DEXMEDETOMIDINE AND POSTOPERATIVE DELIRIUM IN THE ADULT CARDIAC SURGICAL POPULATION: A SYSTEMATIC REVIEW

by

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Abstract

Postoperative delirium (POD) is a major complication following surgery and is considered the most common complication among older adults following cardiac surgery; with up to 87% of patients being affected (Whitlock, Vannucci, & Avidan, 2011). Dexmedetomidine, a highly selective α_2 agonist, inhibits the release of norepinephrine presynaptically causing analgesia and inhibits central nervous system stimulation in the postsynaptic neurons causing decreased blood pressure and heart rate; together, contributing to the effects of analgesia, anesthesia, and sedation (Naaz & Ozair, 2014). The purpose of this systematic review was to analyze the current literature and examine the effects of dexmedetomidine on POD in the adult cardiac surgical population. A comprehensive literature review was completed using CINAHL, PubMed, and Medline focusing on the pathology of postoperative delirium, the physiology of cardiac surgery, and the pharmacodynamics of dexmedetomidine. Guidelines set forth by PRISMA and Inouye and Charpentier's multifactorial model were utilized to assist in the identification of eligible studies. Study analysis was completed by creating study specific and data outcome tables. Critical appraisal of individual RCTs was performed utilizing the Critical Appraisal Skills Programme (CASP) checklist. A cross study analysis table was also created comparing the results of all eligible studies against one another. The findings of this systematic review determined that in the adult cardiac surgical population, dexmedetomidine was associated with a decreased incidence of POD; however, the results for time to extubation, ICU LOS (length of stay), and hospital LOS varied amid the studies examined.

Acknowledgements

I would like to thank my family and friends for the tremendous love, support, and understanding they have shown me throughout this difficult journey. Most importantly, my husband, the amazing man that I'm blessed to call my husband. He has carried me during my lowest points and praised me during my highest. He has and continues to give me the love and support that only he knows I need. To my beautiful children, this has all been for you. My hope is that one day you will look back during your toughest challenges in life and remember that if it were easy everyone would do it. Lastly, to my angels, the beautiful souls that took a piece of my heart to heaven. Paí, you always believed in me and gave me the perseverance to never give up on my dream of becoming a nurse anesthetist. Maé, you were my inspiration, the reason I became a nurse; it was in caring for you that I found a passion I never knew existed. In losing you, I lost a piece of me, and in a moment of sadness and heartache when it would have been easy to admit defeat, I made a promise; I vowed to you that I would never give up, and I would finish what I worked so hard to achieve because after all…I am my mother's daughter.

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Dexmedetomidine and Postoperative Delirium in the Adult Cardiac Surgical Population: A Systematic Review

Background/Statement of the Problem

Delirium is categorized as a neurological/behavioral condition initiated by a temporary disturbance of normal neuronal functioning resulting from systemic dysfunction (Maldonado et al., 2009). Postoperative delirium (POD) is an extremely common and unfortunate occurrence following surgery, particularly cardiac surgery, additionally, it is considered to be the most common surgical complication in older adults. The incidence of POD in the vascular and cardiac surgical population is high (up to 87% of patients); furthermore, the risk of mortality increases 10%-20% for every 48 hours that the surgical patient remains in a delirious state (Whitlock et al., 2011).

Postoperative delirium is an often-unavoidable neurobehavioral disturbance, and places both patients and providers in a precarious situation. Healthcare providers must treat these disturbances as they arise to prevent potential harm to the patient; however, these treatments repeatedly place the cardiac surgical patient at increased risk for developing further complications following an already complex course of recovery. Often, medications administered to treat the delirious behavior have a sedative effect, thus leading to decreased depth and frequency of respiratory effort, as the somnolent patient is now susceptible to the development of atelectasis, and the potential for acquiring pneumonia. Postoperative delirium remains a major and often unforeseen complication following cardiac surgery. This unexpected obstacle can hinder the recovery of cardiac surgical patients, thus increasing the incidence of morbidity and mortality amongst this fragile and vulnerable group. Dexmedetomidine, a highly selective

alpha-$_2$ (α_2) agonist inhibits the release of norepinephrine presynaptically causing analgesia and inhibits central nervous system stimulation in the postsynaptic neurons causing decreased blood pressure and heart rate; together, contributing to the effects of analgesia, anesthesia, and sedation (Ji et al., 2013). Dexmedetomidine provides numerous desirable benefits and effects, including anxiolysis, analgesia, and sympatholysis, producing a decline in the release of systemic norepinephrine subsequently enhancing hemodynamic stability and positively influencing myocardial O_2 supply and demand, all leading to and potentiating the added benefits of myocardial protection (Ji et al., 2013). Dexmedetomidine has also been shown to provide moderate anti-inflammatory effects, in addition to added protective benefits for the organs of the vessel-rich group consisting of the heart, lungs, brain, and kidneys (Ji et al., 2013).

The purpose of this study was to investigate whether dexmedetomidine, an α_2 receptor agonist, decreases the occurrence of POD in cardiac surgical patients. During the postoperative period, pharmacological agents including propofol, midazolam, and morphine are frequently utilized as adjunctive therapy for pain management, anxiolysis, and/or sedation. A systematic review was conducted in order to further explore the topic and disseminate the literature to offer insight and direction regarding this significant and potentially life-altering hindrance.

Next, the review of the literature will be presented.

Literature Review

A comprehensive review of the literature was performed utilizing CINAHL (Cumulative Index to Nursing and Allied Health Literature) as well as MEDLINE/PubMed. An advanced search approach was implemented utilizing keywords "cardiac surgery" AND "dexmedetomidine" AND "delirium." Restrictions applied to the search were English language, peer reviewed, and human subjects. A ten-year time period was utilized for the search (2007-present).

Postoperative Delirium

Postoperative delirium is an acute psychological disorder characterized as restlessness, agitation, combativeness, hallucinations, irritability, and confusion. Additionally, it has been linked to an increase in morbidity and mortality, increased healthcare costs, increased risk of hospital-acquired infections, prolonged ICU and subsequent hospital stay, and significant cognitive and functional decline, often requiring an intermediate or long-term facility placement (Maldonado, et al., 2009). Shehabi et al. (2009) recommended that cardiac surgical patients already considered at increased risk for the development of POD be carefully treated for post-surgical pain management; as opioids have the probability of potentiating the dysfunctional cognitive effects of POD. Moreover, it is believed that there is a correlation between inadequate postoperative pain control and the risk for the development of POD following surgery though no direct statistical information has been published. Approximately 57% of cardiac surgery patients have been diagnosed with POD annually (Park et al., 2014). It is postulated that a number of risk factors increase an individual's probability of developing POD following cardiac surgery. Risk factors include: atrial fibrillation, preexisting cognitive disorder,

perioperative medications, history of delirium, and other metabolic disturbances, however the direct cause of POD has yet to be identified (Park et al., 2014). Additional contributors to POD include hematocrit < 30%, decreased cardiac output, use of an intra-aortic balloon pump, use of inotropic medications, prolonged intubation > 24 hours, postoperative dysrhythmias, infusion of > 4 units of PRBCs or > 1 unit of FFP, CO_2 levels > 45 mmHg, hyper/hypoglycemia, hyperthermia, and elevated levels of urea (Jannati, Bagheri-Nesami, Sohrabi, Yazdani-Cherati, & Mazdarani, 2014). Park et al. (2014) reported that the added stress of major surgery, in particular cardiac surgery, significantly increased the occurrence of POD. This was due to the complexity of the cardiac surgical procedure and pharmacologic ingredients, including anesthetic substances administered throughout the perioperative phase, coupled with complications endured during the postoperative period.

Brown et al. (2016) hypothesized a correlation between POD following cardiac surgical procedures and an increase in postoperative resource use and management. In order to examine the potential association between POD and increased postoperative resource use, Brown et al. (2016) conducted a randomized control trial to examine the effects of POD on increased length of stay in the ICU. A total of 66 participants were included in the study. The study results demonstrated a 56% occurrence of POD (37 out of 66 patients), with 26 patients (39.4%) diagnosed on post-op day 1, 8 patients (12.1%) diagnosed on post-op day 2, and the remaining 3 delirious patients (4.6%) diagnosed on post-op day 3 (Brown et al., 2016).

Brown et al. (2016) also determined a correlation between increased length of stay in the intensive care unit (LOS-ICU) and delirium, revealing that LOS-ICU was

higher in patients that exhibited delirium (75.6 hours for delirious patients compared to 29.7 hours for patients whom did not exhibit delirium; $p = 0.002$). Additionally, overall hospital LOS was increased in patients that exhibited delirium (9 days versus 7 days for patients whom remained cognitively intact; $p = 0.006$).

Leslie, Marcantonio, Zhang, Leo-Summers, and Inouye (2008) conducted a study to determine the overall one-year healthcare costs related to delirium. A total of 841 participants were included in the controlled trial. Of the 841 participants, 109 individuals exhibited delirious behavior. The109 patients that were deemed delirious were then monitored for a 12-month time frame. The total cost of healthcare resources required to treat those individuals was calculated and compared against the cost of healthcare resources required by the remaining 732 patients that did not exhibit delirium. Leslie et al., (2008) determined that the overall cost of healthcare expenses was approximately 40% higher annually for delirious patients ($69,498 per patient compared to $47,958 annually for each of the remaining participants unaffected by delirium; $p < 0.001$). In addition to increased healthcare costs, Leslie et al. (2008) determined that the overall financial impact of delirium was extensive and exceeded the total healthcare costs of both diabetes mellitus and falls. Likewise, they reported that the findings of their study highlighted the necessity for increased efforts to abate this substantial and costly illness (Leslie et al., 2008).

CAM-ICU. Delirium in cardiac surgical patients is measured utilizing the Confusion Assessment Method for the ICU (CAM-ICU), (Ely & Vanderbuilt University, 2002). CAM-ICU is a modified version and adapted from the Confusion Assessment Method (CAM). The CAM-ICU is a brief and convenient method to determine adequate

cerebral perfusion by assessing a patient's mental status. The CAM-ICU is the measurement tool utilized for this specific patient population due in part to the high level of patient acuity coupled with the potential for surgical and procedural complications during the postoperative period. During the immediate postoperative period, cardiac surgical patients are admitted into the intensive care unit following their surgical procedure. It is then that the registered nurse begins the first of many CAM-ICU measurements. These measurements are carefully documented as they serve as a reference point for each consecutive assessment.

CAM-ICU measures four neurological characteristics (Figure 1). The first feature measured with the CAM-ICU includes an acute alteration or variation in mental status from the standard functioning. The second feature is characterized as lack of concentration, followed by an altered level of alertness. and lastly, disorganized thoughts. In order to characterize the patient as being delirious, both characteristics 1 and 2 must be positive, as well as either characteristic 3 or 4 must also exist (Brummel et al., 2013). The CAM-ICU delirium assessment tools provide an easy-to-follow, sequential guide that allows for the early detection and subsequent mediation of potentially harmful cognitive and neurological effects (Brummel et al., 2013). Additionally, the CAM-ICU is the most widely accepted delirium assessment tool utilized by medical experts and is due in part to its ease of use, brevity of measurement, consistency, and validity (Park et al., 2014).

