

Mini Review

Dexmedetomidine Used for Sedation in Cardiovascular Surgery Patients

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Sedation is an essential and important treatment for post-cardiovascular surgery patients and has an important effect on patient's outcomes. Due to the complex influence of cardiopulmonary bypass on all organ systems especially neurological system and the high requirement of hemodynamics stability after surgery, we have been seeking an ideal post-cardiovascular surgery sedation medicine. In recent years, dexmedetomidine has generated immense interest due to its unique sedation profile in the ICU, which is a highly selective α_2 -adrenoceptor agonist, with an α_2 : α_1 receptor binding ratio of 1,600:1, however, non-selective within the α_2 -receptor subtypes. Centrally, α_2A -receptors mediate anesthetic and sympatholytic effects in the brainstem, whereas α_2B -receptors mediate smooth muscle responses in the peripheral vasculature [1]. It is widely used as an adjuvant during general anesthesia and for sedation during mechanical ventilation after surgery [2]. There are studies showed use of dexmedetomidine for sedation in cardiac surgery patients shortened the duration of mechanical ventilation, decreased the incidence of delirium, and even improved the morbidity and mortality [3-5]. In this review, we summarized and analysed the main articles of dexmedetomidine used in cardiac surgery.

Shorten the Duration of Mechanical Ventilation

Dexmedetomidine with a unique of not suppress respiration maybe used to shorten intubation time compared to other analgesics currently in use in the ICU for sedation. Although in the meta analysis in 2012 [3], Dexmedetomidine was shown have an association with shorter length of mechanical ventilation, but it included studies of midazolam, morphine and propofol as control. In almost Dexmedetomidine vs midazolam or morphine studies, it seem like dexmedetomidine have advantage in shorten ventilation time [6-8]. But there are different results in studies of dexmedetomidine vs propofol used postoperative in cardiac surgery patients for the duration of mechanical ventilation.

In a single-center retrospective analysis of 582 cardiac surgery patients, extubation within 6 hours after surgery was achieved

Abstract

Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist. It has sedative, analgesic and opioid-sparing effects and has been widely used as an adjuvant during general anesthesia and for sedation during mechanical ventilation after surgery. Dexmedetomidine was shown associate with a shorter time to extubation and has beneficial effects on delirium than midazolam or propofol in intensive patients. There are also some studies about dexmedetomidine used for cardiovascular surgery patients to identify the effect on ventilation time, delirium, other morbidity and mortality. We reviewed these studies and didn't get clear conclusion about superiority of dexmedetomidine over other sedation medicines in cardiovascular surgery patients, and more strong evidence was needed in the future.

more frequently in the group sedated with dexmedetomidine than with propofol (68.7% v 58.1%; $p=0.008$) [9]. However, many other studies failed to find an expedited extubation or shorter mechanical ventilation course with dexmedetomidine compared to propofol sedation for postcardiac surgical patients [10-15]. And dexmedetomidine therapy resulted in a higher incidence of hypotension and analgesic consumption compared with propofol-based sedation. However, most of this studies were retrospective and descriptive. Further evaluation is needed to assess differences in clinical outcomes of propofol and dexmedetomidine-based therapy in mechanically ventilated cardiac surgery patients.

In summary, there are still not enough strong evidences to support the superiority of dexmedetomidine used for shortenning ventilation time for postcardiac surgery patients. Although dexmedetomidine provided safe and effective sedation for post-CABG surgical patients and significantly reduced the use of analgesics in these studies, it does not seem to have any advantage compared with propofol for short-term sedation after coronary artery bypass graft surgery.

The Effect on Dilirium

Dexmedetomidine has a unique mechanism of action exhibiting sedative, anxiolytic, and analgesic effects without causing respiratory depression [16]. Furthermore, dexmedetomidine improves the quality of sleep in critically ill patients [17], primarily resembling a nonrapid eye movement sleep pattern [18]. In some studies of critical patients, dexmedetomidine was shown decreased the incidence of delirium compare to other sedation medicines. But in cardiac surgery patients, this studies didn't obtain consistent results.

In two randomized trials, postoperative sedation with dexmedetomidine reduced the incidence of delirium (1/30 [3%] with dexmedetomidine vs 15/30 [50%] with propofol vs 15/30 [50%] with midazolam; $P < 0.001$ [4] and 16/91 [17.5%] with dexmedetomidine vs 29/92 [31.5%] with propofol; $P = 0.028$ [19], respectively). The latter was a prospective, randomized, single blinded, controlled clinical trial about dexmedetomidine versus propofol sedation reduces delirium after Cardiac surgery published in last year. The trial included 183

old age patients (>60 years). The infusion of dexmedetomidine was continued for a maximum period of 24 hours after surgery. Dexmedetomidine infusion was not discontinued before extubation. When compared with propofol, dexmedetomidine sedation reduced incidence, delayed onset, and shortened duration of POD in elderly patients after cardiac surgery. In two other randomized trials, however, use of dexmedetomidine sedation did not reduce the incidences of postoperative delirium despite trends of decrease (13/152 [8.6%] with dexmedetomidine vs 22/147 [15.0%] with morphine; $P = 0.088$ [7] and 1/32 [3.1%] with dexmedetomidine vs 5/32 [15.6%] with normal saline; $P = 0.086$ [20], respectively).

