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Role of Dexmedetomidine on Outcomes after Elective Cardiac Surgery

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Abstract

Open heart surgery is commonly performed for coronary artery disease and valvular diseases worldwide. Certain postoperative complications, such as atrial arrhythmias, delirium, renal injury and persistent incisional pain remain common and hinder recovery and have enormous cost implications. The etiologies of these complications are linked with the inflammatory response associated with surgery and cardiopulmonary bypass. There is increasing evidence that, dexmedetomidine, an alpha-2 adrenergic agonist used for conscious sedation, may reduce the risk of these events due to its favorable pharmacologic effects on the heart and anti-inflammatory properties. This paper addresses the pertinent pharmacologic effects of dexmedetomidine on cardiac physiology and the current evidence for use of perioperative dexmedetomidine to prevent postoperative complications after cardiac surgery.

Keywords: Dexmedetomidine; Alpha-2 adrenergic agonist; Cardiac surgery; Atrial arrhythmias; Delirium; Renal function; Chronic postsurgical pain (CPSP)

Abbreviations

AF: Atrial Fibrillation; AV: Atrioventricular; AKI: Acute Kidney Injury; CPB: Cardiopulmonary Bypass; CABG: Coronary Artery Bypass Grafting; CKD: Chronic Kidney Disease; CPSP: Chronic Postsurgical Pain; HR: Heart Rate; ICU: Intensive Care Unit; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; IRI: Ischemia/Reperfusion Injury; JET: Junctional Ectopic Tachycardia; MAP: Mean Arterial Pressure; OAA/S: Observer's Assessment of Alertness Score of Sedation; POD: Postoperative Delirium; PTPS: Post-Thoracotomy Pain Syndrome; RBC: Red Blood Cell; TNF-alpha: Tumor Necrosis Factor-Alpha; VAS: Visual Analogue Scales

Introduction

Dexmedetomidine, an alpha-2 adrenergic agonist with known sedative and analgesic properties [1-3]. U.S. Food and Drug Administration suggested it for procedural and critical care sedation. It is widely used for this purpose and has an excellent efficacy and safety record. Like any drug, dexmedetomidine presumably has ancillary side effects and benefits. Likely consequences are reduced risk of atrial fibrillation (AF) and flutter, delirium, renal injury and reduced persistent incisional pain. It also causes reduction in blood pressure, bradycardia, and inhibition of platelet aggregation, renin release and insulin secretion [3]. Dexmedetomidine has been used successfully in anesthesia for neurosurgery, cardiac surgery, and bariatric surgery, as well as for sedation in the intensive care unit (ICU) [4-8].

Open heart surgery is the mainstay treatment for heart diseases like coronary artery disease, congenital or valvular heart diseases, which requires the use of cardiopulmonary bypass (CPB). A combination of CPB, surgical trauma, and ischemia-reperfusion elicit a systemic inflammation, which is characterized by surge in inflammatory cytokines and activation of immune cells. This response is associated with many postoperative organ injuries. Recovery period after cardiac surgery is frequently affected with different complications [9]. Postoperative atrial arrhythmia and delirium are the most common complications encountered after coronary artery bypass grafting (CABG) surgery. Postoperative atrial arrhythmias affect morbidity, mortality, prolong ICU and hospital stay, and increase costs related to surgery [**10**]. Furthermore delirium is an important prognostic determinant of hospital outcomes [**11**].

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Effect of Dexmedetomidine on Cardiac Function and Coronary Blood Flow

Dexmedetomidine has several complex physiological effects on the heart. Firstly, there is a direct dose-dependent cardio-protective effect of dexmedetomidine on reperfusion injury. Additionally when given at high doses it has favorable subendocardial-to-subepicardial blood flow ratio providing better functional recovery from myocardial stunning [12,13]. With its sympatholytic effect, it reduces heart rate and consequently myocardial oxygen demand, so that dexmedetomidine is a preferable sedative agent particularly in cardiac patients [14].

Dexmedetomidine may cause coronary vasoconstriction attributed to its alpha-agonist effects. Kundra et al. [15] assessed the effect of dexmedetomidine on coronary diameter in patients undergoing percutaneous coronary intervention. Dexmedetomidine was shown to reduce coronary diameter by around 14% but simultaneously reduces heart rate by 13% (myocardial oxygen demand), therefore maintaining myocardial oxygen demand-supply ratio. Also attributed to the alpha agonist effects is mild hypotension and frequently associated with younger patients with high vagal tone.