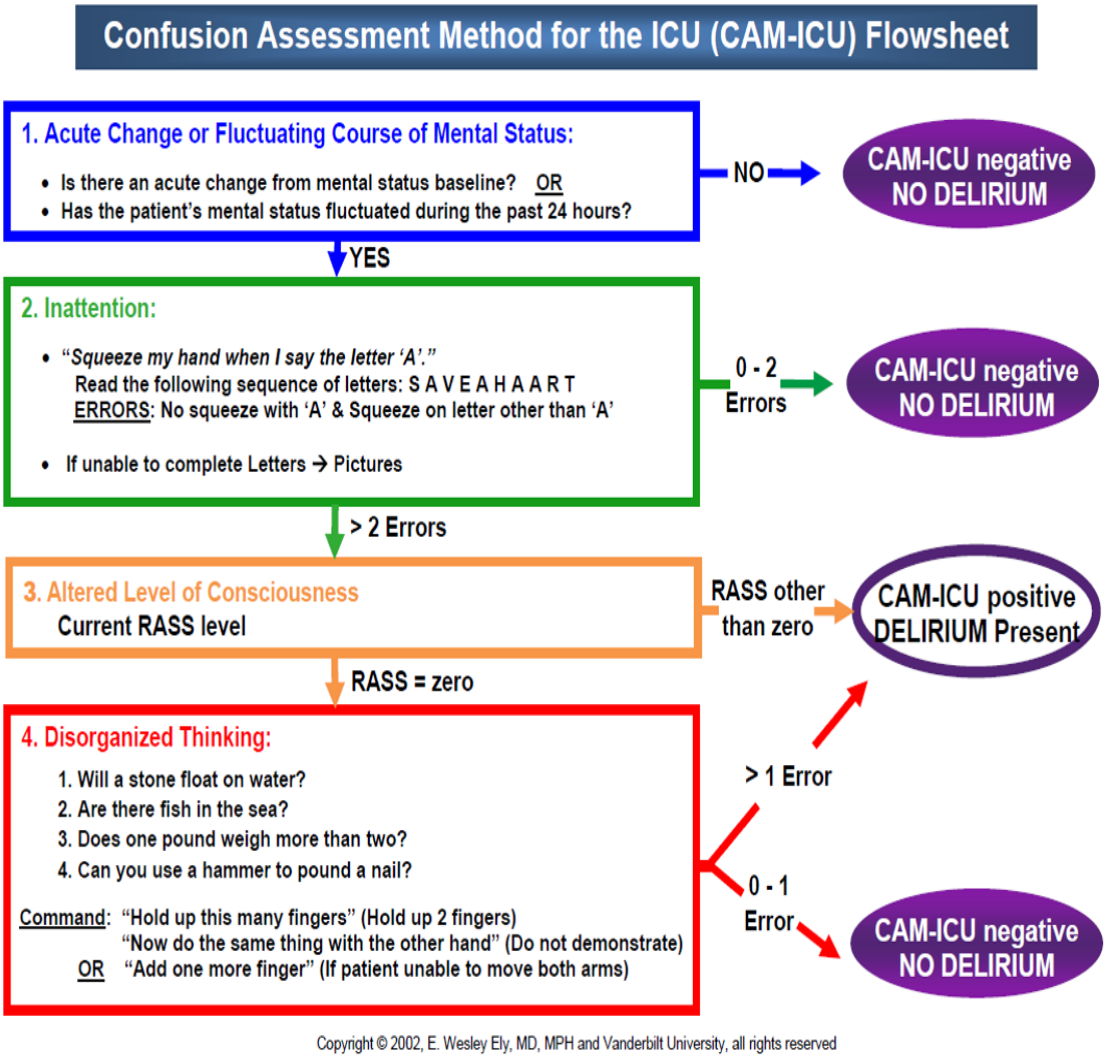

Figure 1. CAM-ICU Assessment Tool

RASS Scoring System. Prior to completing the CAM-ICU, a separate measurement tool must first be utilized. The Richmond Agitation Sedation Scale (RASS) is a required component necessary for accurate measurement and calculation of the CAM-ICU (Nickson, 2015). The RASS measures depth of sedation and assists as an easy and reliable indicator of level of consciousness (Figure 2). A RASS score must be

obtained prior to performing the CAM-ICU. Once a RASS score is obtained, this number is then utilized to assist in the early detection of POD.

RASS score

Richmond Agitation & Sedation Scale				CAM-ICU
Score	**Description**			
+4	Combative	Violent, immediate danger to staff		RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive		
+2	Agitated	Frequent non-purposeful movements, fights ventilator		
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous		
0	Alert & calm			
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice	
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)		
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)		RASS < -2 STOP Recheck later
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Touch	
-5	Un-rousable	No response to voice or physical stimulation		

Figure 2. RASS Scoring Scale (Nickson, 2015).

Guenther et al. (2010) examined the validity and reliability of the confusion assessment method and its ease of use within the intensive care unit. Guenther, et al. (2010), examined the CAM-ICU assessment scores of 54 ICU patients. The CAM-ICU assessments were performed on all participants with the scores then reviewed and confirmed by a psychiatrist and two ICU physicians. Following the accurate diagnosis of delirium utilizing the CAM-ICU flowsheet, it was concluded that the assessment tool had a sensitivity of 88% (95% confidence interval, 69%-98%) and 92% (74%-99%), as well as specificities of 100% (85%-100%), high-level inter-rater reliability (kappa, 0.96; 0.87-1.00), and required 50 seconds (interquartile range, 40-120 seconds) in delirious patients

vs 45 seconds (interquartile range, 40-75 seconds) for those participants without delirium in order to conclude the assessments (Guenther, et al., 2010). Following these findings, Guenther, et al., (2010) concluded that in addition to its sensitivity, specificity, and inter-rater reliability, the CAM-ICU flowsheet is a brief, valid, and reliable bedside delirium assessment instrument. Furthermore, the flowsheet was shown to have infrequent false-negatives, while those that did occur were likely to reflect the fluctuating course along the delirium spectrum.

Cardiac Surgery Procedures

The incidence of POD in vascular and cardiac surgical populations is high (up to 87% of patients) and the risk of mortality increases 10%-20% for every 48 hours that the surgical patient remains in a delirious state (Whitlock et al., 2011). According to Ji et al. (2013), in the United States, coronary artery disease (CAD) remains the leading cause of morbidity and mortality, with a 30-day mortality rate of approximately 1.2% for individuals who have undergone on-pump coronary artery bypass graft (CABG).

Coronary Artery Bypass Graft (CABG). CABG is performed to reestablish adequate blood flow through a coronary vessel that has been significantly narrowed from plaque that has built up over years along the coronary vessel wall occluding blood flow and ultimately the delivery of oxygen to vital organs, primarily the heart. During this procedure, a vessel(s) is harvested from the patient's leg(s) and is reimplanted within the coronary vasculature, bypassing the occluded vessel. During this invasive surgical procedure, the patient requires the use of cardiopulmonary bypass to induce cardioplegia. Cardioplegia allows for the temporary cessation of cardiac activity while continuing to perfuse the vital organs with oxygen-rich blood. The induction of cardioplegia provides

the cardiothoracic surgeon optimal surgical conditions for successful completion of this intricate procedure.

Valve Replacement. Valve replacement procedures are performed to correct a defective or faulty cardiac valve. The malfunctioning valve occurs secondary to coronary disease, as a consequence of an untreated virus occurring throughout the lifespan, or as a result of a congenital disorder. Typically, the mitral and aortic valves are the most commonly replaced. The diseased valve can be stenosed in which the flow of blood is impeded, and this often leads to hypertrophy of the preluding chamber. The replaced valve can either be tissue or mechanical with each offering both advantages and disadvantages to either selection. Additionally, valve replacement surgery can be performed utilizing a transapical approach, penetrating the apex of the heart, transfemorally, guiding the replacement of the valve through the femoral artery, or through a thoracotomy, cutting through the sternum to allow direct access to the heart.

As previously mentioned, the noxious insult of cardiac surgery in and of itself significantly increases the risk of developing POD. According to Ji et al. (2013), major complications following cardiac surgery include POD, acute renal failure (ARF), infection, stroke, perioperative myocardial infarction, coma, heart block, cardiac dysrhythmias, and cardiac arrest. Therefore, the use of dexmedetomidine and survival rates following cardiac surgery have been examined in the literature. Ji et al. (2013) examined the survival rates of cardiac surgical patients during in-hospital stay, at thirty days, and at the one-year mark. A correlation between the intraoperative administration of dexmedetomidine and increased postoperative survival rates were noted. Ji et al. (2013) also noted that following cardiac surgery, the non-dexmedetomidine group

demonstrated an increased morbidity and long-term mortality rate. In the study, it was noted that patients who received dexmedetomidine intraoperatively demonstrated increased survival rates during the in-hospital phase and at the one-year mark, however, no difference was noted in either group at the 30-day mark (Ji et al., 2013). According to Ji et al., (2013) the in-hospital mortality rate for the DEX group was 1.5% versus 4.0% in the non-DEX group (0.357; 95% CI, 0.128 to 0.993; $p = 0.0398$), whereas the one-year mortality rate for the DEX group was 3.2% versus 6.9% in the non-DEX group (0.447; 95% CI, 0.218 to 0.919; $p = 0.0251$). It was also noted that the intraoperative administration of dexmedetomidine during cardiac surgery decreased circulating catecholamines, particularly norepinephrine (NE) concentrations, decreased cardiac contractility and heart rate and decreased overall consumption of myocardial oxygen therefore, ultimately leading to an increase in blood flow to the myocardium (Ji et al., 2013).

Dexmedetomidine

Dexmedetomidine has been found to promote a more natural and physiological sleep cycle without substantial respiratory depression and is associated with reduced opioid requirement (Maldonado et al., 2009). Dexmedetomidine has no effect on acetylcholine, the neurotransmitter located within the neuromuscular junction involved in muscle contraction, therefore it does not contain anticholinergic properties. Furthermore, Dexmedetomidine contains no GABAergic (gamma aminobutyric acid) effects unlike Propofol, that has a direct effect on the GABA neurotransmitter, which is responsible for the inhibition of nerve transmission in the brain (Maldonado et al., 2009).

Dexmedetomidine is a highly-selective α_2 receptor agonist that contains substantial desirable benefits and effects, including anxiolysis, analgesia, sympatholytic, decline in the release of systemic norepinephrine. Thus, significantly enhancing hemodynamic stability, and therefore positively influencing myocardial O_2 supply and demand, thus potentiating the added benefits of myocardial protection (Ji et al., 2013).

Dexmedetomidine is typically used for sedation following cardiac surgery as a bridge to wean patients from mechanical ventilation, however, it also contains the added benefit of anxiolysis following extubation at low-dose infusions. It is also postulated that dexmedetomidine provides anti-delirium capabilities while inflicting minimal respiratory depression and providing significant analgesia (Park et al., 2014). In addition to its sedative properties, dexmedetomidine has also been shown to provide moderate anti-inflammatory effects, as well as a protective benefit for the organs of the vessel-rich group consisting of the heart, lungs, brain, and kidneys (Ji et al., 2013).

Quite often adjuvant pharmacological therapy is utilized in the cardiac surgical population with the intention of treating postoperative pain, anxiety, and delirious behavior. In addition to dexmedetomidine, medications utilized as adjuvant therapy during the perioperative phase include the sedative-hypnotic, propofol; the opioid, morphine; and the benzodiazepine; midazolam or lorazepam.

Adjuvant therapy

Nelson, Muzyk, Bucklin, Burdney, and Gagliardi (2015) explored the use of dexmedetomidine in the prevention of delirium in critically ill ICU patients. In order to examine its effectiveness in decreasing postoperative delirium, Nelson et al. (2015) limited their search to RCTs, controlled trials, and comparative studies. The primary

outcome examined was to assess the effectiveness of dexmedetomidine in the prevention of POD. Additionally, Nelson et al. (2015) theorized that ICU patients sedated with dexmedetomidine would exhibit significantly less episodes of delirium as compared to ICU patients receiving non-dexmedetomidine sedation. By evaluating delirium assessment scores obtained from the Confusion Assessment Method for the ICU (CAM-ICU) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) in conjunction with the Delirium Rating Scale (DRS) combined with the use of dexmedetomidine versus the use of a comparative sedative delirium scores and clinical outcomes were analyzed. Nelson et al. (2015) performed an electronic search in MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews utilizing key search terms including “dexmedetomidine,” “delirium,” and “ICU psychosis.” Study subjects included adults, 18 years of age and older with an ICU hospital admission. A total of 71 studies were initially identified, with 42 of those meeting inclusion criteria, however, an additional 39 were excluded as they were identified as being case reports, nonrandomized trials, or review articles. Ultimately three were evaluated and their findings summarized (Nelson et al., 2015).

In the first RCT examined by Nelson et al. (2015), Pandharipande et al. (2008) performed a randomized, double-blinded study examining ICU patients who were intubated and mechanically ventilated for 24 hours. The patients included in this study were hospitalized for a variety of ailments including sepsis and acute respiratory distress syndrome (ARDS). Individuals with baseline dementia, hemorrhagic stroke, ischemic stroke, and intracranial injury were excluded from the study (Pandharipande et al., 2008). This study consisted of 103 participants ages 45 and older. Study participants were

treated with an infusion of the highly selective α_2 agonist dexmedetomidine, or the benzodiazepine, lorazepam and the occurrence of delirium was evaluated. Participants were followed closely for 12 days and assessed for signs and symptoms of confusion, hallucinations, and restlessness by utilizing the CAM-ICU assessment tool. This study concluded that the patients who received dexmedetomidine as their sedative demonstrated more coma-free days and less delirium, than those treated with lorazepam (7 days dexmedetomidine versus 3 days lorazepam, $p = 0.01$). Additionally, it was noted that these patients had significantly greater time spent within one point of their RASS goal (67% dexmedetomidine versus 55% lorazepam, $p = 0.008$) (Pandharipande et al., 2008). However, although Pandharipande et al. (2008) determined a decrease in the occurrence of delirium, they did note a significant safety issue regarding the occurrence of bradycardia in select patients with the use of dexmedetomidine (Nelson et al., 2015).

In a second RCT study examined by Nelson et al. (2015) authors Shehabi et al. (2008) performed a randomized, double-blinded study and looked at the rates of POD in cardiac surgical patients. The patients included in this study were adults 60 years of age and older who underwent on-pump cardiac surgery. The study consisted of 299 participants; 152 participants were treated with an infusion of the highly selective α_2 agonist dexmedetomidine, versus 147 participants that were treated with the opioid, morphine, and the occurrence of postoperative delirium was then evaluated. Participants were followed closely for the first five days following cardiac surgery and were assessed for delirium utilizing the CAM-ICU assessment tool. Shehabi et al. (2008) concluded that there was no significant difference in the occurrence of postoperative delirium in patients that were sedated with dexmedetomidine versus morphine (8.5% in dexmedetomidine

versus 15% in morphine, $p = 0.088$). However, it is important to note that a severe limitation was noted. The open label use of morphine was used for breakthrough pain in both groups, thus potentially tainting the final outcome of the study. Lastly, Shehabi et al. (2008) also determined a significant safety issue regarding the occurrence of bradycardia in select patients with the use of dexmedetomidine (Nelson et al., 2015).

