

Utility of Dexmedetomidine in Paediatric Cardiac Surgery: A Systematic Review and Meta-Analysis

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Abstract:

Dexmedetomidine is a selective $\alpha 2$ -agonist that provides sedation with sparing respiratory depression, anxiolysis and analgesic adjunct with opioids and benzodiazepines sparing effects and prolongs the duration of regional anaesthesia and allows early tracheal extubation after paediatric cardiac surgery. [1,2,3,1] Recently, dexmedetomidine has been established as a cardioprotective agent in the adult cardiac surgical patients. Some trials show significantly lower myocardial injury markers like interleukin-6 (IL-6) levels, cardiac troponin I (cTnI) and creatinine kinase-myocardial band (CK-MB), after cardiac surgery in the dexmedetomidine group.[²] The majority of published studies have suggested that dexmedetomidine is a seemingly efficacious agent protecting against cardiac injury during CPB.[6] It's administration lowers mechanical ventilation period, ICU stay and length of hospital stay after paediatric cardiac surgery. In addition, it is effective against post operative shivering, refractory JET rhythm and Tet spells and acute kidney injury (AKI) in cyanotic paediatric patients undergoing corrective surgery. However, studies on its application in paediatric heart surgery using cardiopulmonary bypass (CPB) remain limited. This systematic review aimed to provide information on the utility of dexmedetomidine in the patients undergoing pediatric cardiac surgery using CPB: hemodynamic stability, cardioprotective, renal protection, neuroprotective effects, control of refractory JET, and Tet spells, and the early and late outcome.

Keywords: Dexmedetomidine, paediatric cardiac surgery, hemodynamic stability, perioperative sedation, early extubation, Tet spells, JET, organ protection, AKI, mechanical ventilation duration

Introduction:

Dexmedetomidine mediates its diverse responses through $\alpha 2$ -adrenoreceptors agonist actions. Recently dexmedetomidine use has become more prevalent in paediatric cardiac surgical practice due to its respiratory sparing and organ protective effects along with preserving neurocognitive functions. [³]

Intraoperative dexmedetomidine infusion attenuated the hemodynamic and neuroendocrinal response to surgical trauma and cardiopulmonary bypass (CPB) in pediatric patients undergoing corrective surgery for congenital heart disease. It has several applications; used as a premedication, it provides arousable sedation and anxiolysis. As an adjunctive agent of balanced general anaesthesia and epidural anaesthesia. The primary objectives for its administration are attenuation of the neuro-humoral stress response, providing hemodynamic stability, decrease in myocardial oxygen demand particularly in patients undergoing coarctation of aorta and tetralogy of Fallot repair.[^{4,5}] Thus attenuates increases in heart rate, arterial blood pressure, plasma cortisol, and catecholamine concentrations in pediatric patients undergoing open heart surgery. During ICU treatment dexmedetomidine decreases opioids requirement, prevents the risk of postoperative delirium or emergence agitation, prevents shivering, and facilitation of early tracheal extubation and decreases duration of mechanical ventilation, and length of ICU stay. Dexmedetomidine has been successfully used to control the refractory Tet spells and junctional ectopic tachyarrhythmia (JET) in patients undergoing paediatric cardiac surgery. Additionally, there is evidence from large randomized controlled trials that supplemental dexmedetomidine has favourable patient outcomes, and provides cardio protection, neuroprotection, or renoprotection. [⁶] The present review has summarized the role of dexmedetomidine in patients undergoing pediatric cardiac surgery using CPB, and to explore its potential benefits for different clinical applications, like premedication, intraoperative maintenance of anaesthesia and hemodynamic stability, organ protection and outcome benefits.

Methods:

We searched PubMed, google, choline database RCT and review articles for dexmedetomidine utility in paediatric cardiac surgery, sedation, tracheal extubation, length of the ICU stay, and organ protection with dexmedetomidine. Dexmedetomidine for the treatment for JET and Tet spells in paediatric cardiac surgical patients.

