "dexmedetomidine", and "surgical procedures, operative". On MEDLINE Complete, the search terms utilized were "ICU or intensive care unit or critical care" and "dexmedetomidine" and

"delirium" and "surgical procedures, operative". Search limiters applied to both databases included English language, and peer-reviewed journal articles from 2009-2020.

Inclusion/Exclusion Criteria

Eligibility of studies was determined by utilizing the PICO question established for this systematic review: (P) the study was conducted involving surgical intensive care unit patients, (I) a selective alpha-2 adrenoceptor agonist, specifically dexmedetomidine was administered to patients, (C) the study included data on the efficacy of dexmedetomidine in preventing/decreasing severity of delirium, and (O) prevalence of delirium compared to placebo was reported. Studies were excluded if they included an additional intervention in addition to dexmedetomidine, or if they included dexmedetomidine therapy for a reason other than delirium. Dexmedetomidine can benefit the patient in additional ways, such as providing hemodynamic stability to critically ill patients more effectively than other drugs (Chaitanya et al., 2014). Articles to be included were first screened through reading abstracts and going through the inclusion/exclusion criteria. Any discrepancies or uncertainties were consulted with a mentor experienced in writing academic literature. If multiple articles were published from one study, only the most complete and recent information was included.

Data Extraction

Relevant information was identified and extracted from the pertinent articles discovered. Authors, country of study, sample size, methods of data collection, reported results, year published, confounding variables (if any), limits, methods of data collection, and information regarding safety were analyzed throughout all of the relevant articles. The articles were further reviewed to ensure that the results were relevant to the proposed topic and from 2009 or later. The articles were read, and data was extracted, this process was completed twice as to avoid any

missed information. The process results were compared, and any confusion/discrepancies were resolved. If any discrepancies were unable to be resolved, the article was not included in the review.

Quality Assessment of Included Studies

The modified Jadad score with 8 items (Table 2) was utilized to determine quality of the relevant studies. The Jadad scale includes randomization, blinding methods, description of withdrawals and dropouts, clear inclusion and exclusion criteria, adverse effects clearly described, and if the method of statistical evidence was described. The articles were scored twice to ensure appropriate scoring. Any articles with discrepancies in scores were scored again until a consistent score was achieved twice. Articles with a Jadad score of 4 or >4 were included in the systematic review, none needed to be excluded for this reason.