In the third and final study examined by Nelson et al. (2015) authors Maldonado et al. (2009) compared the incidence of POD in cardiac surgery patients by performing an RCT comparing the varying effects of the highly selective α_2 agonist dexmedetomidine, the sedative-hypnotic, propofol, and the benzodiazepine, midazolam. Participants included were between the ages of 18-89 undergoing elective valve surgery. Patients were followed closely for the first three days following cardiac surgery and delirium indicators were evaluated by implementing the DSM-IV-TR criteria in conjugation with the DRS. Maldonado et al. (2009) concluded that the patients who received dexmedetomidine as their sedative demonstrated less delirium than those treated with either propofol or midazolam (10% dexmedetomidine, 44% propofol, and 44% midazolam in intention-to-treat analysis, $p < 0.001$). Additionally, they determined that those individuals treated with dexmedetomidine who exhibited delirious behaviors were in fact noted to have fewer days of delirium than either the propofol or midazolam groups (2 patient days dexmedetomidine, 45 patient days propofol, and 75 patient days midazolam, $p < 0.001$) (Maldonado et al., 2009). A significant limitation was noted however; as all groups were allotted the use of “as-needed” benzodiazepines, therefore, potentially impacting the significance of the study results.

Next, the theoretical framework will be presented.

Theoretical Framework

The utilization of a theoretical framework in research serves as an organized outline pertaining to a particular theory and provides insight into the research topic of choice. The use of a theoretical framework or conceptual model strengthens the research and supports the reasoning behind why a particular topic requires further study or investigation. Following extensive research, Inouye and Charpentier's (1996) multifactorial model was the preferred theoretical framework selected to guide this research plan.

The Multifactorial Model created by Sharon K. Inouye, MD, MPH and Peter A. Charpentier, MPH was the conceptual framework chosen to address the research topic: does the administration of dexmedetomidine decrease the incidence of POD in adult cardiac surgery patients? Inouye and Charpentier's Multifactorial Model explains the complex relationship between delirium; baseline vulnerability factors, or predisposing factors; and precipitating factors, or noxious insults (Inouye & Charpentier, 1996, p. 852) (Figure 3). During their research phase, Inouye and Charpentier discovered a multifaceted association between the vulnerability that patients experience at baseline (during admission) and those that they experience during hospitalization, known as precipitating factors or insults (Inouye & Charpentier, 1996, p. 852).

Inouye and Charpentier's model describes four axes that are believed to be precipitating factors for delirium. *Axis 1* defines the use of urinary catheters, physical restraints, and being bed-bound as *immobility*, whereas *Axis 2* describes the use of narcotics, anticonvulsants, antiemetics, and tranquilizers as *medications* (Inouye & Charpentier, 1996, p. 855). *Axis 3* explains any *iatrogenic event* as a hospital-acquired

pressure ulcer (HAPU), hemorrhage, urinary tract infection, fluid overload, transfusion reaction, or IV catheter complications, and lastly, *Axis 4* is defined as *intercurrent illness*, which includes infection, respiratory compromise, dehydration, or malnutrition (Inouye & Charpentier, 1996, p. 855). Following a prospective study based on their four axes as described above, Inouye and Charpenter (1996) were able to identify five independent precipitating factors for delirium; those five factors consist of malnutrition, the use of physical restraints, the use of a urinary catheter, greater than three medications added, and any iatrogenic event (p. 855). The Multifactorial Model lends itself to a variety of specialty fields interested in the study of factors influencing delirium. One such research study utilized this conceptual framework and adapted it toward postoperative delirium in the cardiovascular intensive care unit.

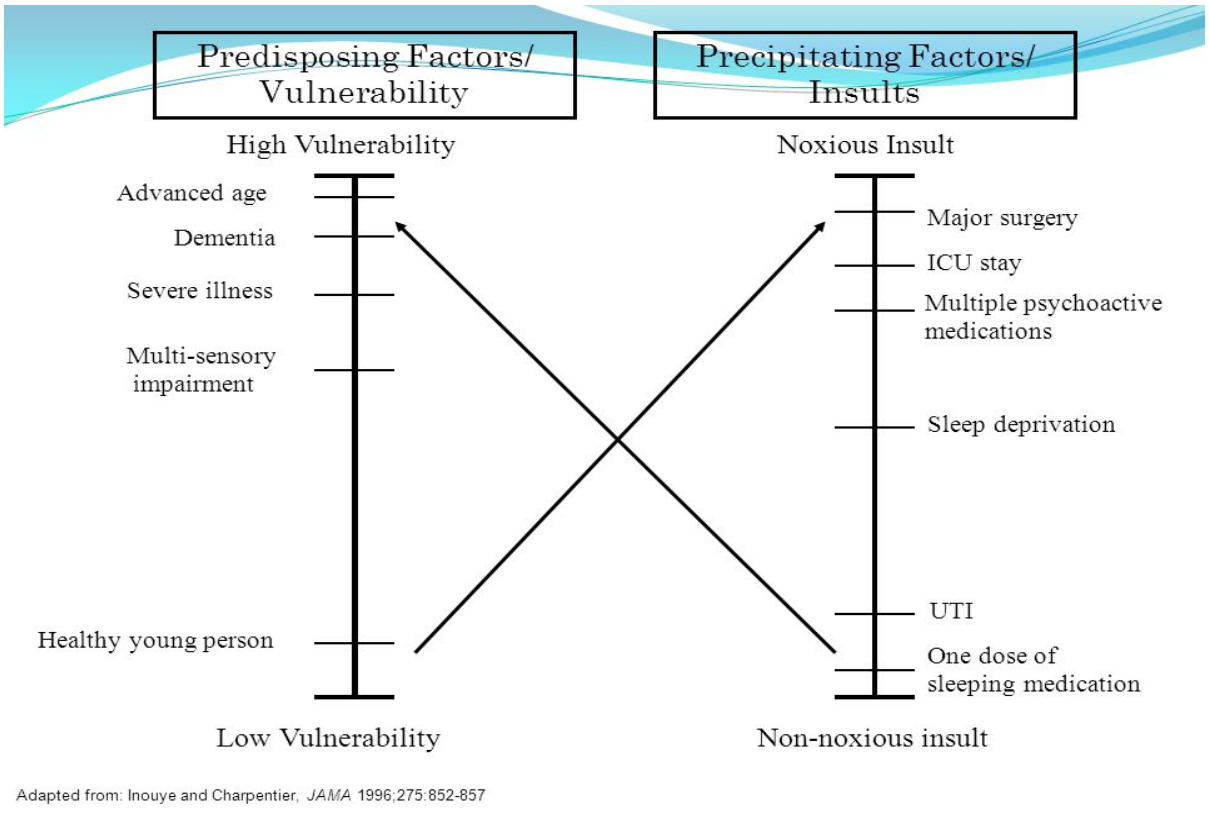

Figure 3. Inouye & Charpentier's Multifactoral Model

Chang, Tsai, Lin, Chen, and Liu (2008) utilized a modified version of Inouye & Charpentier's multifactorial model. In this retrospective chart review, the multifactorial framework for POD in patients following cardiac surgery was described as three phases which include: predisposing factors (preoperative variable), aggravating factors (intraoperative variable), and precipitating factors (postoperative variable). Chang et al., (2008) defined predisposing factors as those that cannot be modified such as body mass index (BMI), ethnicity, age, gender, smoking history, psychiatric history, alcoholism, and past medical history (p. 569). Aggravating factors were explained as: type of surgery performed, time on cardiopulmonary bypass, circulatory arrest time, ischemic time, anesthesia, intraoperative hypothermia and blood transfusions. Additionally, precipitating factors include any of the following: LVEF $\leq$ 30%, postoperative cardiogenic shock, hemorrhage > 1 L, RBC transfusion > 1 L, acute infection (SIRS), HCT < 30%, SaO_2 < 90%, or $PaCO_2$ < 25 or $\geq$ 45 mm Hg (Chang et al., 2008, p. 569). By utilizing Inouye & Charpentier's multifactorial model, Chang et al., (2008) were able to successfully implement a conceptual framework and adapt it toward POD in adult cardiac surgical patients.

The utilization of this conceptual model can be easily adapted toward the research topic questioning the administration of dexmedetomidine and its effects on the incidence of POD in adult cardiac surgical patients. Utilizing the outline presented by Mateo and Foreman (2013), internal factors that should be addressed when reviewing a theory include: clarity, consistency, adequacy, logical development, and level of theory development. In addition, factors that should be addressed regarding external criticism

include reality convergence, utility, significance, discrimination, scope, and complexity (p. 124).

The main concepts of Inouye and Charpentier's Multifactorial Model are clear and easily understood. Key concepts such as the four axes that constitute the conceptual model, as well as the five predisposing independent variables are described sufficiently and are kept consistent throughout their framework. The Multifactorial Model, although adequate to a degree because it explains and covers each of its axes in detail, does require further investigation as to whether early detection of delirium successfully prevents the onset or duration for hospitalized patients. This model has been logically developed, as statements described in the framework are well supported and have been utilized in extensive research. The Multifactorial framework has been utilized and adopted for nearly twenty years and has been frequently applied to numerous medical settings by researchers. Such settings include palliative care, geriatrics, and cardiac surgery.

The Multifactorial Model applies to nursing with the assumption that predisposing factors affect the incidence of delirium in hospitalized patients. The theory does display a utilitarian quality, as it assists the researcher with explaining a phenomenon, as well as generating a hypothesis. However, the theory lends itself to the concept of delirium, therefore it is limited regarding its field of study. Delirium affects a vast number of hospitalized patients; therefore, the utilization of a detailed framework is crucial in the early identification of risk factors affecting patients, thus preventing complications leading to increased length of hospital stay. The Multifactorial Model designed by Inouye and Charpentier does generate a theory that is not sufficiently addressed by other models.

The scope of this theory provides interactive statements that are testable. Additionally, this model is easily applicable to practice within a variety of settings. Lastly, the Multifactorial Model lacks complexity. It is a theory that is easily understood and congruent in regard to its concepts.

Inouye and Charpentier designed a fundamental practice theory that has been adapted toward numerous studies encircling the predisposing factors of delirium. Utilizing the five independent predisposing factors for delirium in addition to the four axes described in the multifactorial model, the effects of dexmedetomidine on the incidence of POD in adult cardiac surgical patients can be further.

In addition to Inouye and Charpentier's Multifactorial Model, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework was also utilized (Moher et al., 2009). PRISMA is an evidenced-based framework that consists of a 27-item checklist (Figure 4) to be used when reporting on or generating a systematic review (PRISMA, 2015). In addition to the PRISMA checklist, the use of a PRISMA flowchart (Figure 5) was implemented. The PRISMA flow diagram consists of four main sections including identification, screening, eligibility, and included studies (Moher, Liberarti, Tetzlaff, Altman, & The PRISMA group, 2009). Utilizing Inouye and Charpentier's Multifactoral Model in conjunction with the PRISMA framework; a systematic review examining the effects of dexmedetomidine on POD in cardiac surgery patients was conducted.

Next, the methods will be presented.

Supplemental Table 2. PRISMA 2009 checklist for reporting of systematic reviews and meta-analyses.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	See title, page 1.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See abstract, page 2.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	See introduction, page 3.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	See introduction, page 3.
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	See methods, page 4.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	See methods, page 3.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	See methods, page 4.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See methods, page 3.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	See methods, page 4.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	See methods, page 4.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	See methods, page 4.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	See supplemental table 1.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	See methods, page 4.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	See supplemental table 1.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	See methods, page 4.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See figure 1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See table 1 and 2.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	See supplemental table 1.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	See table 1 and 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See table 1 and 2.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See results, page 8.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	See results, pages 8-9.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	See discussion, pages 9-10.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	See discussion, pages 10-11.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	See discussion, page 11.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See discussion, page 11.

