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Review Article

USE OF DEXMEDETOMIDINE IN GENERAL ANESTHESIA AND OTHER PROCEDURES (REVIEW)

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ABSTRACT

It is obious that when any intervention is performed to any people, stimulant the brain and spinal cord, became anxious, instantly there is unstable haemodynamic occur. To minimized that unstable haemodynamic changes dexmedetomidine is used. Dexmedetomidine is an alpha-2-adrenergic agonist, has many properties for sedative and anaesthetic drug, it has been reported to provide sedation that parallels natural sleep, anxiolysis, analgesia, sympatholysis, and an anaesthetic-sparing effect with minimal respiratory depression. In addition, there is increasing evidence supporting its organ protective effects against ischaemic and hypoxic injury. It has been shown to be neuroprotective, cadioprotective, reducing apoptosis in animals and humans. Due to multiple properties of dexmedetomidine,we can used it in many procedure like in general anesthesia,local anesthesia, I.C.U, endoscopy, colonscopy, pre medication, dental procedure, painful procedures like extracorporeal shock-wave lithotripsy,lumbar puncture, bone marrow biopsy, burn dressing changes,chest tube insertion, femoral cut-down for tunnelled central venous catheter placemen, , awake fiber-optic intubation and many more. It provides a unique "conscious sedation", analgesia, without respiratory depression. The purpose of this study include effects of dexmedetomidine on attenuation of hemodynamic changes and there effects as adjuvant in anesthesia on analgesic and inhalation anesthetic requirements during laparoscopic surgeries in general anesthesia, sedation at Intensive Care Unit, regional anesthesia, sedation for pediatric procedures, awake fiber-optic intubation.

Key words: Dexmedetomidine, α-2 agonist, perioperative, I.C.U.,regional anesthesia and general anesthesia, awake intubation.

INTRODUCTION

Dexmedetomidine, which was introduced for human use in 1999, is a selective α2 agonist with 8 times more affinity for α2 adrenergic receptors compared to clonidine and possesses all the properties of α2 agonist without respiratory depression [1, 2]. Dexmedetomidine is an imidazoline derivative which selectively acts on the alpha 2 receptors as an agonist. By attenuating sympathetic activity, it inhibits release and uptake of norepinephrine [3]. α-2 adrenergic receptors are transmembrane receptors composed of excitable G-proteins, which cross the cell membrane and link selectively with extracellular ligands: endogenous mediators or exogenous molecules,a-such as drugs.

Physiology of Dexmedetomidine:

Dexmedetomidine acts through three types of α2 receptors- α2 A, α2 B and α2 C situated in brain spinal cord and other organs. Stimulation of α2 A and α2 C in locus ceruleus causes sedation. In the spinal cord, activation of both α2 A and α2 C receptors directly reduce pain transmission by reducing release of substance P which produces analgesia [3, 4]. Agonism at the α-2 B receptor in the hypothalamic thermoregulatory center of the brain suppresses shivering, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. It increases cardiac baroreceptor sensitivity and also blunts stress response to surgical stimuli. This may help to reduce the narcotic and anaesthetic dose, as well as post operative analgesic requirement [3]. Dexmedetomidine has evidence for organs protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection [5]. The presynaptic sites of action are clinically significant because they modulate the release of norepinephrine and adenosine triphosphate through a negative feed-back mechanism. The physiological responses is regulated by α-2 receptors are vary with their locations. α-2 receptors in the brain and spinal cord are responsible for hypotension, bradycardia, sedation and analgesia. The responses of α-2 receptors from other different organs have the response like decreased salivation, secretion, and gastric motility, inhibited renin release, increased glomerular filtration rate, increased secretion of sodium and water in the kidney, decreased intraocular pressure and decreased insulin secretion from the pancreas. The stimulation of α-2 receptors decreases calcium entry into nerve terminals, which may contribute to its inhibitory effect on neurotransmitter release [6]. See figure 1.