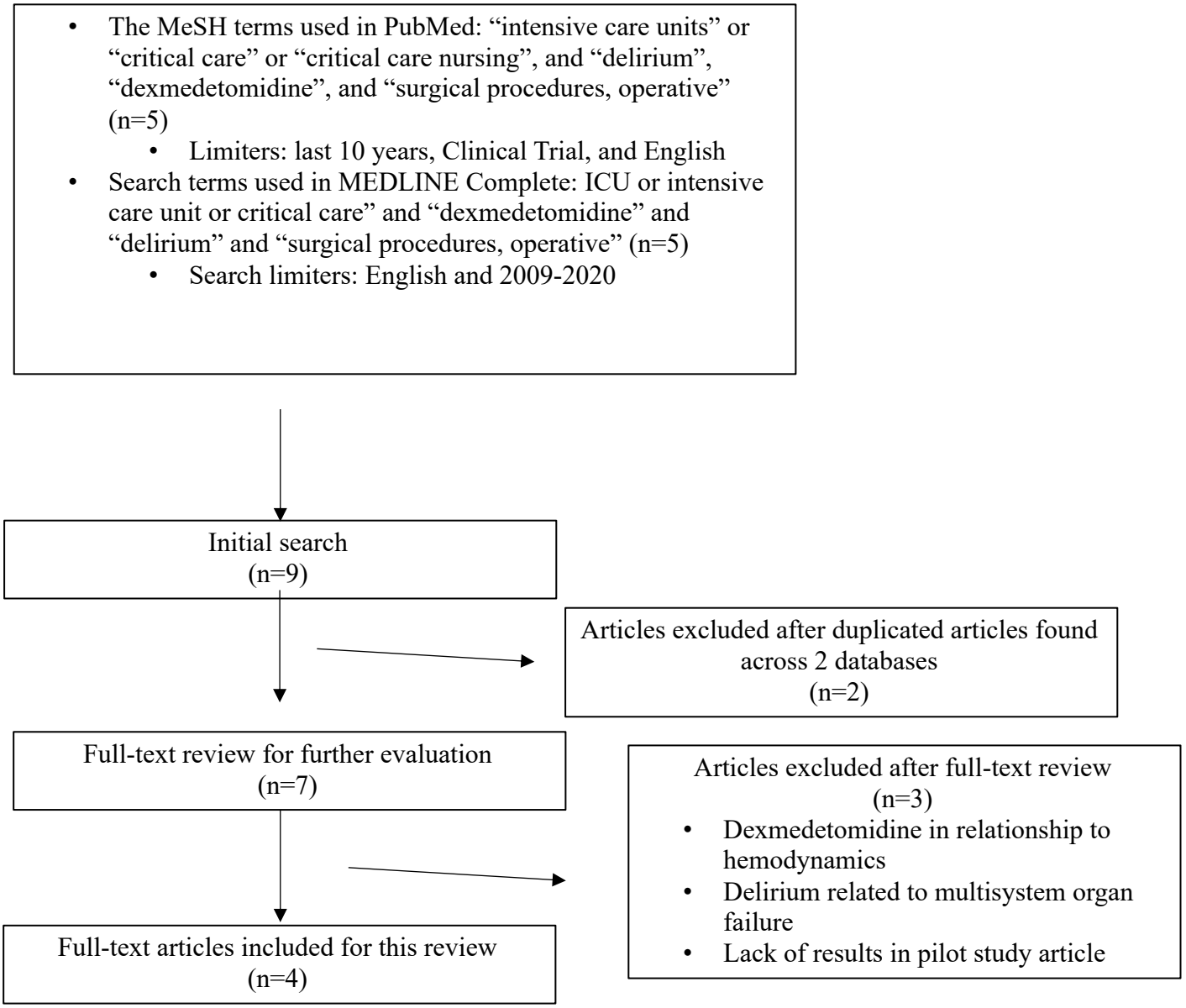
Eight items	Answer	Score
Was the study described as randomized?	Yes	+1
	No	0
Was the method of randomization appropriate?	Yes	+1
	No	-1
	Not described	0
Was the study described as blinding? [a]	Yes	+1
	No	0
Was the method of blinding appropriate?	Yes	+1
	No	-1
	Not described	0
Was there a description of withdrawals and dropouts?	Yes	+1
	No	0
Was there a clear description of the inclusion/exclusion criteria?	Yes	+1
	No	0
Was the method used to assess adverse effects described?	Yes	+1
	No	0
Was the methods of statistical analysis described?	Yes	+1
	No	0

a: double-blind got 1 score, single-blind got 0.5 score.

(Table 2 (Oremus et al., 2001))

Search Results

Four articles were retrieved from MEDLINE Complete, and six articles were retrieved from PubMed. Two articles were duplicates and removed. Seven articles went through full-text analysis. One article was removed because it involved research about dexmedetomidine and its effect on hemodynamics. Another article was removed because it explored delirium as a component in multisystem organ failure and a third article was removed because it was a pilot study and lacked results. After the full text analyses, 4 articles were included in the systematic review. The selection process is represented in the flow chart (fig 1).



(Figure 1)

Results

Study Characteristics

The first study had a sample size of 618 with 281 in the experimental group and 276 in the placebo group. The median age in the experimental group was 68 and the mean age in the placebo group was 69. The mean BMI were 24.6 and 24.3 respectively (Sun et al., 2019). Regarding chronic smoking, 20.6% and 19.9% are chronic smokers, respectively. Hypertension was found in 35.2% and 38.4%. Coronary artery disease 8.5% and 8.0%, diabetes 14.6% and 15.6%, previous stroke 13.5% and 12% respectfully (Sun et al., 2019). All of the variables explored are < P=0.05, except for one. The CCI, median (IQR), in years was found to be statistically significant at 2.0 (0.0-2.0) and 1.0 (0.0-2.0) (P=0.010) (Sun et al., 2019). The study also explored surgical variables between the two groups and the significant difference included cancer, 50.9% in the dexmedetomidine group and 40.9% in the placebo group (P=0.019) (Sun et al., 2019).

The second article had a study group of 32 split into two groups, dexmedetomidine and midazolam. The mean age of 13.6 in the dexmedetomidine group and 14.8 in the midazolam group (Aydogan et al., 2013). The time under mechanical ventilation was found to be significant at 225 minutes in the midazolam group and 107 in the dexmedetomidine group (P=0.035) (Aydogan et al., 2013). Other variables found to be not significant included male/female distribution between the groups (9/7 in the midazolam group and 8/8 in dexmedetomidine

group), height (156 cm and 153 cm respectively), weight (37kg and 28kg respectively), American Society of Anesthesiologists class II/III (10/6 and 11/5), and ICU length of stay (2 days for both groups) (Aydogan et al., 2013).