Figure 4. PRISMA Checklist

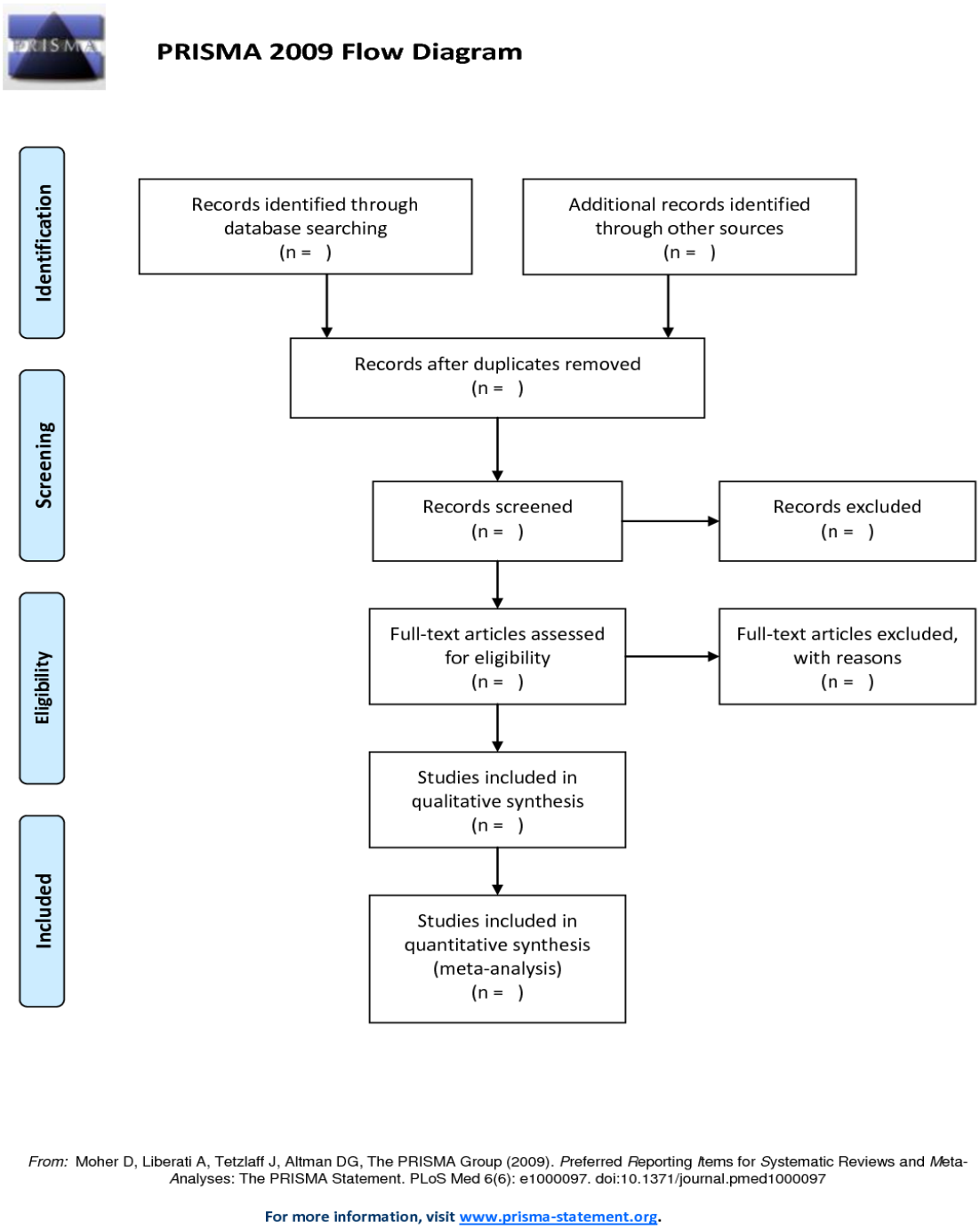

Figure 5. PRISMA Flow Diagram

Method

Purpose

The purpose of this study was to examine if the administration of dexmedetomidine decreased the incidence of POD in adult cardiac surgical patients. According to Mateo and Forman (2014), a study design is the arrangement of research that specifies observations and interventions; and ensures neutrality (p. 135). In order to further investigate this clinical question, a systematic review of multiple RCTs was the method of choice selected. Human subjects did not participate in this evaluation; therefore, International Review Board (IRB) approval was not required for guiding this systematic review.

Inclusion/Exclusion Criteria

Inclusion criteria for the studies included: (a) adults 18 years of age and older, (b) patients undergoing cardiac surgery, (c) the utilization of dexmedetomidine for sedation (d) the use of a comparison sedative(s) for experimental studies, and (e) the use of a delirium assessment tool such as the CAM-ICU or the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-4th Ed.-Text Review), (Spitzer, Gibbon, Skodol, Williams, & First, 2002).

Exclusion criteria for the studies included: (a) pediatric patients, those under the age of 18, (b) surgical patients other than cardiac, (c) dexmedetomidine not utilized as a sedative, and (d) studies that did not include a specific delirium assessment tool (CAM, CAM-ICU, or DSM-IV-TR)

Search Strategy

A detailed search strategy was performed utilizing CINAHL (Cumulative Index to Nursing and Allied Health Literature) as well as MEDLINE/PubMed. An advanced search approach was implemented using keywords “cardiac surgery” AND “dexmedetomidine” AND “delirium.” Restrictions applied to the search were English language and human subjects.

Data Collection

Data collected from individual studies included: study purpose, design, and location; total number of participants, cardiac surgical procedure(s) performed, postoperative sedative protocol initiated including medication and administration dosage. Additionally, the number of patients included in each study group and specific delirium assessment tool implemented were also identified.

Critical Appraisal

Critical appraisal of literature was performed utilizing CASP (*Critical Appraisal Skills Programme*). CASP (Table 1) provides an easy to use 3-step approach for evidence appraisal and offers eight critical appraisal tools to utilize when synthesizing research (Critical Appraisal Skills Programme [CASP], 2017). This invaluable tool assists researchers in determining a study’s strengths, outcomes, and usefulness. Following individual study summary and analysis a complete cross study analysis was implemented.

A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?			
2. Was the assignment of patients to treatments randomized?			
3. Were all of the patients who entered the trial properly accounted for at its conclusion?			
4. Were patients, health workers, and study personnel "blind" to treatment?			
5. Were the groups similar at the start of the trial?			
6. Aside from the experimental intervention, were the groups treated equally?			
B. What are the results?			
7. How large was the treatment effect?			
8. How precise was the estimate of the treatment effect?			
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?			
10. Were all clinically important outcomes considered?			
11. Are the benefits worth the harms and costs?			

Table 1. Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Note. CASP checklist completed on all studies that meet inclusion criteria.

Data Synthesis & Cross Study Analysis

Data synthesis and cross study analysis were completed immediately following critical appraisal of individual studies. The cross-study analysis compared postoperative sedative protocols initiated, including medications administered along with dosage, overall incidence of delirium, total length of delirium, time to extubation, ICU LOS (length of stay), and overall hospital LOS.

Next, the results will be presented.

Results

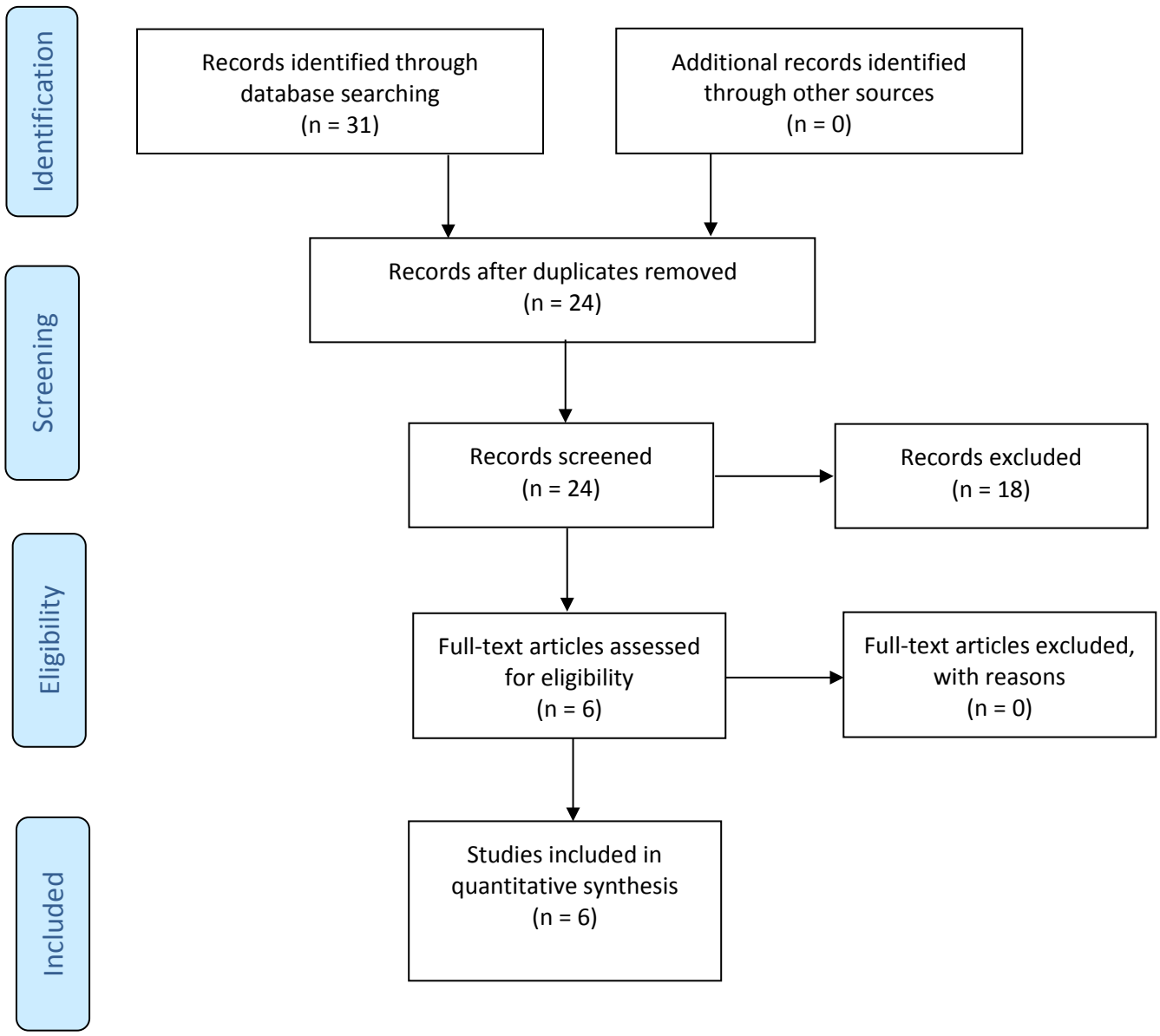

Figure 6. Completed PRISMA flow diagram demonstrating article identification, screening, eligibility, and inclusion (Moher et al., 2009).

The completed flow diagram as depicted in *Figure 6* provides a visual interpretation demonstrating how the final six studies chosen to implement this systematic review were selected. An initial search utilizing the search term “delirium” resulted 14,702 studies among the selected databases. The addition of search term “postoperative” narrowed the resulted studies to 2,047. Next, the search term “cardiac surgery” was added and further narrowed the result to 544 studies. Lastly, “dexmedetomidine” was included in the search terms and a final total of 31 articles resulted. Prior to article screening, 7 articles were excluded as duplicates leaving a total of 24 articles to be screened. Following article screening, 18 studies were excluded for not meeting inclusion criteria as previously identified. Finally, the remaining 6 studies were evaluated and selected to complete this systematic review to determine whether the use of dexmedetomidine in the adult cardiac surgical population decreases the incidence of postoperative delirium.

Each of the six studies identified and reviewed for this systematic review include an explanation of the results with pertinent study findings identified. Study specific data tables are outlined in Appendix A (Tables A1-A6). Key information obtained for the data tables include: study purpose, design, location, sample size, method, and cardiac surgical procedure(s) performed. Next, outcome data collection tables were created with results summarized in Appendix B (Tables B1-B6). Study specific findings identified include: the incidence of delirium, mean length of delirium, time to extubation, ICU LOS (length of stay), and hospital LOS. Critical appraisal data tables of individual studies followed (Appendix C, Tables C1-C6) to assist in assessing the validity, reliability, and

applicability of studies through a series of 11 questions. Lastly, a cross-study analysis data table was created (Appendix D) comparing the results of each study.

Individual Studies

The single-center, randomized, prospective study by Park et al. (2014) (Appendix A, Table A-1) evaluated the postoperative sedative effects of dexmedetomidine associated with a lower incidence of delirium, compared with the postoperative sedative protocol of remifentanil in patients undergoing open-heart surgery with cardiopulmonary bypass (CPB). A total of 142 patients who underwent cardiac surgery were divided into two groups. Group 1, the dexmedetomidine group consisted of 67 participants while the remaining 75 participants were placed in group 2, the remifentanil group. Following cardiac surgery standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine loading dose: 0.5 mcg/kg; maintenance dose: 0.2-0.8 mcg/kg/hr and group 2, remifentanil 1,000-2,500 mcg/hr. The prevalence of delirium was estimated daily in both groups utilizing the CAM-ICU. The CAM-ICU is considered to be the most widely used delirium assessment tool because of its ease of use, reliability, and validity (Park et al., 2014). Cardiac surgical procedures performed included: aortic valvuloplasty, mitral valvuloplasty, coronary artery bypass graft, and tricuspid annuloplasty. All patients underwent cardiac surgery on CPB with a surgical approach utilizing either median sternotomy or right thoracotomy. CPB management for all patients included moderate hypothermia ranging from 26°C-30°C with bypass flows initiated at a rate of 60 mL/kg/min.