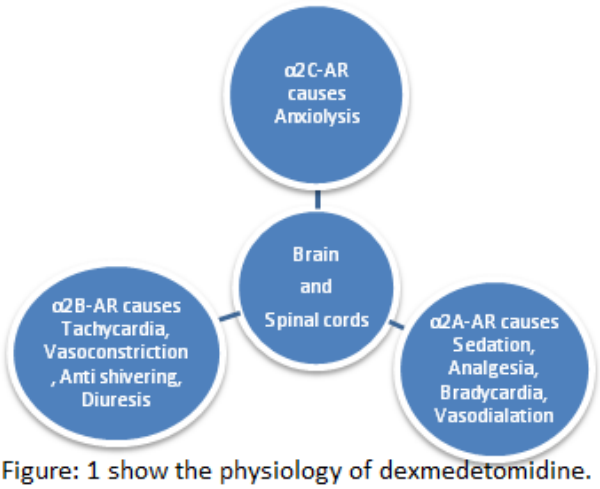

Figure: 1 show the physiology of dexmedetomidine.

Dexmedetomidine has sedative effect like a natural sleep and mimics the deep recovery sleep that is seen after sleep deprivation [7, 8]. This sedative effect is dependent on plasma concentrations blood between 0.2 and 0.3 ng/mL resulting in significant and rousable sedation. Unarousable deep sedation is thought to occur at plasma concentrations above 1.9 ng/mL [9, 10]. It is thought that though the analgesic effects of dexmedetomidine are still unclear and may partly be owing to an altered perception and reduced anxiety, though an opioid-sparing effect. It is thought that when α_2-receptor binding in central and spinal cord α_2-receptors, due to hyperpolarization of interneurons and the release of pronociceptive transmitters such as substance P and glutamate get reduce, causes suppression of pain transmission [11]. Dexmedetomidine has typical biphasic response in cardiovascular system, causes hypotension at low plasma concentrations and hypertension at higher plasma concentrations [9, 10]. When dexmedetomidine intraveinously bolus is given , the results is high (peak) plasma concentration, causes an increase in blood pressure with decrease in heart rate. It is due α_2-receptor activation in the vascular smooth muscles, causing peripheral vasoconstriction and quick reduction in heart rate, presumably caused by the baroceptor reflex [9]. But after certain time,when dexmedetomidine plasma concentrations start to decrease, the vasoconstriction also started to attenuate, as dexmedetomidine also activates α_2-receptors in the vascular endothelial cells, which results in vasodilatation [12, 13]. Together with presynaptic α_2-adrenoreceptors inhibiting sympathetic release of catecholamines and the increased vagal activity, this results in a hypotensive phase. It is said that, Dexmedetomidine does not suppress respiratory function, even at high doses. It acts as the natural heavy sleep state [14, 15]. With therapeutic plasma concentrations up to 2.4 ng/mL, minimal respiratory depression is seen with a preservation of ventilatory response to CO_2 [16-18]. But,in a trial comparing remifentanil with dexmedetomidine upto plasma concentrations (2.4-14.9) ng/mL, there is no respiratory depression except only slight increases in carbon dioxide levels (3–4 mmHg) and respiratory rates on unarousal state, but in arousal phase similar to those during natural sleep [18]. However, a recently published paper by Lodenius et al. said there was significant reduction in respiratory rate to hypercapnia and hypoxia in dexmedetomidine-sedated with mean plasma concentrations of around 0.66 ng/mL [19]. Dexmedetomidine provides stable

cerebral hemodynamics without sudden increase in ICP during intubation, extubation, and head pin insertion by reducing cerebral blood flow and cerebral metabolic requirement of oxygen but its effect on intracranial pressure (ICP) is not yet clear. It act as neuroprotective action by reducing the levels of circulating and brain catecholamines and thus balancing the ratio between cerebral oxygen supplies, reducing excitotoxicity, and improving the perfusion in the ischemic penumbra. It reduces the levels of the glutamate responsible for cellular brain injury, especially in subarachnoid hemorrhage [20]. It has been shown to limit the morphologic and functional effects after ischemic (focal and global) and traumatic injury to the nervous system. We can use dexmedetomidine patient, who has renal impairment also because it does not influence the pharmacokinetics of dexmedetomidine to any significant extent. But, sedative effects lasted longer in patients with renal disease [21]. Whereas, in hepatically impaired patients, a decreased clearance and a higher unbound fraction of dexmedetomidine were observed. the dosing regimen of dexmedetomidine should be reduced in patients with hepatic impairment [22].