The third study was larger and had a study group of 700, with 350 in a dexmedetomidine group and 350 in the placebo group. It was stated in the article that the groups were well matched for baseline/perioperative variables except in the dexmedetomidine group that percentage of patients with renal dysfunction preoperatively was lower in the dexmedetomidine group (creatinine > 177 μmol/L) (Su et al., 2016). The patients recruited were over the age of 65 and excluded aged less than 65 years, non-surgical patients, non-general anesthesia, neurosurgery, patients who required dialysis preoperatively, preoperative coma, and preoperative Parkinsonism. Regarding perioperative variables, 72% in the placebo group and 78.3% in the dexmedetomidine group had surgery for a malignant tumor, and both groups had intra-abdominal as the location of the surgery (67.1% in the placebo group and 68.6% in the dexmedetomidine group) (Su et al., 2016). The only significant difference was the number of patients who required intraoperative blood transfusion (19.1% in placebo group and 13.4% in dexmedetomidine group) (Su et al., 2016).

The last study was a follow-up of the third study Ultimately after 3 years, 221 patients in the dexmedetomidine out of 350 participated (114 died, 13 lost at 3-year follow up, 2 refused assessment) and 213 in the placebo group participated (122 died, 10 lost at 3-year follow up, and 5 refused assessment) (Zhang et al., 2019). The mean age in the placebo group during follow-up was 74.5 and 74.2 in the dexmedetomidine group. Other variables that were not statistically different included but are not limited to: BMI 23.8 and 24.4 respectively, hypertension 64.3%

and 62.9%, diabetes 24.4% and 28.5%, coronary artery disease 30% and 38%, stroke 22.5% and 23.5%, alcoholism 8.9% and 7.2%, liver dysfunction 2.3% in both groups, renal dysfunction 5.2% and 2.3% (Zhang et al., 2019).

The four articles included in this systematic review all explore effects of dexmedetomidine on cognitive functioning/decreasing delirium. The first study began with 618 randomized patients after screening (Sun et al., 2019). 309 patients were placed into a group and ultimately 281 in the dexmedetomidine group received the allocated intervention and 276 received the allocated intervention in the placebo group. Surgical cancellation, study drug infusion interrupted permanently, or unplanned ICU stay were reasons for participants not receiving the allocated intervention (Sun et al., 2019).

Inclusion criteria included: aged 65 years of older, scheduled to undergo major elective noncardiac surgery under general anesthesia, American Society of Anesthesiologist physical status classification I to III, Mini Mental State Examination > or = to 20 points, and agreement to use patient-controlled intravenous analgesia pump. Exclusion criteria included emergency surgery, intracardiac or intracranial surgery, inability to communicate, sick sinus syndrome, sinus bradycardia, higher heart block in the absence of a pacemaker, serious liver dysfunction, serious kidney failure, schizophrenia, myasthenia gravis, Parkinson's, allergy to opioids/a2-adrenergic agonists, or prior recruitment in another clinical trial (Sun et al., 2019).

Randomization was computer-generated to either the dexmedetomidine or placebo group and researchers remained blinded. Delirium was then assessed twice daily during the first five days following surgery with the RASS and CAM-ICU assessment tools (Sun et al., 2019). Postoperative delirium occurred in 12.7% (n=557) out of all patients and there was no significant difference between the placebo and experimental group (11.7% (33/218) in dexmedetomidine

group and 13.8% (38/276) in the placebo group, p=0.47) (Sun et al., 2019). Although there was no statistical significance found between the groups in delirium prevention, the dexmedetomidine group had lower pain scores at four intervals after hour 1 post-surgery and required a lower percentage of pain rescue with flurbiprofen axetil (Sun et al., 2019). The dexmedetomidine group also was found to have higher sleep quality when assessed with the Richards Campbell Sleep Questionnaire (all $p<0.0001$). Additional outcomes included no significant differences in extubating time, 30-day mortality, and length of stay in the hospital (Sun et al., 2019). 5.3% (15/281) in the dexmedetomidine group experienced non-delirium related complications vs 5.1% (14/276) in the placebo group (p=0.89). Incidence on pneumonia was significantly lower in the dexmedetomidine group (0.4% (1/281) vs 2.5% (7/276 with p=0.036) (Sun et al., 2019).