Outcomes of this study by Park et al. (2014) (Appendix B, Table B-1) demonstrated that the overall prevalence of delirium during the initial postoperative

period (first three days) was 16% (23 of 142), with 8.96% (6 of 67) occurring in the dexmedetomidine group and 22.67% (17 of 75) in the remifentanil group, which was statistically significant ($p = 0.027$). According to Park et al. (2014) the initial postoperative period was defined as the first 3 days following surgery as previous studies have shown that the highest prevalence of POD occurs during that timeframe. The study found that the mean length of delirium (days) was slightly shorter in the dexmedetomidine group with 3.5 ± 1.87 versus 3.76 ± 4.13 in the remifentanil group, ($p = 0.882$). Time to extubation (hours) was slightly higher in the dexmedetomidine group 22.72 ± 26.36 compared to the remifentanil group 18.60 ± 19.74, ($p = 0.299$). ICU LOS (hours) was also slightly longer in the dexmedetomidine group 67.71 ± 48.41 as opposed to the remifentanil group 61.24 ± 30.57, ($p = 0.353$). Lastly, hospital LOS (days) was examined and was determined to be marginally increased in the dexmedetomidine group 19.96 ± 11.76 whereas the remifentanil group demonstrated an overall hospital LOS of 18.37 ± 8.45 (days), ($p = 0.364$). Additionally, postoperative complications and hemodynamic side-effects were statistically insignificant between both groups (Park et al., 2014).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-1), it appears that the trial addressed a clearly focused issue, all patients involved in the study were randomized, and both groups were similar at the start of the trial; aside from the experimental intervention, both groups were treated equally throughout the study period however, it was also noted that study personnel, healthcare professionals, and patients were not “blinded” to this study. The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general

anesthesia. This study, however, was noted to have several limitations. The first limitation noted was the lack of evaluating long-term neurocognitive effects that delirium has on the cardiac ICU patient. Secondly, there are limitations to the generalizability of the study results as the experiment was conducted in a single medical facility. Lastly, it was possible that POD was underrated because CAM-ICU was estimated only once daily for the first 3 days postoperatively (Park et al., 2014). It was concluded that the administration of dexmedetomidine as a postoperative sedative was associated with significantly lower rates of POD in adult patients undergoing cardiac surgery with CPB (Park et al., 2014).

The prospective, single-blinded, single-center, randomized control trial by Djaiani et al. (2016) (Appendix A, Table A-2) evaluated whether the administration of dexmedetomidine would reduce the incidence of delirium when compared with propofol for postoperative sedation in patients undergoing cardiac surgery with CPB. A total of 183 patients who underwent cardiac surgery were randomly divided into two groups. Group 1, the dexmedetomidine group consisted of 91 participants while the remaining 92 participants were placed in group 2, the propofol group. Following cardiac surgery standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine loading dose: 0.4 mcg/kg; maintenance dose: 0.2-0.7 mcg/kg/hr and group 2, propofol 25-50 mcg/kg/min. The prevalence of delirium was estimated in both groups utilizing the CAM-ICU. Assessment was performed preoperatively (baseline) and postoperatively every 12 hours or more if warranted by the patient's condition for the first 5 days following surgery (Djaiani et al., 2016). Cardiac surgical procedures performed included: coronary revascularization, single-valve repair or replacement, combined coronary

revascularization with a valve repair/replacement, multiple valve repairs/replacements, and redo-sternotomy. All patients underwent cardiac surgery on CPB. CPB management included deep hypothermic circulatory arrest 20°C with bypass flow rates ranging 2.0-2.4 l/min/m^2.

Outcomes of this study by Djaiani et al. (2016) (Appendix B, Table B-2) demonstrated that the overall prevalence of delirium during the initial postoperative period (first five days) was 24.6% (45 of 183), with 17.5% (16 of 91) occurring in the dexmedetomidine group and 31.5% (29 of 92) in the propofol group, ($p = 0.028$). Differences were calculated utilizing a two-tailed Student's t-test. The study demonstrated that the median (range) length of delirium (days) was significantly shorter in the dexmedetomidine group with 2 days (1-4) versus 3 days (1-5) in the propofol group, ($p = 0.04$). Median time to extubation (hours) was also significantly lower in the dexmedetomidine group 5.5 hours (3.5-14.2) compared to the propofol group 7.6 hours (3.8-202.2), ($p = 0.0007$). ICU LOS (hours) was also decreased, but not significantly in the dexmedetomidine group 67.8 (20-214) as opposed to the propofol group 76.5 (17.8-956.5), ($p = 0.38$). Lastly, median hospital LOS (days) was examined and was determined to be decreased in the dexmedetomidine group 7.5 (5-32) whereas the propofol group demonstrated an overall hospital LOS of 10 days (6-74), ($p = 0.054$). Additionally, the overall incidence of postoperative complications, requirement for inotropic support, and hemodynamic side-effects were similar between both groups (Djaiani et al., 2016).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-2), it appears that the trial addressed a clearly focused issue. All patients involved in the study were randomized and both groups were similar at the start

of the trial. Aside from the experimental intervention, both groups were treated equally throughout the study period however, it was also noted that this was a single-blinded study. Therefore, while lack of blinding of dexmedetomidine and propofol infusions was identified for healthcare personnel only, testers of CAM-ICU were unaware of study objectives (Djaiani et al., 2016). The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general anesthesia. This study however was noted to have several limitations. The first limitation noted was the lack of blinding of the dexmedetomidine and propofol infusions. Secondly, there are limitations to the generalizability of the study results as the experiment was conducted in a single medical center. Lastly, the dexmedetomidine infusion was limited to the first 24 hours only and if patients required sedation beyond that time then the infusion was switched to propofol, thus potentially delaying the onset of delirium in the dexmedetomidine group (Djaiani et al., 2016). At the completion of the study, Djaiani et al. (2016) concluded that the administration of dexmedetomidine as a postoperative sedative was associated with significantly lower rates, delayed onset, and shortened duration of POD in adult patients undergoing cardiac surgery with CPB.

The single-center, randomized, prospective study by Maldonado et al. (2009) (Appendix A, Table A-3) evaluated whether the use of dexmedetomidine was associated with a lower incidence of delirium when compared with the current postoperative sedative protocol of either propofol or midazolam in patients undergoing cardiac surgery with CPB. A total of 90 patients who underwent cardiac surgery were divided equally into three groups. Following cardiac surgery standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine loading dose: 0.4 mcg/kg;

maintenance dose: 0.2-0.7 mcg/kg/hr, group 2, propofol 25-50 mcg/kg/hr, and group 3, midazolam 0.5-2 mg/hr. The prevalence of delirium was estimated daily in all groups utilizing the DSM-IV-TR. Cardiac surgical procedures performed included: mitral valve repair/replacement, aortic valve repair/replacement, coronary artery bypass graft, aortic root replacement, and ascending aortic replacement. All patients underwent cardiac surgery on CPB with a surgical approach via a median sternotomy. CPB management included moderate hypothermia ranging from 28°C-30°C with bypass flows maintained between 2.0-2.4 L/min/mP2P.

Outcomes of this study by Maldonado et al. (2009) (Appendix B, Table B-3), demonstrated that the overall prevalence of delirium during the initial postoperative period (first three days) was 34% (31 of 90), with 3% (1 of 30) occurring in the dexmedetomidine group, 50% (15 of 30) occurring in the propofol group, and 50% (15 of 30) occurring in the midazolam group, which was statistically significant ($p < 0.001$). According to Maldonado et al., (2009) the initial postoperative period was defined as the first 3 days postoperatively as previous studies have identified that the highest incidence of POD occurs during that period. The study demonstrated that the mean length of delirium (days) was slightly shorter in the dexmedetomidine group with 2.0 days, versus 3.0 days in the propofol group and 5.4 days in the midazolam group, ($p = 0.82$). Time to extubation (hours) was slightly higher in the dexmedetomidine group 11.9 hours compared to the propofol group 11.1 hours, but lower when compared to the midazolam group 12.7 hours, ($p = 0.64$). ICU LOS (days) was also shorter in the dexmedetomidine group 1.9 days as opposed to the propofol group 3.0 days and midazolam group 3.0 days, ($p = 0.11$). Lastly, hospital LOS (days) was examined and was determined to be

decreased in the dexmedetomidine group 7.1 days versus 8.2 days in the propofol group and 8.9 days in the midazolam group, (p = 0.39).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-3), it appears that the trial addressed a clearly focused issue. All patients involved in the study were randomized, and all 3 groups were divided equally at the start of the trial. Additionally, aside from the experimental intervention, all groups were treated equally throughout the study period. However, it was noted that study personnel, healthcare professionals, and patients were not "blinded" to this study due in part to the milky-white physical characteristic of propofol (Maldonado et al., 2009). The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general anesthesia. This study, however, was noted to have several limitations. The first limitation noted was the lack of blinding of the dexmedetomidine, propofol, and midazolam infusions primarily due to the physical characteristics of the medications. Secondly, there are limitations to the generalizability of the study results as the experiment was conducted in a single medical center, and lastly, there was a dropout rate of 24% (28/118). However, no particular group was favored by the number of patients excluded (Maldonado et al., 2009). Upon completion of the study, Maldonado et al. (2009) concluded that the administration of dexmedetomidine as a postoperative sedative was associated with lower rates of POD in adult patients undergoing cardiac surgery with CPB.

The single-center, double-blinded, randomized controlled clinical trial by Shehabi et al. (2009), (Appendix A, Table A-4) assessed the effect of dexmedetomidine when compared to a morphine-based regimen at equivalent levels of sedation and analgesia, on

the prevention of delirium in patients undergoing cardiac surgery on CPB. A total of 299 patients who underwent cardiac surgery were divided into two groups. Group 1, the dexmedetomidine group consisted of 152 participants while the remaining 147 participants were placed in group 2, the morphine group. Following cardiac surgery standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine loading dose: none; maintenance dose: 0.1-0.7 mcg/kg/hr and group 2, morphine 10-70 mcg/kg/hr. The prevalence of delirium was estimated daily in both groups utilizing the CAM-ICU. Cardiac surgical procedures performed include: CABG, valve replacement procedure, and combination CABG and valve replacement procedure. All patients underwent cardiac surgery on CPB. Standard, nonpulsatile CPB management with cold blood cardioplegia was utilized while MAP (mean arterial pressure) was maintained between 50-70 mmHg with bypass flow rate of 2.4 l/min/m^2.

Outcomes of this study by Shehabi et al. (2009) (Appendix B, Table B-4) demonstrated that the overall incidence of delirium during the initial postoperative period (first five days) was 11.7% (35 of 299), with 8.6% (13 of 152) occurring in the dexmedetomidine group and 15% (22 of 147) in the morphine group, ($p = 0.088$). The study demonstrated that the mean length of delirium (IQR-interquartile range) was significantly shorter in the dexmedetomidine group with 2 days (1-7) versus 5 days (2-12) in the morphine group, ($p = 0.031$). Mean time to extubation (hours) was also significantly lower in the dexmedetomidine group 14 hours (10-18.5) compared to the morphine group 15 hours (10-22), ($p = 0.036$). ICU LOS (hours) was similar in both groups with 45 hours (24-71) in the dexmedetomidine group and 45 hours (24-75) in the morphine group, ($p = 0.148$). Lastly, mean hospital LOS (days) was examined and was

determined to be identical in both groups at 8 days (7-11), (p = 0.501). Additionally, requirement for vasopressor and inotropic support were similar between both groups, however the incidence of bradycardia was higher in the dexmedetomidine group, whereas the occurrence of hypotension was greatest in the morphine group (Shehabi et al., 2009).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-4), it appears that the trial addressed a clearly focused issue. All patients involved in the study were randomized, and both groups were similar at the start of the trial. Additionally, aside from the experimental intervention, both groups were treated equally throughout the study period. Healthcare professionals, patients, and study personnel were "blinded" to the treatment. The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general anesthesia. This study however was noted to have several limitations. The first limitation noted was lack of cerebral perfusion monitoring. Secondly, there are limitations to the generalizability of the study results as the experiment was conducted in a single medical facility, CAM-ICU was performed during the first 5 days only, and the open-label use of morphine in the dexmedetomidine group, although this was noted to take place in a small number of participants (Shehabi et al., 2009). At the completion of the study, Shehabi et al. (2009) concluded that the administration of dexmedetomidine as a postoperative sedative did not reduce the occurrence of POD, however, it was shown to dramatically decrease the duration of delirium, promote early extubation, and attain adequate sedation and analgesia without increasing hypotension in adult patients undergoing cardiac surgery with CPB.

The two-center, double-blinded, placebo-controlled, randomized clinical trial by Li et al. (2017) (Appendix A, Table A-5) investigated the perioperative effects of dexmedetomidine administration on the incidence of postoperative delirium in elderly patients undergoing cardiac surgery. A total of 285 patients who underwent cardiac surgery were divided into two groups. Group 1, the dexmedetomidine group consisted of 142 participants while the remaining 143 participants were placed in group 2, the normal saline (control group). Following cardiac surgery standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine OR loading dose: 0.6 mcg/kg (1^{st} 10 mins) followed by 0.4 mcg/kg/hr intra-operatively, maintenance dose: 0.1 mcg/kg/hr until end of mechanical ventilation. Group 2, normal saline: no administration protocol followed. The prevalence of delirium was estimated daily in both groups utilizing the CAM-ICU. Cardiac surgical procedures performed included: CABG, valve replacement procedure (single or multiple), and combination CABG and valve replacement procedure. CPB with AOC (aortic cross-clamp). Hypothermia management was not a requirement and was utilized in 58% of the cardiac surgical procedures performed.