In most recently published a randomized, double-blinded, and placebo-controlled trial [21], which included 285 old patients (≥ 60 years), dexmedetomidine did not decrease the incidence of delirium (4.9% in the DEX group vs 7.7% in the control group; or 0.62, 95% CI 0.23 to 1.65, $p = 0.341$). Dexmedetomidine administered during anesthesia and early postoperative period did not decrease the incidence of postoperative delirium in elderly patients undergoing elective cardiac surgery. However, considering the low delirium incidence, the trial might have been underpowered [22]. However, a recently published meta analysis have shown dexmedetomidine sedation could reduce postoperative delirium and was associated with shorter length of intubation, but might increase bradycardia in patients after cardiac surgery compared with propofol.

There are lots of studies about dexmedetomidine on delirium postoperation compare to other sedation medicines, however, as concern to if the short-term use during perioperation could decrease the incidence of delirium still need more strong evidence.

Improve the Morbidity and Mortality

There were studies shown intravenous infusion of dexmedetomidine to patients undergoing Coronary Artery Bypass Grafting (CABG) and vascular surgery intraoperatively decreased intraoperative sympathetic tone, attenuated hyperdynamic responses and improve perioperative hemodynamics [23,24]. Dexmedetomidine exerts a profound protection in multiple organs, including the heart, brain, kidneys, liver, intestine and lungs [25-29]. In a published meta analysis in 2012 [30], Dexmedetomidine was shown have an association with shorter length of mechanical ventilation and lower risk of delirium following cardiac surgery. But there was no significant difference in ICU stay, hospital stay, and morphine equivalents between the included studies [3].

Another meta analysis published in 2016 included comparative studies of postoperative complications of perioperative dexmedetomidine use with another drug or placebo in adult patients who underwent cardiac surgery. This meta-analysis revealed that the perioperative use of dexmedetomidine in patients undergoing cardiac surgery can reduce the risk of postoperative ventricular tachycardia and delirium, and showed a decreased risk of atrial fibrillation, shorter length of ICU stay and hospitalization with dexmedetomidine.

In a recent large retrospective cohort study published in *Circulation* [5], Ji and colleagues investigated the use of perioperative dexmedetomidine and postoperative mortality in 724 post-cardiac surgical patients. The all-cause mortality benefits with dexmedetomidine infusion at in-hospital, 30-day, and 1-year points

are notable (1.5 v 4.0%; 3.2 v 4.5%; and 3.2 v 6.9%, respectively, for dexmedetomidine v non-dexmedetomidine groups). However, in this retrospective research there were maybe some selective bias, the patients who received dexmedetomidine had significantly shorter cardiopulmonary bypass duration and lower incidence of intra-aortic balloon pump requirement, and the multivariate model assessing did not include cardiopulmonary bypass duration and IABP requirement. There were also significant unmatched preoperative medication use between the groups. Furthermore, dexmedetomidine was only used during a short period from initiation of cardiopulmonary bypass to 24 hours after surgery. The authors attributed a benefit of dexmedetomidine on postoperative mortality to its sympatholysis, anti-inflammatory and cardioprotection. However, many patients in this population may not tolerate its systemic antiadrenergic effects [31] and hadn't got optimal cardioprotection because of inadequate dosage regimen.

And all these above 3 studies did not directly compare dexmedetomidine with propofol. Current guidelines suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated adult Intensive Care Unit (ICU) patients [32].

Even though there are lots of clinical evidence to identify the effect of dexmedetomidine on delirium postoperation, however, as concern to the other complications and mortality there are still not enough strong evidence especially in compared to propofol.

The Clinical Use of Dexmedetomidine

Because of the moderate sedation and the most common side effects of bradycardia and hypotension, the use of dexmedetomidine was limited. In order to attain adequate sedation with dexmedetomidine alone in the ICU population, patients may experience hemodynamic disturbances of bradycardia and hypotension, especially during the loading phase, also in maintaining the huge dose infusion for enough sedation. These hypotensive or bradyarrhythmia events might be well tolerated by healthy subjects but could prove particularly detrimental for many post-cardiac surgical patients with marginal hemodynamic reserves. Sometimes patients can't reach adequate sedation using dexmedetomidine alone usually require other analgesic such as propofol.

In our experience, we have seen the benefits of this drug most often after aortic surgery, especially in patients with aortic dissection who are often combined a state of high sympathetic tone, presenting postoperative hypertension and tachycardia. It seems like more easy to extubation using dexmedetomidine in the delirium patients after aortic dissection surgery. And it often have a satisfied sedation state in delirium patients maybe due to no respiratory depression and normal sleep pattern. Despite our successful use of dexmedetomidine in this small patient population and select others, we are unable to promote the broad use of dexmedetomidine for its potential benefits in cardiac surgery based on this study

The high cost also limited its broad use. The actual cost benefit of dexmedetomidine utilization in the ICU requires further investigation. Dexmedetomidine was thought to provide superior

comfort for the mechanically ventilated patient, however, there are no evidence to support this yet.

Conclusion

Considering the limitations of current dexmedetomidine evidence, questionable beneficial outcomes and cost-savings, unidentified patient satisfaction perception, and potential hemodynamic disturbances with its use, to utilize dexmedetomidine routinely for sedation in all post-cardiac surgical patients remains controversial at this point in time.

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