Discussion:

Dexmedetomidine is a highly specific, potent, and selective α^2 adrenoceptor agonist with a relatively high ratio of α^2/α^1 activity (1620:1 as compared to 220:1 for clonidine). Therefore, it is considered a full agonist of the α^2 receptor and so, ensures its potent action and selective for the central nervous system, without unwanted cardiovascular effects from α^1 receptor activation.[⁷] Dexmedetomidine is an imidazole compound, and therefore, it has the potential to produce similar inhibitory effects to etomidate on cortisol synthesis.[⁶] Dexmedetomidine is an α -2 agonist agent with sedative, hypnotic, analgesic, and central sympatholytic properties. In addition to the intravenous use, Intranasal dexmedetomidine has a promising role for preoperative sedation.[⁵] Dexmedetomidine most likely has a favourable effect on myocardial perfusion, as it has been shown to increase the endocardial-to-epicardial blood flow ratio in the postischemic myocardium, with an overall decrease in the myocardial oxygen demand in parallel with oxygen supply and energy requirements.[⁸] A decrease in HR and arterial pressure within 20% of baseline occurs with intra-nasal administration { $0.5\text{--}3 \mu\text{g kg}^{-1}$) which is less than the decrease observed with equivalent doses of i.v. dexmedetomidine.[⁹] Therefore, it's a multipurpose drug with diverse responses; used as a premedication, provides arousable sedation and anxiolysis; intraoperative adjunctive agent of balanced general anaesthesia as it attenuates the neuro-humoral stress response and facilitates the early tracheal extubation in patients undergoing paediatric cardiac surgery. In addition, it spares opioids, benzodiazepines and prevents the risk of postoperative delirium or emergence agitation and impacts on

important patient-centred outcomes, such as duration of mechanical ventilation, restart of enteral nutrition or length of ICU stay and hospital length of stay.[2] Its effect in reducing inflammatory responses of CPB may have a protective role in myocardial ischemic–reperfusion injury. The use of dexmedetomidine as a cardio-protector can be applied during preconditioning, intra-conditioning, and postconditioning periods of cardiac surgery. Therefore, at any of these stages its use can prevent myocardial necrosis and apoptosis caused by CPB. Totonchiet *al.* and Abdelrahman *et al.* and Qiu *et al* and others have reported on the measurement of IL-6, IFN- γ , TNF- α , and NF- κ B that dexmedetomidine can attenuate the inflammatory response after CPB in paediatric cardiac surgery, and also reported a significantly lower in the dexmedetomidine group compared to the control at all operative and postoperative measurements.[^{10, 11, 12, 13, 14}] clinically intravenous administration of the dexmedetomidine causes a reduction in HR and blood pressure, but without decrease in cardiac output The decrease in HR and MAP are not due to low cardiac output syndrome rather is the result of sedation, analgesia, and possibly the result of activation alpha-2 adrenergic receptors in the central nervous system.[¹⁵] The bradycardic response observed with dexmedetomidine can be augmented by the concurrent use of other medications with negative chronotropic and/or vagal effects like in children receiving digoxin, beta adrenergic blockers, calcium channel blockers, propofol, fentanyl, beta- blockers and vecuronium bromide or other agents predisposing bradycardia or hypotension. An earlier case report cites extreme bradycardia in an infant receiving dexmedetomidine and digoxin.[1] Moreover, one should be cautious while simultaneously administering multiple drugs with negative chronotropic effects to avoid fatal bradycardia particularly in neonates undergoing corrective procedures, as cardiac output is heart rate dependent. Ahmad M.M. et al. have used a bolus dose of dexmedetomidine (0.5 μ g/kg) over 10 min, followed immediately by a continuous infusion of 0.5 μ g / kg/hr. Relative to baseline, arterial blood pressure and heart rate decreased significantly after the administration of dexmedetomidine through skin incision.[8] some authors have reported a cardiac arrest in infants following cardiac surgery after administration of dexmedetomidine in the patients being treated with amiodarone for tachycardia. A review of the ECGs of the patient prior to the event demonstrated ominous atrioventricular abnormalities with dexmedetomidine. [¹⁶]Therefore, a co-administering dexmedetomidine and amiodarone should be avoided during the treatment of the tachycardia following paediatric cardiac surgery. In addition, intraoperative dexmedetomidine infusion attenuates the hemodynamic and neuroendocrinal response to surgical trauma and cardiopulmonary bypass in paediatric patients undergoing corrective surgery for congenital heart disease.[5] These authors have demonstrated that the use of dexmedetomidine in paediatric cardiac surgery results in decreasing HR and MAP, with a concomitant reduction in cortisol, catecholamines, and blood glucose levels as markers of stress response. Several other authors have reported the clinically non-significant downward trends of systolic blood pressure, mean arterial pressure and diastolic BP after dexmedetomidine treatment during or after paediatric cardiac surgery, but a clinically significant decrease in heart rate. [8,^{17, 18, 19, 20}] However, the incidence of bradycardia due to dexmedetomidine treatment in children with trisomy 21 syndrome reported to be significantly higher than that in normal children. [²¹] Junctional ectopic tachycardia(JET) is a tachyarrhythmia related to surgery for congenital heart disease which could cause serious hemodynamic instability in the perioperative period. JET occurs frequently after pediatric cardiac surgery for congenital heart disease, with an incidence ranging from 2% to 22% and usually occurs in the first 48 hours after pediatric cardiac surgery. [²²] JET is defined as tachycardia with normal QRS similar to sinus rhythm QRS, and a ventricular rate of more than 170 bpm, and AV dissociation with or without haemodynamic compromise. The exact aetiology of JET is not