The second article explored pain, fentanyl consumption, and delirium following scoliosis surgery in adolescents (Aydogan et al., 2013). Inclusion criteria included admittance to ICU requiring mechanical ventilation with an endotracheal tube following scoliosis surgery. Exclusion criteria included allergy to dexmedetomidine or midazolam, delirium, developmental day, cognitive impairment, American Society of Anesthesiologists class > III, previous anesthetic adverse reactions, digoxin use, history of hypertension, chronic use of opioids/sedatives, or neuromuscular scoliosis/neurogenerative disease (Aydogan et al., 2013).

As the previous study was, this study was also randomized and double-blinded. One group was to receive midazolam 0.1mg/kg/h IV and the other was to receive dexmedetomidine 0.4 μg/kg/h IV and quality of sedation was assessed hourly through use of the RASS scale then the medication was titrated until desired RASS score was achieved (Aydogan et al., 2013). Pain relief was aimed to be kept between 0-4 on the Numeric Visual Analog Scale and if it was

outside of the parameters then the medication would be titrated up or down. Delirium was assessed twice daily with the CAM-ICU scale in patients within the desired RASS score range (-1 to +1) by a neurologist associated with the study (Aydogan et al., 2013). Haloperidol was given for treatment of agitation/delirium.

Overall, the pain scores and cumulative fentanyl consumption were significantly higher in group MDZ than DEX. Pain was assessed at 1, 2, 4, 6 and 24 hours and at all hours the pain values in group DEX were lower and significant compared to MDZ group ($p<0.05$): hour 1 ($P=0.012$), hour 2 ($P=0.003$), hour 4 ($P=0.001$), hour 6 ($P=0.003$) and hour 24 ($P=0.004$). Fentanyl consumption was also assessed at the same hours following surgery and the MDZ group consistently had statistically significant higher values: hour 1 ($P=0.006$), hour 2($P=0.002$), hour 4 ($P=0.023$), hour 6 ($P=0.001$) and hour 24 ($P=0.002$). Furthermore, delirium was significantly higher in the MDZ group (31.3% vs 12.5% and $P<0.05$) (Aydogan et al., 2013). Haloperidol was given to treat delirium in 1/16 (4%) of the patients in the DEX group as opposed to 4/16 (25%) of the patients in group MDZ. No significant differences occurred in mean arterial pressure. More patients in group DEX developed adverse events related due to treatment (6/16 [37.5%] vs 3/16 [18.7%]), most likely due to the significantly higher instance of bradycardia in the DEX group at all measured time intervals ($P<0.05$).

The third article was a larger double-blind randomized control trial specifically exploring administration of dexmedetomidine and its effect on prevention of delirium in elderly patients following non-cardiac surgery. Dexmedetomidine was given at 0.1µg/kg/hr usually within one hour after ICU admission until 0800 the following day after surgery for non-intubated patients. Intubated and mechanically ventilated patients received the study drug infusion only after

sedatives were titrated to achieve RASS of -2 or higher (Su et al., 2016). For pain, morphine or flurbiprofen axetil were given IV.

Approaches to mitigating delirium were initiated as standard procedures for ICU patients (reorientation, cognitive stimulation, early ambulation, hearing/vision aids, sleep-promotion, and dehydration protocols) (Su et al., 2016). If a patient demonstrated delirium, first nonpharmacological strategies were implemented followed by haloperidol administration if needed (RASS +3 or greater). The primary endpoint of the study was calculating delirium incidence in the first week following surgery. The first assessment of delirium was performed 24 hours after surgery then delirium was assessed twice daily (between 0800-1000 and 1800-2000) utilizing the CAM-ICU scale (Su et al., 2016).

Like the other studies, RASS was utilized to gauge sedation level. In this study, if the RASS score was -3 to +4, delirium was assessed. Other factors assessed included extubation time, ICU/hospital length of stay, non-delirium postoperative complications, pain intensity, sleep quality (subjective), and 30-day mortality (Su et al., 2016). Pain was measured utilizing the Numeric Rating Scale (NRS: 0=no pain and 10=worst possible pain) at 3-, 6-, and 24-hours following surgery.