Similarly in a recently published study by Chi et al. [16] dexmedetomidine reduces myocardial damage in patients undergoing off-pump CABG. Versus placebo, dexmedetomidine significantly decreased levels of serum cardiac troponin I and creatinine kinase MB. The attenuation of cardiac enzymes suggested the cardio-protective role of dexmedetomidine, although the exact mechanism has yet to be identified [16].

In a pharmacodynamics study of healthy males, low concentrations of dexmedetomidine reduced myocardial perfusion by 27% from baseline and a 23% reduction in myocardial oxygen demand [17]. High dexmedetomidine plasma concentration had no effect on either myocardial perfusion or rate–pressure product. In this study it has been shown that during the low infusion rate systolic myocardial function was attenuated by sympatholysis, and during the high infusion rate after load was increased. This study showed that levels that exceed the therapeutic level appear to be well tolerated, while maintaining myocardial perfusion and do not provoke myocardial ischemia.

Dexmedetomidine shows an anti-ischemic effect also related to sympatholysis and improves myocardial oxygen balance with preferred blood flow distribution to the endocardium [16]. Dexmedetomidine inhibits the increase in cTnI and CK-MB, and attenuates the pro-inflammatory cytokines production such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and interleukin-8 (IL-8), and increases anti-inflammatory cytokine interleukin-10 (IL-10) production. These findings show that dexmedetomdine attenuates inflammation in addition to myocardial protection potential in CABG with bypass. Increased concentrations of dexmedetomidine caused to decreases in both cardiac output and heart rate (HR), and memory as well as progressive increases in sedation and analgesia [18]. Moreover biphasic dose–response relation for mean arterial pressure (MAP), pulmonary arterial pressure, and vascular resistances, and a reduction of the cold presser response also were observed.

After the administration of dexmedetomidine the respiratory rate, end-tidal carbon dioxide, and systolic-diastolic-mean arterial pressure did not change, however significant bradycardia was seen [19]. As two markers of sinus nodal function, baseline sinus cycle length, and corrected sinus node recovery time were both lengthened with the administration of dexmedetomidine. Atrioventricular (AV) nodal function was lengthened significantly. Dexmedetomidine increased the atrial refractory period and reduced atrial excitability. Dexmedetomidine depressed sinus and AV nodal function in pediatric patients significantly without electrocardiogram interval changes, showed a trend toward lower heart rates. While neither spontaneous AV nodal block nor significant bradycardia were not reported in this study. In an animal study dexmedetomidine inhibited electrophysiological effects on pacemaker cells in sinoatrial nodes which may not be facilitated by alpha 2-adrenoreceptor [20]. In a recent study the incidence of AF was significantly lower in patients given dexmedetomidine compared those who received propofol (13.6% vs. 36.4%). Similarly in another study the median onset of AF watched to be delayed in patients who had received dexmedetomidine compared with control patients [21]. After repair of tetralogy of Fallot the incidence of junctional ectopic tachycardia (JET) is 5.6%-14% [22], and dexmedetomidine has shown to be beneficial for preventing perioperative JET in this kind of patients.

There are many rationales to use dexmedetomidine in cardiac surgery. In a study by Kabukçu et al. [23] HR and mean arterial pressure were reported to be relatively decreased with dexmedetomidine infusion when compared to baseline values. Authors did not encounter severe bradycardia or hypotension requiring intervention. They determined no response to sternotomy and bypass. During the CABG, dexmedetomidine provides a stable hemodynamic status and can be safely used. Furthermore, dexmedetomidine was found to decrease the need of inhalational anesthetics required for cardiac surgery and another recent study demonstrated that dexmedetomidine combined with ketamine had significant cardio-protective effects in cardiac surgery compared to inhalational agent combined with opioids [24].

Cardiac surgery and CPB strongly triggers an inflammatory response. Increased levels of pro-inflammatory cytokines can be detected during and after cardiac surgery [25]. AF after cardiac surgery seems to be in response to a pro-inflammatory state [26]. Sepsis and subsequently multi organ dysfunction remains as one of the leading reasons of death after cardiac surgery and both states are characterized by an uncontrolled inflammatory response. Clinical studies suggest that dexmedetomidine has anti-inflammatory effects [27]. IL-6, IL-8 and TNF-α levels were significantly decreased with dexmedetomidine treatment. Moreover, in a model of septic shock it has shown that the administration of dexmedetomidine is associated with less impairment of exogenous lactate clearance, and lower arterial and portal lactate levels [28].