known, but it is believed to result from mechanical trauma to the proximal conduction tissue due to suture placement or indirect stretch injury with resultant oedema which can occur during resection of muscle bundles, correction of right ventricular outflow tract or correction of ventricular septal defects.[²³] Postoperative JET is managed using several protocols, such as mild hypothermia(35degrees C), decreasing doses of inotropes, use of digoxin, propranolol, amiodarone, flecainide, and magnesium sulphate, and ablation in cardiac catheterization lab in the refractory cases to the standard treatment. Although it is better to prevent JET, but none of the current medications are useful in preventing or reducing its incidence after paediatric cardiac surgery. It can lead to significant hemodynamic instability after cardiac surgery and dexmedetomidine can be effectively used to prevent the frequency or treat the refractory JET after paediatric cardiac surgery. [^{24,25}] Even Prophylactic use of dexmedetomidine is associated with significantly decreased incidence of postoperative JET in children after congenital heart surgery without significant side effects. [^{25,26}] Hassan PF and colleague 2024 have used dexmedetomidine 0.5 mcg/kg over 20 min after induction followed by 0.5mcg/kg per hour infusion for 72 hours and magnesium sulphate (50 mg/kg) bolus administered at the time of aortic cross clamp release and continued an infusion of 30 mg/kg /day for 72 hours and reported that dexmedetomidine alone or combined with MgSO4 has a therapeutic role in prevention of JET in children after congenital heart surgery.[²⁷]

Dexmedetomidine has a vital role in controlling the refractory Tet spells; at a dose of 0.2 mic/kg/min without a loading bolus injection leads to a drop-in heart rate by approximately 20 beats/min and reduces RVOT contractility and degree of right to left shunt, and so, SpO2 remains stable during dexmedetomidine infusion in patients of TOF with Tet spells, and without any apparent respiratory depression or marked change in blood pressure. The effect is because of its central sympatholytic effect and reducing the catecholamine levels, and so, effective in alleviating the perioperative Tet spells in TOF refractory to the standard treatment. [²⁸]

Infants undergoing cardiac surgery under CPB are susceptible to postoperative neurodevelopmental delays. Dexmedetomidine has been shown to have protective effects on the heart, kidneys, and brain in animals and adults undergoing cardiac surgery with CPB. In various animal studies, dexmedetomidine prevents anesthesia-induced neurotoxicity, and has a protective effect on cerebral ischemic reperfusion injury by reducing neuroinflammation.[^{29,30}] Dexmedetomidine exerts a cell-protective effect on nervous tissue under ischemic conditions mediated by its α_2A -agonistic properties and also by imidazoline type 1-receptors.[³¹]

Dexmedetomidine can alleviate the brain damage induced by anaesthetics by reducing the apoptosis in several cortical and subcortical regions. It is also useful in protection of spinal cord against lignocaine induced spinal neurotoxicity via activation of the α^2 adrenergic receptors which subsequently stimulate protein kinase C and inhibiting glutamate release. [^{32,33}] A loading dose of 1 μ g/kg of dexmedetomidine was infused for 10 min and subsequently, a maintenance dose of 0.5 μ g/kg/h of dexmedetomidine was infused, in addition, 0.01 μ g/cardiopulmonary priming volume was mixed with the priming volume of the CPB circuit. Anti-inflammation by dexmedetomidine after CPB has been suggested to be due to inhibition of nuclear factor κ B.[³⁴]