Patients were followed up weekly following the first week for mortality rate (Su et al., 2016). Before the final analysis, 143 patients were discharged before the first 7 days, 2 patients died (one in each group), 48 patients had to have the study drug modified due to adverse events. Delirium occurred in 79/350 (22.6%) of patients in the placebo group and in 32 (9.1%) out of the 350 patients in the dexmedetomidine group (odds ratio 0.35, 95% CI 0.22-0.54; $P<0.0001$) (Su et al., 2016). Furthermore, daily prevalence of delirium was significantly higher in the placebo group on postoperative days 1 through 3 (day 1: 0.28, 0.16–0.50; $P<0.0001$, day 2: 0.43, 0.24–

0.77; P=0.005, day 3: 0.26, 0.13–0.53; P<0.0001) (Su et al., 2016). Regarding the secondary results, median time to extubation was longer in the placebo group (6.9h vs 4.6h) and percent of non-delirium complications was higher in the placebo group as well (21% vs 15% with P=0.039). There was no significance in length of hospital stay between the two groups or 30-day mortality, but post-hoc analysis demonstrated a higher percentage of patients discharged from the hospital within 7 days in the dexmedetomidine group (83 [24%] vs 60 [17%], P=0.032) (Su et al., 2016). Pain scores were found to be significantly lower in the dexmedetomidine group at 3-, 6-, and 24- hours following surgery (all P<0.0001, except for one P=0.001 at 24-hours). The subjective sleep scores were also significantly better in the dexmedetomidine group the first 3 days following surgery (P<0.001).

The fourth and final article included in this review explored long-term (up to 3 years) effects and also postoperative outcomes up to 30 days in the patients that completed 3-year assessments of the trial that explored administration of dexmedetomidine and its effect on prevention of delirium in elderly patients following non-cardiac surgery (Su et al., 2016). The follow up was conducted by an investigator who was not involved in the original study and was blinded to the group assignments. For individuals who survived 3 years following surgery, cognitive function, was assessed with the modified Telephone Interview for Cognitive Status (TCIS-m) and the World Health Organization Quality of Life brief version (WHOQOL-BREF) involving physical, psychological, social relationship and environment domain assessment (Zhang et al., 2019).

As aforementioned, these patients had been randomly assigned to receive dexmedetomidine 0.1μg/kg/h or normal saline at the same infusion rate. Of the original 700 patients, 23 (3.3%) had passed away at follow-up, including 10 (2.9%) in the placebo group and

13 (3.7%) in dexmedetomidine group (P=0.698) (Zhang et al., 2019). Of the 441 survivors at 3 years, 7 refused assessment (5 in placebo group and 2 in dexmedetomidine group). The remaining 434 completed the assessments previously mentioned (Zhang et al., 2019).

Overall, the 3-year survival rate did not differ significantly (mean survival length 29.9 months, 95% CI 28.8 – 31.0 vs 28.2, 95% CI 26.9 – 29.5; and the 3-year survival rate of 67.0%, 95% CI 62.1–71.9 vs 64.4%, 95% CI 59.3 – 69.5) and [hazard ratio (HR) for death 0.87, 95% CI 0.68– 1.13, P=0.303) (Zhang et al., 2019). At shorter intervals, survival rates at 6 months were found to be higher in dexmedetomidine group (rate difference 5.2, 95% CI 1.1 – 9.3, P=0.012), 1 year (5.3, 95% CI 0.0 – 10.6, P= 0.049), and 2 years (6.7, 95% CI 0.3–13.1, P=0.040) (Zhang et al., 2019). TICS-m (mean difference 4.7, 95% CI 3.8 – 5.6, P < 0.0001) and WHO- QOL-BREF (including physical: 13.6, 95% CI 10.6 – 16.6, P < 0.0001; psychological: 15.2, 95% CI 12.5 – 18.0, P < 0.0001; social relationship: 8.1, 95% CI 5.5 – 10.7, P < 0.0001; and environment: 13.3, 95% CI 10.9 – 15.7, P < 0.0001) assessments were higher in the dexmedetomidine group than in the placebo group, suggesting better cognitive functioning (Zhang et al., 2019). Involving delirium, the major interest in this review, incidence of delirium within the first 7 postoperative days (in the patients who completed 3-year assessments) was 41 (19.2%) in the placebo group and 18 (8.1%) in the dexmedetomidine group (P=0.001) (Zhang et al., 2019). Duration of delirium was found to not have a statistically significant relationship between the two groups (P=0.905).