Atrial Arrhythmias after Cardiac Surgery

The incidence of AF after cardiac surgery ranges from 15%-50% depending on the cardiac surgical procedure, patient population, and perioperative exposure to prophylactic interventions [29,30]. A large single-center clinic trial (N = 999: University-affiliated medical center) found a 30.5% incidence of AF after coronary and/or valve surgery [29]. The risk of AF after cardiac surgery was excessive in patients older than 65 years with left atrial enlargement and mitral valve disease. In a recent registry analysis the overall incidence of AF was 17.1% [31]. Independent risk factors for AF in this trial included advanced age, smoking history, hypertension, congestive heart failure, urgent surgery, and emergency coronary artery bypass grafting. Although AF may occur at any time after cardiac surgery,

it most commonly occurs within 4 days of surgery, with a peak incidence on postoperative day 2 [32].

Inflammation seems to play a significant role in pathogenesis of AF after cardiac surgery [26]. Cardiac surgery causes local and systemic inflammation, which has been shown to be related with AF and facilitate re-entry. Previously defined effect on cardiac electrophysiology and inflammation makes dexmedetomidine a reasonable prophylactic drug for postoperative AF. Supporting these, in a recent retrospective study, including 765 cardiac patients received dexmedetomidine for postoperative sedation in ICU, and 17,011 cardiac patients who did not [33], the incidence of atrial arrhythmias were reported lower for patients who received dexmedetomidine postoperatively. In another study, the results suggest that in cardiovascular surgery patients incidence of AF after extubation can be reduced by adequate sedation with dexmedetomidine during the nighttime [34].

Delirium after Cardiac Surgery

Delirium is an acute cognitive dysfunction defined by confusion, pathological changes in consciousness, and fluctuating inattention [35]. This is a symptom of acute illness and usually occurs in patients after cardiac surgery [36] and prolongs ICU and hospital stay. Particularly patients undergoing on-pump cardiac surgery are considered at high risk [11]. In a review article, old age, history of cerebrovascular disease, psychiatric impairment and cognitive dysfunction, receiving peri-operative Red Blood Cell (RBC) transfusions, and type of surgery and were preoperative and intraoperative predictors for postoperative delirium development. Intra-operative variables, such as length of CPB or intra- operative platelet transfusion were not investigated yet [36,37]. In a recent study delirium occurred in 26 % of ICU patients who underwent cardiac surgery [38]. Authors stated that CPB duration, low MAP, low hemoglobin levels, low body temperature, high norepinephrine requirements, and transfusions of blood products were significant intra-operative risk factors in terms of intra-operative variables. Platelet transfusions were only independent predictor in multivariate logistic regression analysis. This suggests that during cardiac surgery different events might promote post-operative delirium.

Dexmedetomidine has anti-inflammatory properties, decreases use of opioids and benzodiazepines that contribute to delirium, and provides sedation very similar to natural sleep that can attenuate delirium seen after cardiac surgery. In a recent analysis of 194 patients who underwent cardiac surgery, delirium occurred in 26 % of the ICU patients [38]. In another study article in press postoperative delirium and stroke also were decreased significantly in the dexmedetomidine group [38]. This study found that perioperative use significantly reduced in-hospital and operative mortality and was correlated with improved early survival rates in elderly patients undergoing cardiac surgery. The authors' results further suggested that perioperative intravenous dexmedetomidine was related with a reduced incidence of postoperative stroke and delirium after cardiac surgery.

Studies estimating delirium after cardiac surgery with dexmedetomidine have mixed results. In a prospective randomized clinical study, results showed that dexmedetomidine based postoperative sedation significantly reduced delirium when compared with propofol in elderly patients after cardiac surgery [39]. Dexmedetomidine administration resulted in reduced incidence, delayed beginning, and shortened interval of Postoperative Delirium (POD). The study suggests that dexmedetomidine sedation prevents one out of every eight delirium cases. Furthermore, due to reduced incidence and shortened length of POD, this approach was cost effective. Postoperative sedation practices have undergone an evolution process by targeting a more balanced regimen of hypnotic- and analgesia-based sedation. Unlike other sedatives, which are frequently used in the critically ill patients, dexmedetomidine has a unique mechanism of exhibiting sedative, anxiolytic, and analgesic effects without respiratory depression. Moreover, in critically ill patients dexmedetomidine improves the quality of sleep, primarily affecting the non REM sleep pattern [40,41]. Since it is a α2-adrenergic receptor agonist, has also been shown to have notable opioid-sparing effect. In addition, dexmedetomidine has poor anticholinergic effects and has been shown to reduce the inflammatory response of CPB [42]. Dexmedetomidine may contribute to the decreased incidence and duration of POD with a combination of all of these unique properties.