Acute kidney injury (AKI) is a common postoperative complication in patients undergoing paediatric cardiac surgery with CPB. The incidence of AKI after pediatric cardiac surgery varies from 20 to 86% depending on different diagnostic methods and medical centres [³⁵] Acute renal injury caused by cardiac surgery is estimated to occur in 30–50 % of children with congenital heart disease. Factors like elevated reactive oxygen species, haemolysis and systemic inflammatory response induced by CPB are the

potential mechanisms of developing AKI after paediatric cardiac surgery. In addition, several risk factors of AKI have been identified, such as younger age, complex cyanotic CHD, perioperative poor hemodynamic, longer CPB time, fluid overload. Perioperative development of AKI is a risk factor for adverse prognosis such as prolonged ICU and hospital stay, and increased mortality.[³⁶] Jo *et al.* have reported that intraoperative dexmedetomidine infusion might reduce the incidence of AKI and the incidence of post CPB eGFR decline after pediatric congenital heart surgery under CPB, or prevents the aggravation of AKI, or dexmedetomidine might be a promising prevention strategy for cardiac surgery associated AKI.[^{32,37,38}] Gu *et al.* Studied the protective role of dexmedetomidine on ischemia-reperfusion induced kidney and reported that dexmedetomidine decreases the incidence of cell death in a dose-dependent manner, preserves the tubular architecture and reduces cell death. So, the level of renal dysfunction is minimized, and renal failure is prevented. The organ-protective effect has been abolished with α_2 adrenoreceptor antagonist, indicating that dexmedetomidine acts in an α_2 adrenoreceptor-dependent manner. [32,38]

Dexmedetomidine in combination with ketamine has been used successfully in patients at risk of fatal airway collapse with big anterior mediastinal mass manifested with symptoms of SVC compression. Dexmedetomidine is a useful analgesic adjunct in epidural analgesia with opioid-sparing effects and prolongs the duration of sensory block, motor block and analgesia. [³⁹] It allows for early extubation after paediatric cardiac surgery.

Doses of Dexmedetomidine:

Dexmedetomidine has been used clinically at variable doses by different authors like Su *et al.* 2013. have used 1 $\mu\text{g}/\text{kg}$ loading dose with infusion rate of 0.25 $\mu\text{g}/\text{kg}/\text{h}$, 0.50 $\mu\text{g}/\text{kg}/\text{h}$, 0.75 $\mu\text{g}/\text{kg}/\text{h}$ respectively. Chen *et al.* 2014 have used 0.20 to 0.30 $\mu\text{g}/\text{kg}/\text{h}$ with a 0.30 $\mu\text{g}/\text{kg}$ loading dose. Amrousy *et al.* 2017. Have proposed as 0.5 $\mu\text{g}/\text{kg}$ over 20 min followed by a continuous infusion of 0.5 $\mu\text{g}/\text{kg}/\text{h}$. Shuplock *et al.* 2015 have used dexmedetomidine as 0.5–0.84 $\mu\text{g}/\text{kg}/\text{h}$ infusion.[^{40,41,42,43}]

Conclusion:

Perioperative administration of dexmedetomidine can be a useful adjuvant in paediatric cardiac surgical patients, as it provides arousable sedation, spares the opioids doses, and attenuates the hemodynamic and neuroendocrinal response of surgery and CPB. Moreover, administered orally or intranasally, it provides a satisfactory level of sedation, facilitates parental separation, and makes the child easy to receive a mask.[⁴⁴] It has cardiac and neuroprotective effects after CPB in paediatric cardiac surgical patients mediated via the cholinergic anti-inflammatory pathway.[^{14,45}] Recently, it has been successfully used in the perioperative treatment of JET arrhythmia and Tet spells in patients undergoing TOF and D-TGA corrective surgeries. [23,24] During ICU treatment dexmedetomidine decreases opioids requirement, prevents the risk of postoperative delirium or emergence agitation and impacts on important patient-centred outcomes, prevents shivering, and decreases duration of mechanical ventilation, and length of ICU stay. Co-administration of dexmedetomidine and amiodarone in infants following cardiac surgery to treat tachycardia should be avoided.[16]

Author Contributions

Professor Vishnu Datt designed the research framework and wrote the manuscript, reviewing the relevant literature as main author. Professor Vishnu Datt, Diksha Datt, Anumeha and Garima Sangwan, Sneha

Satya- Manuscript preparation, literature search, editing. Datt V, Karan Juneja, Diksha Datt- Approval of final manuscript and attestation to data integrity. Priyanka Professor, Dr Vishnu Datt and all other authors have also contributed, read, and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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