Authors	Country of Study	Year Published	Sample Size	Methods of Data Collection
Yuanyuan Sun, Mingming Jiang, Yunjing Ji, Yue Sun, Yao Liu, and Wen Shen	China	2019	-281 received dexmedetomidine -276 received NS 0.9%	-delirium assessed by trained research team members in PACU and twice daily for 5 days using Confusion Assessment Method for ICU (CAM) -before delirium assessment, Richmond Agitation Sedation Scale was utilized and if patient was deeply sedated or unarousable, CAM assessment was not utilized at that time -For patients who were discharges or died during the 5 day process, the results of the last delirium assessment were considered as the missing data
Mustafa S. Ayodogan, Mehmet F. Korkmaz, Ulkü Ozgül, Mehmet A. Erdogan, Aytac Yucel, Abdurrahman Karaman, Turkan Togal, Mahmut Durmus, Cemil Colak	Turkey	2013	-32 total -16 in dexmedetomidine group -16 in midazolam group	-standardized anesthetic technique with no analgesics or sedatives used preoperatively -BP, ECG, capnography, and SpO2 monitored in OR - quality of sedation was assessed hourly through Richmond Agitation Sedation Scale (RASS) by a single anesthesiologist not involved in the study -Patients within RASS range of -2 to +1 were asked to perform four tasks -quality of pain relief was assessed using Numeric Visual Analog Scale (NVAS) -delirium was assessed twice daily in patients in the RASS range of -2 to +1 using the CAM-ICU
Xian Su, Zhao-Ting Meng, Xin-Hai Wu, Fan Cui, Hong-Liang Li, Dong-Xin Wang, Xi Zhu, Sai-Nan Zhu, Mervyn Maze, and Daquing Ma	China	2016	700 -350 to placebo -350 to dexmedetomidine	-outcome assessments performed by trained research members -first assessment of delirium was done 24 hours following surgery -Delirium was then assessed twice daily (between 0800 and 1000) (between 1800 and 2000) until 7th day after surgery -Assessed delirium with CAM-ICU -RASS score was assessed and if RASS was within -3 to +4 delirium was assessed -patients with delirium subclassed into 3 subtypes (hyperactive, hypoactive, mixed) -adverse events monitored until 24 after surgery -Pain intensity assessed with Numeric Rating Scale (NRS) on 11-point scale (0-10)
Zhang DF, Su X, Meng ZT, Li HL, Wang DX, Zue-Ting Li, Maze M, Ma D	China	2019	-Follow up of the 700 patients in the study above -434 patients completed follow-up assessments	-434 patients completed cognitive function, and quality of life assessments (physical, psychological, social relationship, environment domains) - 3-year follow-up was performed by an investigator not involved in the original trial -pathological results were obtained from medical records (inpatient and outpatient) -follow-up occurred over the telephone utilizing the modified Telephone Interview for Cognitive Status (TICS-m) and World Health Organization Quality of Life brief version (WHOQOL-BREF) -scores range from 0-50 with a higher number indicating better function -Early postoperative outcomes (30 days) were assessed, including delirium (duration, delirium within first 7 postoperative days)