Pharmacokinetics and Pharmacodynamics of Dexmedetomidine:

Dexmedetomidine absorb through iv routes of administration is more benefitial than through the intranasal and buccal mucosae is better than oral with bioavailability percentage (94% 84% 16%) respectively [14, 23-25]. It is a highly protein-bound drug. In plasma, 94% of dexmedetomidine is bound to albumin and α_1-glycoprotein, shows a rapid and wide distribution throughout the body. dexmedetomidine can crosses the blood–brain and placenta barriers [15, 26]. Distribution half-life of dexmedetomidine about 6 min [27, 28]. It is eliminated mainly through biotransformation by the liver. A hepatic extraction ratio of 0.7 was found [29]. Metabolites are excreted in the urine (about 95%), in the feces (4%) and less than 1% is excreted unchanged [15, 26, 28]. An elimination half-life is 2.1–3.1 per h in healthy person [21, 23, 27, 28, 30, 31]. But, excreation of dexmedetomidine can be affected by hypoalbuminemia [32, 33] and changes in liver blood flow, via changes in cardiac output [29].

Dexmedetomidine follows first order kinetics in which constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour. The half-life of distribution of dexmedetomidine is very fast approximately 6 minutes and elimination half life of 2 hours.The average protein binding is 94% with constant across the different plasma concentrations and has negligible protein binding displacement by drugs commonly used during anesthesia and in the ICU like fentanyl, ketorolac, theophylline, digoxin, and lidocaine [34]. Bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication [27]. Dexmedetomidine has biphasic role in blood pressure. Firstly, A short hypertension and subsequent hypotension. The two phases are considered to be mediated by two different α2-AR subtypes: the α-2B AR is responsible for the initial hypertensive phase, whereas hypotension is mediated by the α2A-AR [35]. Dexmedetomidine has capacity to modulates spatial working memory.It does not suppress respiratory function, even at high doses and maintaining sedation without cardiovascular instability so facilitate weaning and extubation in

trauma/surgical ICU patients who have failed previous attempts at weaning because of agitation and hyperdynamic cardiopulmonary response [18, 36, 37]. Dexmedetomidine activates peripheral presynaptic α2- AR which reduces the release of catecholamines, and hence reduces sympathetic response to surgery [9]. It help to decreases oxygen consumption in intraoperative period (up to 8%) and in postoperative period (up to 17%) [38]. Intraoperative administration of dexmedetomidine in lower concentrations has reduced the requirement of other anesthetic agents, fewer interventions to treat tachycardia and a reduction in the incidence of myocardial ischemia [39]. It attenuates hemodynamic stress response to intubation and extubation by sympatholysis [39-42].

But,in younger patients with high levels of vagal tone, bradycardia and sinus arrest have been described which were effectively treated with anticholinergic agents (atropine, glycopyrrolate). High doses of dexmedetomidine can cause transient hypertension mediated by peripheral α2B- AR vasoconstriction [43]. Hypotension and bradycardia may occur with ongoing therapy mediated by central α2A-AR, causing decreased release of noradrenaline from the sympathetic nervous system. Long-term use of dexmedetomidine leads to super sensitization and up regulation of receptors. So, with abrupt discontinuation, a withdrawal syndrome of nervousness, agitation, headaches, and hypertensive crisis can occur[44]. Dexmedetomidine is not recommended in patients with advanced heart block and ventricular dysfunction [45]. FDA has classified it as a category C pregnancy risk, so the drug should be used with extreme caution in women who are pregnant.

Multiple Usages of Dexmedetomidine:

Now-a-days laparoscopic surgeries are most popular because of cosmetically small incision, short time hospital stay, early mobilization ,short recovery time and less post operative pain. Although, there are more advantages of laparoscopic surgery, some disadvantages like hemodynamic changes such as hypertension, tachycardia and other surgical-related complications are there too. To attenuate this activities and complication we can use many drugs, among them from recent year a great enthusiasm has been shown toward the use of α2 agonists in anesthesia practice because of their anxiolytic, sedative, sympatholytic, analgesic-sparing and Cardio, Neuro and Renoprotective properties i.e dexmedetomidine [46].

The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide (CO_2). CO_2 gas used into the abdominal cavity causes significant release of catecholamines, cortisol, rennin angiotensin-aldosterone and vasopressin, thus leading to increase in Systemic Vascular Resistance (SVR) causing systemic hypertension,tachycardia and increased myocardial oxygen requirement. CO2 is readily absorbed from the peritoneal cavity into the circulation resulting in hypercapnia, increase in Pulmonary Vascular Resistance (PVR), inotropic effects on heart [47]. It causes alteration in acid base balance, stress response, cardiovascular and pulmonary physiology. Trendelenburg position given intraoperatively, increases intra-abdominal pressure which in turn reduces venous return and cardiac output, leading to cardiac dysfunction.