Renal Function after Cardiac Surgery

Adult cardiac surgery is significantly associated with the occurrence of postoperative acute kidney injury (AKI). According to its definition the incidence and outcomes of AKI may vary [43]. AKI increases the morbidity and mortality substantially after operation. In a prospective cohort study the overall incidence of AKI was found 31.2% [44]. The overall hospital mortality was 1.9% and was significantly higher in AKI group (5.4%). Especially CABG combined valve surgery, aneurysm surgery, heart transplantation, is considered as high-risk surgeries. Male gender, high age and BMI, incidence of hypertension and chronic heart failure, preexisting chronic kidney disease (CKD), long CPB time, intra-operative hypotension were preoperative and intraoperative risk factors of AKI occurrence after cardiac surgery.

The effect of dexmedetomidine on the renal function has been extensively studied. There are multiple mechanisms that dexmedetomidine can influence kidney functions. Cardiac surgery activates sympathetic nervous system; dexmedetomidine-induced sympatholysis might reduce risky hemodynamic events resulting in prevention of AKI.

Ischemia-reperfusion injury is one of the most important causes of acute renal failure. In a recent animal model was studied to explore whether dexmedetomidine has any protective effect against renal ischemia/reperfusion injury (IRI) [45]. Renal IRI resulted more CD3 T-cell infiltration and unregulated the expression of TNF-α, ICAM-1, IL-1β, HMGB1 and TLR4. Additionally renal IRI resulted in significant renal injury, as evidenced by inflammatory reaction and renal parenchymal loss characterized by tubular atrophy, rarefaction of peritubular capillaries, and podocyte depletion. While, all these changes were reduced by the administration of dexmedetomidine.

In accordance with the above, several small clinical studies have investigated the renal protective role of dexmedetomidine after cardiac surgery. In a randomized trial by Cho et al. of 200 patients (100 treatment vs. 100 placebo) undergoing valvular heart surgery. Those who receive perioperative dexmedetomidine infusion had a lower incidence of AKI versus placebo (21% vs. 38%) and shorter length of ICU stay [46]. Furthermore, of those who developed AKI, dexmedetomidine group had significantly lower severity versus the control group. Similarly, a randomized placebo-controlled trial by Balkanay et al. [47] reported that dexmedetomidine use after CABG showed a dose-dependent renal protective effect. Although

conventional renal function tests such as creatinine were not significantly different among control and treatment groups, serum levels of neutrophil gelatinase-associated lipocalin, a sensitive biomarker for renal injury, were significantly lower in the treatment group.

In another study it has been showed that dexmedetomidine infusion after CPB surgery reduced the incidence of AKI (26.1% vs. 33.75%) [48]. In addition, dexmedetomidine use after surgery was more likely to reduce the occurrence of AKI in those with preoperative normal kidney function and mild CKD after cardiac surgery. Administration of dexmedetomidine after surgery was also associated with reduced incidence of any complication and mortalities within 30-days.

Chronic Pain after Cardiac Surgery

Chronic postsurgical pain (CPSP) is frequently seen complication after many surgical procedures, including cardiac surgery. After cardiac surgeries the incidence of CPSP varies from 9.5% to 56%. Pain following thoracotomy is of moderate to severe nature. Treatment of thoracotomy pain is a critical task. Thoracotomy pain has acute effects throughout postoperative period and affects the respiratory mechanics, which has an important impact on morbidity. Inadequately treated thoracotomy pain in the acute phase may also cause to chronic pain syndrome. In their study on 948 cases that had undergone thoracotomy, Maguire et al. [27] determined the postoperative chronic pain as 57% between 7-12 months, 36% between 4-5 years and 21% between 6-7 years [49]. In a recent study authors reported the prevalence of CPSP at 5 years after cardiac surgery of 3.8% is lower than previously reported [50]. The majority of patients (89.8%) did not report postsurgical pain, neither 1 year for 5 years after surgery.

The present Italian survey is the largest one assessing the prevalence of postsurgical pain after rehabilitation following cardiac surgery, up to 3 years after the intervention. Their results show that 20% of patients were still suffering from pain 3 years after surgery, mainly at the sternotomy site, which was severe in one-quarter of the patients. Results from this large multicenter survey indicate that the prevalence of pain at the 3-year time point after cardiac surgery was significantly lower than that reported by the 3-month and 1-year groups; however, one out of five patients still complained of pain at 3 years after the intervention, with the symptom scored as severe in one quarter of the patients. Moreover, up to one-third of the patients aged above 75 years in the 3-year group still reported pain [51].