Outcomes of this study by Li et al., (2017) (Appendix B, Table B-5) demonstrated that the overall prevalence of delirium during the initial postoperative period (first five days) was 6.67% (18 of 285), with 4.9% (7 of 142) occurring in the dexmedetomidine group and 7.7% (11 of 143) in the control group. The study demonstrated that the mean length of delirium (days) was equal in both groups with 2 days (1-3) in the dexmedetomidine group and 2 days (1-4) in the control group. Mean time to extubation (hours) was again similar in both groups with 15.0 hours (13.7-16.3) in the dexmedetomidine group compared to 15.0 hours (13.9-16.1) in the control group. ICU

LOS (hours) was also comparable in both groups with 45 hours (43.5-46.5) in the dexmedetomidine group and 46 hours (44.8-47.2) in the control group. Lastly, mean hospital LOS (days) was examined and there were no differences determined between groups at 9 days (8-10). Additionally, the number of patients needing treatment intraoperatively for tachycardia was decreased in the dexmedetomidine group, whereas the incidence of hypotension intraoperatively requiring treatment was lower in the control group (Li et al., 2017).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-5), it appears that the trial addressed a clearly focused issue. All patients involved in the study were randomized and both groups were similar at the start of the trial. Aside from the experimental intervention, both groups were treated equally throughout the study period. Healthcare professionals, patients, and study personnel were "blinded" to the treatment. The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general anesthesia. This study however was noted to have several limitations. The first limitation noted was the exclusion of patients at high-risk for developing POD (visual/auditory dysfunction, psychiatric disorder, language barrier, and liver/renal impairment). Secondly, CAM-ICU was performed once daily during the first 5 days only, potentially underestimating the number of patients exhibiting delirious symptoms. Lastly, due to the low occurrence of delirium in the control group, the trial was considered underpowered to identify discrepancies between the two groups (Li et al., 2017). At the completion of the study, Li et al. (2017) concluded that the administration of dexmedetomidine as a postoperative sedative did not reduce the

occurrence of POD, however, it was shown to decrease the occurrence of intraoperative tachycardia in adult patients undergoing cardiac surgery.

The single-center, retrospective, cohort study by Wanat et al. (2014), (Appendix A, Table A-6) evaluated the duration (hours) of mechanical ventilation following cardiac surgery in patients receiving dexmedetomidine versus propofol for sedation as a primary endpoint, as well as the incidence of postoperative delirium, ICU LOS, hospital LOS, and requirement of a secondary sedative in patients receiving dexmedetomidine versus propofol for sedation following cardiac surgery as a secondary endpoint. A total of 352 patients who underwent cardiac surgery were divided into two groups. Group 1, the dexmedetomidine group consisted of 33 participants while the remaining 319 participants were placed in group 2, the propofol group. Following cardiac surgery, standardized postoperative sedative protocols were initiated: group 1, dexmedetomidine loading dose: none; maintenance dose: 0.4-0.6 mcg/kg/hr and group 2, propofol 30-50 mcg/kg/hr. The prevalence of delirium was estimated daily in both groups utilizing the CAM-ICU. Cardiac surgical procedures performed included: CABG, CABG with aortic valve surgery, CABG with mitral valve surgery, aortic valve surgery only, and mitral valve surgery only.

Outcomes of this study by Wanat et al. (2014) (Appendix B, Table B-6) demonstrated overall prevalence of delirium during the initial postoperative period was 7.67% (27 of 352), with 9.09% (3 of 33) occurring in the dexmedetomidine group and 7.53% (24 of 319) in the propofol group, with a ($p = 0.747$). The authors determined that the requirement of a second sedative agent was decreased in the dexmedetomidine group with 8 (24.2%) versus 86 (27.0%) in the propofol group, ($p = 0.737$). Time to extubation

(hours) was significantly decreased in the dexmedetomidine group 7.37 ± 4.30 compared to the propofol group 12.88 ± 15.42, (p = 0.042). ICU LOS (days) was somewhat decreased in the dexmedetomidine group 2.55 ± 2.95 as opposed to the propofol group 3.99 ± 4.78, (p = 0.091). Lastly, hospital LOS (days) was examined and was determined to be decreased in the dexmedetomidine group 9.79 ± 6.77 whereas the propofol group demonstrated an overall hospital LOS of 12.42 ± 7.44 (days), (p = 0.052).

When evaluating the integrity of the study utilizing the CASP questionnaire (Appendix C, Table C-6), it appears that the trial addressed a clearly focused issue. This was a retrospective study, therefore, all patients involved in the study were not randomized. At the start of the trial, it was found that both groups were not similar in size. All participants were properly accounted for at its conclusion. It is difficult to surmise if aside from the experimental intervention whether both groups were treated equally throughout the study period. Again, because this study was retrospective in nature, study personnel, healthcare professionals, and patients were not "blinded." The results of this study can be applied to adults undergoing a variety of surgical procedures requiring general anesthesia. This study however was noted to have several limitations. The first limitation noted was that specific medication side effects were not documented; secondly, the large discrepancy among the number of patients who received dexmedetomidine versus the number of patients who received propofol; and lastly, lack of randomization (Wanat et al., 2014). Failure to randomize potentially led to patients being prescribed a sedative based on physician preference, therefore potentially producing a source of bias (Wanat et al., 2014). It was concluded at the completion of the study that the administration of dexmedetomidine as a postoperative sedative was

associated with a significant reduction of mechanical ventilation time, however, no difference was noted regarding the incidence of delirium between both study groups (Wanat et al., 2014).

Cross-Study Analysis

The cross-study analysis table (Appendix D) demonstrates the postoperative sedative protocol initiated for each study, as well as the major outcomes investigated including: incidence of delirium, mean length of delirium, time to extubation, ICU LOS, and hospital LOS. There was one study by Wanat et al. (2014) that did not measure mean length of delirium as a variable. Wanat et al. did, however, investigate the requirement of an additional sedative agent and noted that the incidence was decreased in the dexmedetomidine group (8) when compared with the propofol group (86).

All sedative protocols consisted of dexmedetomidine as the main sedative agent and was compared against Remifentanil (study 1), propofol (study 2, 3, and 6), midazolam (study 3), morphine (study 4), and normal saline (study 5). Overall, the incidence of delirium was decreased in the dexmedetomidine groups (study 1, 2, 3, 4, and 5), but was higher in study 6 when compared to the propofol group. Mean length of delirium was also found to be decreased in the dexmedetomidine groups (study 1,2, 3, and 4), but was equal when compared with normal saline group (study 5) and was not a variable examined in study 6. Time to extubation was found to decreased in the dexmedetomidine groups (study 2, 3, 4, and 6), whereas it was increased when compared to remifentanil (study 1), propofol (study 3), and equal to normal saline (study 5). ICU LOS was decreased in the dexmedetomidine groups (study 2, 3, 5, and 6), but was increased when compared to remifentanil (study 1), yet equal when compared to

morphine (study 4). Lastly, hospital LOS was decreased in the dexmedetomidine groups (study 2, 3, and 6), yet increased when compared with remifentanil (study 1), and equal when compared with morphine (study 4) and normal saline (study 5).

Next, the summary and conclusions will be presented.

Summary and Conclusions

POD is a major complication following surgery and is considered the most common complication among older adults following cardiac surgery with up to 87% of patients being affected (Whitlock et al., 2011). The untoward effects of POD are characterized as restlessness, agitation, combativeness, hallucinations, irritability, and confusion. These consequences place patients and medical personnel in potentially precarious situations. This troublesome behavior is both distressing and perplexing to patients and their loved ones. Furthermore, the risk of mortality increases 10-20% for every forty-eight hours that a patient remains in a delirious state following cardiac surgery (Whitlock et al., 2011). POD increases the duration of mechanical ventilation, increases both ICU and overall hospital length of stay, decreases patient functional status, and increases the risk of mortality. The use of antihistamines, benzodiazepines, muscle relaxants, and meperidine (often used to treat postoperative shivering) should be avoided in this vulnerable population (Whitlock et al., 2011).

Dexmedetomidine, a highly selective α_2 agonist, inhibits the release of norepinephrine presynaptically causing analgesia and inhibits central nervous system stimulation in the postsynaptic neurons causing decreased blood pressure and heart rate; together, contributing to the effects of analgesia, anesthesia, and sedation (Naaz &Ozair, 2014). Benefits of dexmedetomidine for sedation include the promotion of a biological sleep pattern, production of minimal respiratory depression, and its association with decreased narcotic use (Maldonado et al., 2009).

The purpose of this systematic review was to investigate whether dexmedetomidine decreases the occurrence of POD in the adult cardiac surgical

population. A comprehensive literature review was completed using CINAHL, PubMed, and Medline focusing on the pathology of postoperative delirium, the physiology of cardiac surgery, and the pharmacodynamics of dexmedetomidine. A dual theoretical framework was chosen to assist in the identification of eligible studies based on inclusion criteria. PRISMA was the primary framework utilized for this systematic review and consists of a 27-item checklist and four-phase flowchart. Additionally, the multifactorial model by Inouye and Charpentier was also utilized. The multifactorial model describes four axes that explain the complex relationship between baseline vulnerability or predisposing factors; and precipitating factors or noxious insults contributing to the development of delirium (Inouye & Charpentier, 1996).

Individual study analysis was completed on the final six studies that met inclusion criteria. Study specific data tables were created identifying key information pertinent to each study. Data outcome tables were then created to determine the effect of dexmedetomidine on postoperative delirium following cardiac surgery. Next, critical appraisal of individual RCTs was performed utilizing the Critical Appraisal Skills Programme (CASP) checklist. Lastly, a cross study analysis table was created comparing the postoperative sedative protocol initiated, the incidence of delirium, the duration of delirium, time to extubation, ICU LOS, and overall hospital LOS among the six studies selected.

The use of dexmedetomidine as a postoperative sedative is becoming increasingly popular, particularly among ICU and anesthesia providers. Due to its highly selective α_2 properties, dexmedetomidine provides patients the benefits of pain control and anxiolysis with minimal respiratory depression, thus making it a frontrunner for fragile patient

populations. However, dexmedetomidine does not come without its share of potential adverse effects. Dexmedetomidine has been associated with hypotension at low concentrations and hypertension at high concentrations; therefore, it is considered to have a biphasic effect on blood pressure. One of the most notable adverse effects is transient bradycardia which can be exaggerated with rapid infusion or bolus.

There were several limitations identified when completing this systematic review. Lack of blinding was a limitation noted in some studies. Two of the studies included in the systematic review were double-blinded; one was single-blinded; and the remaining three were not blinded. Another limitation noted was the length of time that certain studies allowed patients to remain on a dexmedetomidine infusion. One study in particular transitioned patients who required intubation greater than 24 hours from a dexmedetomidine infusion to a propofol infusion; therefore, potentially affecting study results. Additionally, delirium assessment was performed once per day for the postoperative period defined by that study's designers. Some studies defined the initial postoperative period as the first three days; whereas other studies identified the postoperative period as the first five days. Delirium that occurred after that initial postoperative period was not included thus potentially affecting study results. Lastly, the lack of a definitive preoperative cognitive screening tool to assess patients at risk for postoperative cognitive dysfunction was also noted to be lacking in some studies.

The findings of this systematic review determined that in the adult cardiac surgical population, dexmedetomidine was associated with a decreased incidence of POD. Additionally, of those that did develop POD, the mean length of delirium was

decreased in the dexmedetomidine group. Lastly, the results for time to extubation, ICU LOS, and hospital LOS varied amongst the six studies examined.

Next, the recommendations and implications for advanced nursing practice will be presented.

Recommendations and Implications for Advanced Nursing Practice

With the induction of general anesthesia for cardiac surgery, patients succumb to the multitude of anesthetic agents administered to them. It is of paramount importance for the anesthesia provider to ensure that medications are administered to the patient based on necessity and not on habit alone. Often, medications administered during induction can render side effects lasting beyond the perioperative period. Potential triggers of postoperative delirium that can occur during the perioperative period include hypotension, hypoxemia, electrolyte imbalances, pain, sepsis, and alcohol/drug withdrawal (Mantz, Hemmings, & Boddaert, 2010). It is imperative that the anesthesia provider heed the slightest changes during the operative period and intervene appropriately in order to avert potentially devastating outcomes.

A study by Riker et al. (2009), found that patients who were sedated with dexmedetomidine spent significantly less time on mechanical ventilation and developed less delirium when compared to midazolam, a benzodiazepine. This study and others like it provide a viable option in the selection of postoperative sedatives for mechanically vented patients following cardiac surgery. The anesthesia provider should initiate the dexmedetomidine infusion in the operating room prior to patient transfer of care to the ICU, thus allowing for maximum benefit and efficacy. Avoiding medications such as benzodiazepines in the older population during the perioperative period has also been shown to decrease the incidence of POD. Medications are one of the most common causes of postoperative delirium and are also the most treatable (Mantz et al., 2010). Avoiding polypharmacy, particularly in the elderly population decreases the incidence of POD significantly. Educating anesthesia providers and advanced practice nurses

concerning this significant predicament is essential. Additionally, educating providers regarding the multifactorial components associated with the development of POD is crucial for prevention or at a minimum decreasing the severity of cognitive dysfunction. According to Mantz et al., (2010), sleep deprivation is a major contributor to the development of POD, thus it is essential to avoid unnecessary disturbances to the postoperative patient particularly during periods of rest or while asleep. Additionally, the use of dexmedetomidine is known to resemble a natural sleep pattern, therefore it is a frontrunner for cardiac surgery patients requiring sedation, anxiolysis, and pain relief with minimal respiratory depression.