Confounding Variables (If Applicable)	Limits	Safety	Reported results
-no significant differences in demographic and perioperative variables between two groups except: -Charleston Comorbidity Index lower in placebo (P=0.010) -Percentage of patients with cancer lower in placebo group (P=0.019)	-delirium could be missed due to only assessing twice daily and dementia is transient/fluctuates -low-dose dexmedetomidine was utilized -No data collected regarding motor subtypes of delirium -larger sample size is needed to determine efficacy	-in emergency situation, study group allocation could be unmasked for patient safety	-No significant difference between the two groups regarding incidence of delirium in first 5 days post-op -11.7% (33/281) Dexmedetomidine group -13.8% 38/276 in placebo group P=0.47
-Patient characteristics did not differ significantly between the two groups -concurrent treatment with fentanyl for pain	-Small study group size -Study only explored scoliosis surgery in adolescents	-If patients were over-sedated, medication was stopped until desires RASS score was achieved -Haloperidol administered	-Delirium was significantly higher in the midazolam group when analyzed as the endpoint of CAM (31.3% vs 12.5%) ($p<0.05$) -Haloperidol was used to read delirium in 4% (1/16) in DEX group and 25% (4/16) in MDZ group -NVAS pain scores and fentanyl consumption at all evaluation points significantly higher in MDZ group than those in DEX group ($p< 0.05$)
-trial participants and researchers blinded to treatment group assignments -concurrent pain treatment -Delirium treatment	-ICU environment places patients at risk for delirium due to excessive noise and tasks to be performed -only surgical ICU patients were included so there is no certainty that dexmedetomidine will lessen sleep disruptions/delirium in non-ICU postoperative patients -participants did not have baseline delirium assessment with cognitive function assessment -despite strict randomization, some baseline and perioperative parameters were not well balanced -CAM-ICU may not be as sensitive as 3D-CAM	-In emergency situations, such as rapid deterioration of a patient, unmasking was allowed or adjustment of study drug	-Postoperative delirium occurred in 79 (23%) of 350 patients given placebo and in 32 (9%) 0f 350 patients given dexmedetomidine (odds ratio 0.35 95% CI 0.22-0.54 $p<0.0001$) -daily prevalence of delirium was significantly lower in dexmedetomidine group in postop days 1-3 ((day 1: 0·28, 0·16–0·50; $p<0·0001$, day 2: 0·43, 0·24–0·77; $p=0·005$, day 3: 0·26, 0·13–0·53; $p<0·0001$)
-trial participants and researchers blinded to treatment group assignments	- because patients were recruited after ICU admission, there was not evaluation of baseline cognitive function and quality of life prior to surgery -this study was a follow-up of a RCT, and initial sample size was powered to detect difference of delirium but not long -term survival -the TCIS-m may not have been very ‘ instrumental’ ’	-Ethics Committee agreed to waive written informed consent for the telephone calls -protocol was approved by the Clinical Research Ethics Committee of Peking University First Hospital	-3-year survival rate did not differ significantly (mean survival length 29.9 months, 95% CI 28.8 – 31.0 vs 28.2, 95% CI 26.9 – 29.5; and the 3-year survival rate of 67.0%, 95% CI 62.1–71.9 vs 64.4%, 95% CI 59.3 – 69.5) and [hazard ratio (HR) for death 0.87, 95% CI 0.68– 1.13, P 1⁄ 4 0.303 -survival rates at 6 months higher in dexmedetomidine group (rate difference 5.2, 95% CI 1.1 – 9.3, P 1⁄ 4 0.012), 1 year (5.3, 95% CI 0.0 – 10.6, P 1⁄ 4 0.049), and 2 years (6.7, 95% CI 0.3–13.1, P 1⁄ 4 0.040) -TICS-m (mean difference 4.7, 95% CI 3.8 – 5.6, $P < 0.0001$) and WHO- QOL-BREF (including physical: 13.6, 95% CI 10.6 – 16.6, $P < 0.0001$; psychological: 15.2, 95% CI 12.5 – 18.0, $P < 0.0001$; social relationship: 8.1, 95% CI 5.5 – 10.7, $P < 0.0001$; and environment: 13.3, 95% CI 10.9 – 15.7, $P < 0.0001$) assessments were higher in the dexmedetomidine group than in the placebo group

Discussion

Overall, dexmedetomidine was found to reduce incidence of delirium in patients who had received surgery in 2 studies (Aydogan et al., 2013; Su et al., 2016). In the other study conducted, there was no statistical significance between delirium incidence between the placebo and experimental group; and the last study was a follow-up of another one of the studies explored in this review. The groups of individuals included in the studies were individuals 65 years or older undergoing major elective noncardiac surgery, adolescents receiving scoliosis surgery, and individuals aged 65 years or older, who were admitted to intensive care units after non-cardiac surgery. Besides delirium, secondary outcomes were also assessed across these studies such as: long-term effects, pain management, sleep, cognitive functioning (short and long-term), quality of life, mortality, hospital stay, time to extubation, and non-delirium related complications. Dexmedetomidine was found to have mixed results on delirium prevalence/severity across the studies explored in this review, but the majority of studies concluded statistical significance between dexmedetomidine and reduction in delirium (Aydogan et al., 2013; Su et al., 2016).