Tissue injuries during surgeries can lead to stress response [48]. Surgical stress response activates the sympathetic nervous system and increases the release of catabolic hormones. Changes in heart rate, blood pressure and cortisol levels also may occur [49]. To attenuates all these effects the best way is to uses of the dexmedetomidine on perioperative period along with another analgesic. Respiratory depression is also very minimal with use of dexmedetomidine[1, 2]. It also reduces intraoperative requirement of anesthetic agents and analgesics.

Lovina et al 2017; Gourishankar Reddy Manne et al 2014; Gaurav Acharya et al 2016; Laxmi Narsaiah G et al 2016 showed that used of low dose of dexmedetomidine was useful in general anesthesia. It adjuvant to control hemodynamic stress response to laryngoscopy and intubation, without any significant adverse effects, if dexmedetomidine was infused in maintainance dose [50-53]. But, Guan Zhan-Ying et al 2015 has shown loading dose of 0.25μg/kg DEX does not serve as a very useful anaesthesia adjuvant to control haemodynamic stress response while intubation in the elderly patients [54]. Sulhyan SR et al 2014, Belleville JP et al 1992, has shown a dose of 1μ g/kg or more caused increased sedation levels and need for oxygen supplementation due to irregular breathing with episodes of apnoea [16, 55]. Whereas Smitha K. S et al 2014 found out that dexmedetomidine 1μ g/kg was more effective than dexmedetomidine 0.5 μg/kg in controlling haemodynamic responses to tracheal intubation [56]. The inter group comparison revealed a statistically significant reduction in HR by dexmedetomidine than normal saline. Chittaranjan Panigrahi et al 2017; H K Sale et al 2015; Amruta S. Pathak et al 2016 revealedon loading dose of 1μ g/kg has given better haemodynamic stability, post operative analgesia, sedation and reduction in the dose of inhalational anesthetic agent [57-59]. Chirag et al 2012; Lovina et al 2017 studied has shown that there were post operative delay recovery occur [50, 60]. But, Shirishkumar et al 2016 said there was no evidence for delay of post operative delay recovery. On my opinion, Infusion Dexmedetomidine obiously attenuates hemodynamic stress response during laparoscopic surgery and there is effects on post operative recovery time ,but in a dose-dependent manner.

These day,dexmedetomidine is more recommended drug use in operation and I.C.U because of its good affect on human being without adverse effects like patients remain awake, calm, and are able to communicate their needs. It does not interfere with the respiratory drive or produce any agitation, hence facilitating early weaning from ventilator [61]. In 2008 Arpino PA et al, when dexmedetomidine was initiated in a group of mechanically ventilated patients who failed previous attempts at weaning and extubation secondary to agitation. After dexmedetomidine initiation, 65% of the patients was successfully extubated. It was associated with a reduction in concomitant sedative and analgesic use with minimal adverse effect. Currently FDA approved for use of dexmedetomidine in I.C.U but for not more than 24 hours; but there are many studies have been reported its safe use for longer duration [62]. Thomas Breuer et al (2018) described when dexmedetomidine was used for 24 hours, patients on mechanical ventilation,sedation led to a worsening of ventilation-induced diaphragm dysfunction, possibly through impaired Glut-4 translocation.

Although dexmedetomidine prevented diaphragmatic fiber atrophy, it did not inhibit oxidative stress and activation of the proteolytic pathways. Similarly, Shutes BL et al (2018) concluded children admitted to the pediatric critical care unit who got dexmedetomidine for more than 24 hours without other infusions for sedation during noninvasive positive pressure ventilation has predictable hemodynamic effects including bradycardia and hypertension. Although withdrawal was associated with higher cumulative dose, these symptoms were effectively managed with short-term enteral clonidine. Haenecour AS et al (2017) also said when pediatric patients received dexmedetomidine for longer than 48 hours, A withdrawal syndrome may occur. But, all that patients were also exposed to opioids so that effect might be affected by the opioid used. Banasch HL et al (2018) data suggested, when prolonged infusion of dexmedetomidine median duration is 27 hours in non invasively ventilated patients. Adverse effects appeared more common in younger patients. A high rate of withdrawal effects was seen, no association with age, dose, or duration were found. It help preventing emergence delirium after general anesthesia and controlling delirium in the intensive care unit [63, 64]. This medicine used in the intensive care because it allows sedated patients to be quickly aroused and oriented upon demand [65]. Dexmedetomidine is an antisialogouge,can be used while doing fiber optic awake intubation because it creates a dry field for the anesthesiologist and no need to discontinuation of the dexmedetomidine prior to weaning from mechanical ventilation [66].