Prevention is key! Minimizing risk factors, identifying at risk patients, early recognition, and swift intervention are all crucial steps necessary to avoid untoward sequela of POD. Although anesthesia providers have limited interaction with the surgical patient prior to surgery; thorough pre-admission testing including identification of at-risk or high-risk patients should be determined by the APRN and must be communicated with the patient care team. Collaboration between the surgeon, anesthesia provider, and healthcare team is necessary when an at-risk or high-risk patient is identified. Providing a seamless transition for patients from one care team to the next prior to and throughout their surgical process is paramount to ensure that gaps and possibly misdiagnosis of POD is averted. Continuity of care is essential to providing this seamless transition beginning with thorough preoperative testing, continuing through the perioperative period, progressing through recovery, and culminating with patient discharge. This partnership among healthcare providers allows for optimal patient care and satisfactory outcomes.

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Appendix A

Table A-1

Study Specific Data

Study 1: Park, J. B., Bang, S. H., Chee, H. K., Kin, J. S., Lee, S. A., & Shin, J. K. (2014). Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. *The Korean Journal of Thoracic and Cardiovascular Surgery*, 47(3), 249-254.

Aim	Design	Site	Sample	Method	Procedure
Investigate the postoperative sedative effects of dexmedetomidine associated with a lower incidence of delirium, compared with the current postoperative sedative protocol of remifentanil in patients undergoing open-heart surgery with CPB.	Single-center, randomized, prospective study. Group 1-dexmedetomidine Group 2-remifentanil	Konkuk University Medical Center, Department of Thoracic and Cardiovascular Surgery; Seoul, Korea.	142 patients who underwent cardiac surgery were divided into two groups. Group 1 (n=67) dexmedetomidine Group 2 (n=75) remifentanil All patients underwent cardiac surgery on CPB.	Postoperative sedative protocol initiated: Group 1-dexmedetomidine loading dose: 0.5 mcg/kg; maintenance dose: 0.2-0.8 mcg/kg/hr. Group 2-remifentanil 1,000-2,500 mcg/hr. Prevalence of delirium estimated daily via the CAM-ICU.	AVP only, AVP with MVP, AVP with CABG, MVP only, and MVP with TA. Surgical approach utilizing either median sternotomy or right throracotomy in conjunction with CPB. CPB management included moderate hypothermia ranging from (26°C-30°C) with bypass flows initiated at a rate of 60 mL/kg/min.

Note. CPB-cardiopulmonary bypass, AVP-aortic valvuloplasty, MVP-mitral valvuloplasty, CABG-coronary artery bypass graft, TA-tricuspid annuloplasty, CAM-ICU-confusion assessment method for the intensive care unit

Appendix A

Table A-2

Study Specific Data

Study 2: Djaiani, G., Silverton, N., Fedorko, L., Carroll, J., Styra, R., Rao, V., & Katznelson, R. (2015). Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: A randomized controlled trial. *American Society of Anesthesiologists,* 124 (2), 362-368.

Aim	Design	Site	Sample	Method	Procedure
Investigate whether the administration of dexmedetomidine would reduce the incidence of delirium when compared with propofol for postoperative sedation in patients undergoing cardiac surgery with CPB.	A prospective, randomized, single-blinded, single-centered, controlled clinical trial. Group 1- dexmedetomidine Group 2- propofol	Toronto General Hospital, University Health Network, Department of Anesthesia and Pain Management, Division of Cardiovascular Surgery; Toronto, Ontario, Canada.	183 patients who underwent cardiac surgery were randomly divided into two groups. Group 1 (n=91) dexmedetomidine Group 2 (n=92) propofol All patients underwent cardiac surgery on CPB.	Postoperative sedative protocol initiated: Group 1- dexmedetomidine loading dose: 0.4 mcg/kg; maintenance dose: 0.2-0.7 mcg/kg/hr. Group 2- propofol 25-50 mcg/kg/min. Presence of delirium estimated daily via the CAM-ICU.	Coronary revascularization, single-valve repair or replacement, combined coronary revascularization with a valve repair/replacement, multiple valve repairs/replacements, redo-sternotomy. CPB management included deep hypothermic circulatory arrest (20°C) with bypass flow rates ranging 2.0-2.4 l/min/m^2.

Note. CPB-cardiopulmonary bypass, CAM-ICU-confusion assessment method for the intensive care unit

Appendix A

Table A-3

Study Specific Data

Study 3: Maldonado, J. R., Wysong, A., Van Der Starre, P. J. A., Block, T., Miller, C., & Reitz, B. A. (2009). Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*, 50(3), 206-217.

Aim	Design	Site	Sample	Method	Procedure
Investigate whether the use of dexmedetomidine (a selective α_2-adrenergic receptor-agonist with analgesic, sedative, and antinociceptive effects) was associated with a lower incidence of delirium when compared with the current postoperative sedative protocol of either propofol or midazolam in patients undergoing cardiac surgery with CPB.	Single-center, randomized, prospective study. Group 1-dexmedetomidine Group 2-propofol Group 3-midazolam	Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Department of Anesthesiology, and the Department of Cardiovascular Surgery; Stanford, California.	90 patients who underwent cardiac surgery were divided equally into three groups. Group 1 (n=30) dexmedetomidine Group 2 (n=30) propofol Group 3 (n=30) midazolam All patients underwent cardiac surgery on CPB.	Postoperative sedative protocol initiated: Group 1-dexmedetomidine loading dose: 0.4 mcg/kg; maintenance dose: 0.2-0.7 mcg/kg/hr. Group 2-propofol 25-50 mcg/kg/min. Group 3-midazolam 0.5-2 mg/hr. Prevalence of delirium estimated daily via the DSM-IV-TR.	MVR, AVR, MVR & AVR, aortic root replacement, ascending aortic replacement, and CABG Surgical approach via median sternotomy in conjunction with CPB. CPB management included moderate hypothermia ranging from (28°C-30°C) with bypass flows maintained between (2.0-2.4 L/min/mP2P).

Note. CPB-cardiopulmonary bypass, MVR-mitral valve repair/replacement, AVR-aortic valve repair/replacement, CABG-coronary artery bypass graft, DSM-IV-TR-Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Text Revision)

Appendix A

Table A-4

Study Specific Data

Study 4: Shehabi, Y., Grant, P., Wolfenden, H., Hammond, N., Bass, F., Campbell, M., & Chen, J. (2009). Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: A randomized controlled trial (dexmedetomidine compared to morphine-DEXCOM study). *Anesthesiology*, 111(5), 1075-1084.

Aim	Design	Site	Sample	Method	Procedure
To assess the effect of dexmedetomidine (an α_2 agonist) when compared to a morphine-based regimen at equivalent levels of sedation and analgesia, on the prevention of delirium in patients undergoing cardiac surgery.	Single-center, randomized, double-blinded, controlled clinical trial. Group 1- dexmedetomidine Group 2- morphine	Prince of Wales Hospital, Division of Cardiac and Critical Care Services, Clinical Program of Acute Care; Sydney, Australia.	299 patients who underwent cardiac surgery were divided into two groups. Group 1 (n=152) dexmedetomidine Group 2 (n=147) morphine All patients underwent cardiac surgery on CPB.	Postoperative sedative protocol initiated: Group 1- dexmedetomidine loading dose: none maintenance dose: 0.1-0.7 mcg/kg/hr. Group 2- morphine 10-70 mcg/kg/hr. Prevalence of delirium estimated daily via the CAM-ICU.	CABG, valve replacement procedure, combination CABG and valve replacement procedure. Standard, nonpulsatile CPB management with cold blood cardioplegia was utilized. MAP maintained between 50-70 mmHg with bypass flow rate of 2.4 l/min/m^2.

Note. CPB-cardiopulmonary bypass, CABG-coronary artery bypass graft, CAM-ICU-confusion assessment method for the intensive care unit, MAP-mean arterial pressure

Appendix A

Table A-5

Study Specific Data

Study 5: Li, X., Yang, J., Nie, X. L., Zhang, Y., Li, X. Y., Li, L. H., Wang, D. X., & Ma, D. (2017). Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS ONE*, 12(2), 1-15.

Aim	Design	Site	Sample	Method	Procedure
Investigate the perioperative effects of dexmedetomidine administration on the incidence of postoperative delirium in elderly patients undergoing cardiac surgery.	Randomized, double-blinded, placebo-controlled, two-centered clinical trial. Group 1- dexmedetomidine Group 2- normal saline	Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine; Beijing, China. Fuwai Hospital, National Center for Cardiovascular Diseases, Department of Anesthesiology, Chinese Academy of Medical Sciences and Peking Union Medical College; Beijing, China.	285 patients who underwent cardiac surgery were divided into two groups. Group 1 (n=142) dexmedetomidine Group 2 (n=143) normal saline (control group)	Perioperative sedative protocol: Group 1- dexmedetomidine in OR: 0.6 mcg/kg (1st 10 mins) followed by 0.4 mcg/kg/hr intra-op, maintenance dose: 0.1 mcg/kg/hr until end of mechanical ventilation. Group 2- normal saline no administration protocol followed. Prevalence of delirium estimated daily via the CAM-ICU.	CABG, valve replacement (single or multiple), CABG and valve replacement(s). CPB with AOC and hypothermia management was not a requirement and was utilized in 58% of the cardiac surgical procedures performed.

Note. CABG-coronary artery bypass graft, CAM-ICU-confusion assessment method for the intensive care unit, AOC-aortic cross clamping, CPB-cardiopulmonary bypass

Appendix A

Table A-6

Study Specific Data

Study 6: Wanat, M., Fitousis, K., Boston, F., & Masud, F. (2014). Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery. *Methodist DeBakey Cardiovascular Journal*, 10(2), 111-117.

Aim	Design	Site	Sample	Method	Procedure
Primary endpoint: Investigate duration (hrs) of mechanical ventilation following cardiac surgery in patients receiving dexmedetomidine versus propofol for sedation. Secondary endpoints: investigate incidence of postoperative delirium, ICU LOS, hospital LOS, and requirement of a secondary sedative in patients receiving dexmedetomidine versus propofol for sedation following cardiac surgery.	Single-center, retrospective, cohort study. Group 1- dexmedetomidine Group 2- propofol	Houston Methodist Hospital, Houston Methodist DeBakey Heart & Vascular Center; Houston, Texas.	352 patients who underwent cardiac surgery were divided into two groups. Group 1 (n=33) dexmedetomidine Group 2 (n=319) propofol	Postoperative sedative protocol initiated: Group 1- dexmedetomidine 0.4-0.6 mcg/kg/hr. Group 2- propofol 30-50 mcg/kg/hr. Prevalence of delirium estimated daily via the CAM-ICU.	CABG, CABG with aortic valve surgery, CABG with mitral valve surgery, aortic valve surgery only, mitral valve surgery only.

Note. LOS-length of stay, CABG-coronary artery bypass graft, CAM-ICU-confusion assessment method for the intensive care unit

Appendix B

Table B-1

Outcome Data Collection

Study 1: Park, J. B., Bang, S. H., Chee, H. K., Kin, J. S., Lee, S. A., & Shin, J. K. (2014). Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. *The Korean Journal of Thoracic and Cardiovascular Surgery*, 47(3), 249-254.

	Dexmedetomidine (n=67)	Remifentanil (n=75)	*P*-value
Incidence of delirium	6 (8.96)	17 (22.67)	0.027
Mean length of delirium (days)	3.5 ± 1.87	3.76 ± 4.13	0.882
Time to extubation (hrs)	22.72 ± 26.36	18.60 ± 19.74	0.299
ICU LOS (hrs)	67.71 ± 48.41	61.24 ± 30.57	0.353
Hospital LOS (days)	19.96 ± 11.76	18.37 ± 8.45	0.364

Note. The overall prevalence of delirium during the initial postoperative period (first three days) was 16% (23 of 142), with 8.96% (6 of 67) occurring in the dexmedetomidine group and 22.67% (17 of 75) in the remifentanil group, with a p value <0.05. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing the Student t-test.

Appendix B

Table B-2

Outcome Data Collection

Study 2: Djaiani, G., Silverton, N., Fedorko, L., Carroll, J., Styra, R., Rao, V., & Katznelson, R. (2015). Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: A randomized controlled trial. *American Society of Anesthesiologists*, 124 (2), 362-368.

	Dexmedetomidine (n=91)	Propofol (n=92)	*P*-value
Incidence of delirium	16 (17.5)	29 (31.5)	0.028
Duration of delirium (days), median (range)	2 (1-4)	3 (1-5)	0.04
Time to extubation (hrs), median (range)	5.5 (3.5-14.2)	7.6 (3.8-202.2)	0.0007
ICU LOS (hrs), median (range)	67.8 (20-214)	76.5 (17.8-956.5)	0.38
Hospital LOS (days), median (range)	7.5 (5-32)	10 (6-74)	0.054

Note. The overall prevalence of delirium during the initial postoperative period (first five days) was 24.6% (45 of 183), with 17.5% (16 of 91) occurring in the dexmedetomidine group and 31.5% (29 of 92) in the propofol group, with a p value <0.05. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing a two-tailed Student's t-test.