Why some patients develop persistent incisional pain remains unknown. But one theory is that severe acute pain, such as a scalpel blade cutting through skin, provokes activation of high-threshold peripheral sensory neurons which signal the presence, location, and intensity of the injury. Normally, peripheral sensory neuron activation fades once the stimulus is removed. Inflammatory pain is the increased pain sensitivity that occurs in reaction to tissue injury and inflammation and is termed peripheral sensitization. Peripheral sensitization results from the local effect of inflammatory mediators, including prostanoids released from injured and inflammatory cells, on the peripheral terminals of high-threshold sensory neurons. Inflammatory pain remains until the surgical wound has healthy. If a focus of ongoing inflammation persists, so will the pain. But peripheral pain can also provoke central sensitization, which is an increase in the excitability of spinal neurons because of persistent nociceptive afferent input from peripheral neurons. It thus seems likely that good control of acute postoperative pain and inflammation by aggressive early pain management reduces the risk of persistent incisional pain by blunting central sensitization [52,53].

Dexmedetomidine has anti-inflammatory and analgesic properties. Anti-inflammatory properties of dexmedetomidine have been previously described. Clonidine has been widely given as an analgesic adjuvant treatment in perioperative conditions and chronic pain therapy [54]. Dexmedetomidine comes from same family of drugs with clonidine using the same receptors with different affinity.

The incidence of post-thoracotomy pain syndrome (PTPS) in the dexmedetomidine group was 22% patients, however 52% patients in the control group had PTPS [2]. In the progression neuropathic syndromes the role of the sympathetic nervous system of has been well known. Sympathetic overstimulation can provoke a sympathetic pain. Additionally sympathetic stimulation may also be aggravating the increased inflammatory processes in neuropathic pain syndromes. Dexmedetomidine prevents sympathetic stimulation by exhibiting sympatholytic activity, and could be an effective pre-emptive therapy for neuropathic pain syndrome in PTPS.

It has been shown that when dexmedetomidine added to intravenous patient-controlled analgesia, the efficacy of morphine had improved. This combination decreased the postoperative analgesia and postoperative morphine consumption by 30%, and decreased the morphine-induced side effects [55]. Alpha 2-adrenerjic receptor agonists and opioids act by different mechanisms and therefore their combination makes a synergistic analgesic effect without increasing the complications [54].

Dexmedetomidine can be effective on persistent postoperative pain formation either by decreasing inflammation, which plays a crucial role in maintaining of peripheral sensation, and/or providing better acute pain control which is blamed as an important factor in chronic pain formation. In a recent study authors aimed to compare fentanyl, remifentanil and dexmedetomidine in terms of hemodynamic stability, postoperative pain control and achievement of sedation postoperatively. Results showed that showed that compared with other groups, hypnosis, and the modified observer's assessment of alertness (OAA/S) score of sedation were significantly lower in dexmedetomidine group after arrival at the PACU, whereas the pain Visual analogue scales (VAS) scores and BIS were not significantly different from other groups [27]. HR and blood pressure in the dexmedetomidine-received group were significantly lower than those of other groups. At sedative doses the patients received dexmedetomidine showed better postoperative hemodynamic stability than those received remifentanyl or fentanyl, and demonstrated a similar effect of pain control as remifentanyl group and fentanyl group with patient awareness during sedation.

Pharmaco-Economics

Using dexmedetomidine in the postoperative period is that it is relatively expensive compared to other sedative drugs? However, the complications including AF associated with other cheaper sedative drugs are extremely costly. The costs of using Dexmedetomidine for preventing atrial arrhythmias as compared to the cost of cheaper sedatives and the costs of treating the associated complications has not been addressed. Therefore, assessing the cost-effectiveness of Dexmedetomidine needs to be investigated as well.

Summary

Dexmedetomidine, an alpha-2 agonist, is a proven effective and safe sedative for use in the intensive care setting and for conscious sedation. Dexmedetomidine has gradually gained popularity in the perioperative period due to its ability to reduce anesthetics and opioid consumption. There is increasing clinical evidence that perioperative infusion of dexmedetomidine is protective against myocardial complications, delirium, renal injury and persistent incisional pain after cardiac surgery. Existing studies are limited by heterogeneous surgical population and infusion rates, but nonetheless it demonstrates dexmedetomidine is a useful adjunct in patients in elective cardiac surgery. However, large multi-center prospective studies are required to truly measure the benefits of routine use of perioperative dexmedetomidine in cardiac surgery, especially its economic impact.

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