When dexmedetomidine was used while doing optic awake intubation there was no patients had on end-tidal carbondioxide evidence of respiratory depression [67]. We can use dexmedetomidine as a regional ansthesia [68], intra-articularly [69] [70], in intravenous regional anesthesia (IVRA) [71]. It also help to prolong the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural [72], caudal [73], or spinal [74]). Dexmedetomidine use mixed with other analgesic for fast onset time and prolong the duration of the affects. Compared with clonidine, an α_2-agonist dexmedetomidine has a greater selectivity for α_2-receptors (α_2:α_1 ratio of 1620:1 vs. 220:1) [75]. According to Nazia Nazir et al (2016), dexmedetomidine was an effective adjuvnta to bupivacaine for supraclavicular block resulted in faster onset of block, prolonged motor and sensory block, prolonged analgesia with hemodynamic stability and adequate sedation. But, Hussain N et al (2017) and Ping Y, Ye Q, Wang W, Ye P, You Z (2017) team concluded that dexmedetomidine has a potential anesthetic adjuvant that can facilitate better anesthesia and analgesia when administered in brachial plexus block. But, it also increased the risk of bradycardia, hypotension, and somnolence. 2017 Jian Zhang et al suggested that dexmedetomidine was safe and effective for neonates who were delivered by caesarean section with no significant differences in Apgar scores at 1 and 5 min, and umbilical blood gas parameters compared with the placebo group.Administration of dexmedetomidine via intravertebral injection could improve the characteristics of motor and sensory block and prolong the pain-free period. Dexmedetomidine can also reduce the incidence of postoperative adverse effects, such as nausea/vomiting and shivering. Callaway CW (2015) and team were also with dexmedetomidine decreases shivering in normal volunteers. This effect is

associated with decreased systolic blood pressure and sedation, but no respiratory depression.

SS Nethra (2015) when dexmedetomidine 5 μg added to intrathecal bupivacaine as adjuvant, administered in sitting position with patients made supine after 5 min of the subarachnoid block provided prolonged post-operative analgesia and it also prolonged the duration of motor blockade, time for ambulation and time to void which could be a hindrance to its routine use in ambulatory care. Waurick K (2017); Xiang Q et al (2013) Caudal anesthesia combined with dexmedetomidine sedation were an effective anesthetic technique for lower abdominal and extremity. When Li X and team on 2017 investigated how the combined use of dexmedetomidine with intravenous anesthetics influences seizure duration and circulatory dynamics in electroconvulsive therapy (ECT). They found that the used of dexmedetomidine in ECT did not interfere with motor and EEG seizure durations but could reduce maximum MAP and HR after ECT.

Some of the literature said,

- Dexmedetomidine has been used successfully in the treatment of withdrawal from benzodiazepines, opioids, alcohol, and recreational drugs.
- Used as an adjunct in otorhinolaryngology anesthesia for middle ear surgery and rhinoplasty.
- Used as an adjunct in the repair of aortic aneurysms.
- Management of tetanus in ICU.
- Used as an antishivering agent.
- Dexmedetomidine is effective in preventing ethanol-induced neurodegeneration.
- Dexmedetomidine used in both noninvasive and invasive procedural sedation in infants and children like MRI and CT scans, and for invasive procedures, like placement of central venous lines in infants,bronchoscopy and laryngoscopy, cardiac catheterization and others [76, 77].

CONCLUSION

Dexmedetomidine induces sedation, analgesia, amnesia, and perioperative sympatholytic, anaesthetic-sparing, and hemodynamic-stabilizing properties without depressing respiratory function. It provides a unique type of sedation,“conscious sedation”, in which patients appear to be sleepy but are easily aroused, cooperative and communicative when stimulated. But, Patients should be in closed monitor observation while we used dexmedetomidine.

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