Regarding secondary outcomes, significantly lower pain scores were reported in all three studies. The first study reported a lower percentage of pain rescue, the second study reported statically significant lower pain scores 1-, 2-, 4-, 6-, and 24-hours following surgery delirium, and the third study reported lower pain scores at 3-, 6-, and 24 hours (Aydogan et al., 2013; Su et al., 2016; Sun et al., 2019). Two of the studies explored a placebo group versus dexmedetomidine while one study explored midazolam instead of a placebo group compared to dexmedetomidine. In the study involving midazolam, the midazolam group required significantly higher fentanyl consumption in order to lower pain levels (Aydogan et al., 2013). Regarding

sleep quality, statistically significant higher sleep quality was reported in the two studies that explored this outcome (Su et al., 2016; Sun et al., 2019). In the two studies that extubation time was explored, there was no statistical significance found between the placebo groups and dexmedetomidine groups. The 30-day mortality rates showed no significant differences between the groups in the same two studies. (Su et al., 2016; Sun et al., 2019). All of the studies explored effects of dexmedetomidine on non-delirium related complications with three different findings. Firstly, one study showed no significance between the dexmedetomidine and placebo groups for non-delirium related complications (Sun et al., 2019). The second study found that more patients in the dexmedetomidine group experienced non-delirium related complications than in the midazolam group, and this number was found to be significant. Lastly, the third study found that the dexmedetomidine group had a significantly lower incidence in non-delirium related complications (Su et al., 2016). The two studies that explored length of stay between placebo and dexmedetomidine groups found no statistical significance (Su et al., 2016; Sun et al., 2019). In one study, it was found that there was a higher percentage in the dexmedetomidine group that were discharged from the hospital within 7 days.

Regarding long-term effects, this study was a follow-up of the study conducted in 2016 (Su et al., 2016). The 3-year survival was found to have no significant difference between the two groups, but the 3-month and 6-month survival rates were found to be higher in the dexmedetomidine group. It was specifically noted in this study that 80.1% of the patients in this study underwent surgery for cancer, and although tumor stages among the participants in two groups were comparable, this could still impact the survival rates between the two groups. In non-cancer patients (19.9%), survival in the dexmedetomidine group was significantly higher (Zhang et al., 2019). Furthermore, the initial study had found that delirium occurred significantly

more in the placebo group than in the dexmedetomidine group. The follow-up also included a further analysis of the initial data and although the dexmedetomidine group had significantly lower instances of delirium, the duration of delirium was not found to differ significantly between the dexmedetomidine and placebo groups (Zhang et al., 2019). Regarding the assessment portion utilizing the Telephone Interview for Cognitive Status (TCIS-m) and the World Health Organization Quality of Life brief version (WHOQOL-BREF), psychosocial, social relationship, physical, and environmental domains were found to be significantly better in the dexmedetomidine group, suggesting better long-term cognitive functioning after receiving dexmedetomidine (Zhang et al., 2019).

The overall results across the three studies and follow-up suggest that when given dexmedetomidine following surgery, a patient has a better chance of not acquiring delirium. The three studies also suggest that pain and sleep quality are also improved when given dexmedetomidine. The three studies explored three different groups of individuals: individuals 65 years or older undergoing major elective noncardiac surgery, adolescents receiving scoliosis surgery, and individuals aged 65 years or older, who were admitted to intensive care units after non-cardiac surgery. Although the different groups allow for data to be collected among different populations, a limit of this review is that there needs to be multiple trials over multiple age groups in order to determine the efficacy of dexmedetomidine. Similarly, this topic has very limited high-quality research with randomized control trials. There is great room for an increase in research on this topic. Overall, the results show promising trends, but there is not enough data to concretely determine the effects of dexmedetomidine when given to postoperative patients.

Although the results are limited, they are encouraging. Further research in this field could lead to new protocols for postoperative patients who have undergone major surgeries. Positive

findings possible include reduced incidence in delirium, better long-term cognitive functioning, decreased time to extubation, decreased pain medication consumption, decreased overall pain, and better sleep quality. This review has explored three randomized control trials and one follow up of one of the randomized control trials. Recommendations in order to advance findings may include conducting randomized control trials in the United States/other countries where demographics are different, conducting trials among all age groups, and conducting high-quality long-term follow up studies of the trials like the one explored in this review.

Conclusion

Currently, there is insufficient evidence regarding use of dexmedetomidine in prevention/decreasing severity of postoperative delirium in the surgical ICU setting. Although there is limited evidence, the evidence is still encouraging and has shown evidence in being effective in mitigating delirium. As aforementioned, across the 3 randomized trials and the 3-year follow up article, there has been other positive findings found with dexmedetomidine use including better long-term cognitive functioning, decreased time to extubation, decreased pain medication consumption, decreased overall pain, and better sleep quality. Overall, there needs to be more research and deeper exploration into the use of dexmedetomidine in order to create a solid foundation of knowledge on the benefits and risks of utilizing this medication in patients undergoing surgery in order to prevent/decrease delirium severity.

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