Appendix B

Table B-3

Outcome Data Collection

Study 3: Maldonado, J. R., Wysong, A., Van Der Starre, P. J. A., Block, T., Miller, C., & Reitz, B. A. (2009). Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*, 50(3), 206-217.

	Dexmedetomidine (n=30)	Propofol (n=30)	Midazolam (n=30)	*P*-value
Incidence of delirium	1/30 (3%)	15/30 (50%)	15/30 (50%)	<0.001
Mean length of delirium (days)	2.0 (0)	3.0 (3.1)	5.4 (6.6)	0.82
Intubation time (hrs)	11.9 (4.5)	11.1 (4.6)	12.7 (8.5)	0.64
ICU LOS (days)	1.9 (0.9)	3.0 (2.0)	3.0 (3.0)	0.11
Hospital LOS (days)	7.1 (1.9)	8.2 (3.8)	8.9 (4.7)	0.39

Note. The overall prevalence of delirium during the initial postoperative period (first three days) was 34% (31 of 90), with 3% (1 of 30) occurring in the dexmedetomidine group, 50% (15 of 30) occurring in the propofol group, and 50% (15 of 30) occurring in the midazolam group, with a p value <0.05. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing independent *t*-tests.

Appendix B

Table B-4

Outcome Data Collection

Study 4: Shehabi, Y., Grant, P., Wolfenden, H., Hammond, N., Bass, F., Campbell, M., & Chen, J. (2009). Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: A randomized controlled trial (dexmedetomidine compared to morphine-DEXCOM study). *Anesthesiology*, 111(5), 1075-1084.

	Dexmedetomidine (n=152)	Morphine (n=147)	*P*-value
Incidence of delirium (%)	13 (8.6%)	22 (15%)	0.088
Mean length of delirium (IQR)	2 [1-7]	5 [2-12]	0.031
Time to extubation (hrs)	14 (10-18.5)	15 (10-22)	0.036
ICU LOS (hrs)	45 (24-71)	45 (24-75)	0.148
Hospital LOS (days)	8 (7-11)	8 (7-11)	0.501

Note. IQR-interquartile range. The overall incidence of delirium during the initial postoperative period (first five days) was 11.7% (35 of 299), with 8.6% (13 of 152) occurring in the dexmedetomidine group and 15% (22 of 147) in the morphine group, with a *p* value of 0.088. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing an unpaired Student t-test.

Appendix B

Table B-5

Outcome Data Collection

Study 5: Li, X., Yang, J., Nie, X. L., Zhang, Y., Li, X. Y., Li, L. H., Wang, D. X., & Ma, D. (2017). Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS ONE,* 12(2), 1-15.

	Dexmedetomidine (n=142)	Normal Saline (n=143)	*P*-value
Incidence of delirium	7 (4.9%)	11 (7.7%)	0.341
Mean length of delirium (days)	2 (1-3)	2 (1-4)	0.328
Time to extubation (hrs)	15.0 (13.7-16.3)	15.0 (13.9-16.1)	0.044
ICU LOS (hrs)	45.0 (43.5-46.5)	46.0 (44.8-47.2)	0.788
Hospital LOS (days)	9 (8-10)	9 (8-10)	0.826

Note. The overall prevalence of delirium during the initial postoperative period (first five days) was 6.67% (19 of 285), with 4.9% (7 of 142) occurring in the dexmedetomidine group and 7.7% (11 of 143) in the control group, with a *p* value of 0.341. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing the Student t-test.

Appendix B

Table B-6

Outcome Data Collection

Study 6: Wanat, M., Fitousis, K., Boston, F., & Masud, F. (2014). Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery. *Methodist DeBakey Cardiovascular Journal*, 10(2), 111-117.

	Dexmedetomidine (n=33)	Propofol (n=319)	*P*-value
Incidence of delirium	3 (9.09%)	24 (7.53%)	0.747
Requirement of 2nd sedative agent	8 (24.2%)	86 (27.0%)	0.737
Time to extubation (hrs)	7.37 ± 4.30	12.88 ± 15.42	0.042
ICU LOS (days)	2.55 ± 2.95	3.99 ± 4.78	0.091
Hospital LOS (days)	9.79 ± 6.77	12.42 ± 7.44	0.052

Note. The overall prevalence of delirium during the initial postoperative period was 7.67% (27 of 352), with 9.09% (3 of 33) occurring in the dexmedetomidine group and 7.53% (24 of 319) in the propofol group, with a *p* value of 0.747. *P* values less than 0.05 were recognized as statistically significant. *P*-values calculated utilizing the Student t-test.

Appendix C

Table C-1

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 1: Park, J. B., Bang, S. H., Chee, H. K., Kin, J. S., Lee, S. A., & Shin, J. K. (2014). Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. *The Korean Journal of Thoracic and Cardiovascular Surgery,* 47(3), 249-254.

A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?			X
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B) What are the results?			
7. How large was the treatment effect?	142 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	Significant decrease in POD in dexmedetomidine group		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. POD-postoperative delirium

Appendix C

Table C-2

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 2: Djaiani, G., Silverton, N., Fedorko, L., Carroll, J., Styra, R., Rao, V., & Katznelson, R. (2015). Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: A randomized controlled trial. *American Society of Anesthesiologists*, 124 (2), 362-368.

A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment? **	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B) What are the results?			
7. How large was the treatment effect?	183 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	Significant decrease in POD in dexmedetomidine group vs propofol group		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. **Lack of blinding of dexmedetomidine and propofol infusions was identified, however testers of CAM-ICU were unaware of study objectives.

Appendix C

Table C-3

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 3: Maldonado, J. R., Wysong, A., Van Der Starre, P. J. A., Block, T., Miller, C., & Reitz, B. A. (2009). Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*, 50(3), 206-217.

A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?			X
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B) What are the results?			
7. How large was the treatment effect?	90 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	Significant decrease in POD in dexmedetomidine group versus propofol and midazolam groups		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. POD-postoperative delirium

Appendix C

Table C-4

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 4: Shehabi, Y., Grant, P., Wolfenden, H., Hammond, N., Bass, F., Campbell, M., & Chen, J. (2009). Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: A randomized controlled trial (dexmedetomidine compared to morphine-DEXCOM study). *Anesthesiology*, 111(5), 1075-1084.

A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B) What are the results?			
7. How large was the treatment effect?	299 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	Reduced duration, but not incidence of POD in dexmedetomidine group versus the morphine group		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. POD-postoperative delirium

Appendix C

Table C-5

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 5: Li, X., Yang, J., Nie, X. L., Zhang, Y., Li, X. Y., Li, L. H., Wang, D. X., & Ma, D. (2017). Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS ONE*, 12(2), 1-15.

A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B) What are the results?			
7. How large was the treatment effect?	285 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	Incidence of POD was not decreased in the dexmedetomidine group when compared with the control group		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. POD-postoperative delirium

Appendix C

Table C-6

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 6: Wanat, M., Fitousis, K., Boston, F., & Masud, F. (2014). Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery. *Methodist DeBakey Cardiovascular Journal*, 10(2), 111-117.			
A) Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?			X
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?			X
5. Were the groups similar at the start of the trial?			X
6. Aside from the experimental intervention, were the groups treated equally?		X	
B) What are the results?			
7. How large was the treatment effect?	352 cardiac surgical patients		
8. How precise was the estimate of the treatment effect?	No significant decrease in POD in dexmedetomidine group versus propofol group		
C) Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context? (or to the local population?)	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Note. POD-postoperative delirium

Appendix D

Cross Study Analysis

Author, Year	**Postoperative Sedative Protocol**	**Outcome: Incidence of Delirium**	**Outcome: Mean Length of Delirium (days)**	**Outcome: Time to Extubation (hrs)**	**Outcome: ICU LOS (hrs)**	**Outcome: Hospital LOS (hrs)**
Study 1 (Park et al., 2014)	Dexmedetomidine Loading dose: 0.5 mcg/kg Maintenance dose: 0.2-0.8 mcg/kg/hr Remifentanil Infusion: 1,000-2,500 mcg/hr	The overall prevalence of delirium during the initial postoperative period (first three days) was 16% (23 of 142), with 8.96% (6 of 67) occurring in the dexmedetomidine group and 22.67% (17 of 75) in the remifentanil group.	Decreased in the dexmedetomidine group when compared to the remifentanil group (3.76 ± 4.13).	Increased in the dexmedetomidine group (22.72 ± 26.36) when compared to the remifentanil group (18.60 ± 19.74).	Increased in the dexmedetomidine group (67.71 ± 48.41) when compared to the remifentanil group (61.24 ± 30.57).	Increased in dexmedetomidine group (19.96 ± 11.76) when compared to the remifentanil group (18.37 ± 8.45).
Study 2 (Djaiani et al., 2015)	Dexmedetomidine Loading dose: 0.4 mcg/kg Maintenance dose: 0.2-0.7 mcg/kg/hr Propofol Infusion: 25-50 mcg/kg/min	The overall prevalence of delirium during the initial postoperative period (first five days) was 24.6% (45 of 183), with 17.5% (16 of 91) occurring in the dexmedetomidine group and 31.5% (29 of 92) in the propofol group.	Decreased in the dexmedetomidine group (2 days) when compared to the propofol group (3 days).	Decreased in dexmedetomidine group (5.5 hrs) when compared to the propofol group (7.6 hrs).	Decreased in dexmedetomidine group (67.8 hrs) when compared to the propofol group (76.5 hrs).	Decreased in dexmedetomidine group (7.5 days) when compared to the propofol group (10 days).

Study 3 (Maldonado et al., 2009)	Dexmedetomidine Loading dose: 0.4 mcg/kg Maintenance dose: 0.2-0.7 mcg/kg/hr Propofol Infusion: 25-50 mcg/kg/min Midazolam Infusion: 0.5-2 mg/hr	The overall prevalence of delirium during the initial postoperative period (first three days) was 34% (31 of 90), with 3% (1 of 30) occurring in the dexmedetomidine group, 50% (15 of 30) occurring in the propofol group, and 50% (15 of 30) occurring in the midazolam group.	Decreased in the dexmedetomidine group (2 days) when compared with the propofol (3 days) and midazolam groups (5.4 days).	Increased in the dexmedetomidine group (11.9 hrs) when compared with the propofol group (11.1 hrs) but decreased when compared with the midazolam group (12.7 hrs).	Decreased in the dexmedetomidine group (1.7 days) when compared with the propofol and midazolam groups (3.0 days) respectively.	Decreased in the dexmedetomidine group (7.1 days) when compared with the propfol (8.2 days) and midazolam groups (8.9 days) respectively.
Study 4 (Shehabi et al., 2009)	Dexmedetomidine No loading dose Maintenance dose: 0.1-0.7 mcg/kg/hr Morphine Infusion: 10-70 mcg/kg/hr	The overall incidence of delirium during the initial postoperative period (first five days) was 11.7% (35 of 299), with 8.6% (13 of 152) occurring in the dexmedetomidine group and 15% (22 of 147) in the morphine group.	Decreased in the dexmedetomidine group (2 days) when compared with the morphine group (5 days).	Decreased in dexmedetomidine group (14 hrs) when compared to the morphine group (15 hrs).	Equal in both the dexmedetomidine and morphine groups (45 hrs).	Equal in both the dexmedetomidine and morphine groups (8 days).

Study 5 (Li et al., 2017)	Dexmedetomidine In OR: 0.6 mcg/kg (1st 10 mins) followed by 0.4 mcg/kg/hr intra-op Maintenance dose: 0.1 mcg/kg/hr until end of mechanical ventilation. Normal saline No administration protocol followed	The overall prevalence of delirium during the initial postoperative period (first five days) was 6.67% (19 of 285), with 4.9% (7 of 142) occurring in the dexmedetomidine group and 7.7% (11 of 143) in the control group.	Equal in both the dexmedetomidine and control groups (2 days).	Equal in both the dexmedetomidine and morphine groups (15 hrs).	Slightly decreased in the dexmedetomidine group (45 hrs) compared to the control groups (46 hrs).	Equal in both the dexmedetomidine and control groups (9 days)
Study 6 (Wanat et al., 2014)	Dexmedetomidine Infusion: 0.4-0.6 mcg/kg/hr. Propofol Infusion: 30-50 mcg/kg/hr.	The overall prevalence of delirium during the initial postoperative period was 7.67% (27 of 352), with 9.09% (3 of 33) occurring in the dexmedetomidine group and 7.53% (24 of 319) in the propofol group.	Mean length of delirium was not a variable measured in this study, conversely, the requirement of an additional sedative agent was reviewed and revealed that the incidence was decreased in the dexmedetomidine group (8) when compared with the propofol group (86).	Decreased in the dexmedetomidine group (7.37 ± 4.30) when compared with the propofol group (12.88 ± 15.42).	Decreased in the dexmedetomidine group (2.55 ± 2.95) when compared with the propofol group (3.99 ± 4.78).	Decreased in the dexmedetomidine group (9.79 ± 6.77) when compared with the propofol group (12.42 ± 7.44).

Note. All data tables discussed in the cross-study analysis are included under Appendices A, B, and C.