Role of Intravenous Dexmedetomidine in Prolonging Postoperative Analgesia and Quality of Block Following Spinal Anaesthesia. A Systemic Review and Update

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Abstract

Intravenous dexmedetomidine is being increasingly used in perioperative setting including as an adjunct to local anaesthetic in various regional techniques with an intent either to improve the block quality, to increase the duration of block or to provide sedation and patient comfort during the postblock period. Intravenous dexmedetomidine when used just before or after spinal anaesthesia has many desirable effects such as adequate sedation and patient comfort, longer sensory-motor blockade, prolong postoperative analgesia and reduces post-anaesthesia shivering. A systemic review was done to evaluate and provide update on the use of intravenous dexmedetomidine as an adjunct for spinal anaesthesia. The optimal dose or method of administration of intravenous dexmedetomidine under spinal anaesthesia has not been defined yet. Current literatures suggest a ceiling effect on prolonging post-spinal analgesia after 0.5 mcg/kg boluses. With increasing the dose beyond 0.5 mcg/kg resulted in unwanted side effects notably bradycardia and excessive sedation. Further study with diverse population is needed to define the optimal dose of intravenous dexmedetomidine.

Keywords: Intravenous; Dexmedetomidine; Spinal anaesthesia; Postoperative analgesia; Sedation; Shivering

Introduction

Although spinal anaesthesia has been established as simple and safe anaesthetic technique for short to intermediate duration of infra umbilical surgeries, it may not be very comfortable for all, specially those with high level of anxiety, prolonged surgeries with uncomfortable positions and inadequate level of spinal block. These patients at times may need supplementation with sedative-analgesic or conversion to general anaesthesia, with potential risk of respiratory depression and consequent hypoxia. Dexmedetomidine being a sedative with analgesic without respiratory depressant property provides, intraoperative sedation, alleviates position related discomfort and to an extend can cover up inadequate block height along with prolonging the postoperative analgesia. Adequate sedation after spinal anaesthesia reduces patient anxiety level, physiological and psychological stress, and increases the patient and surgeon satisfactions [1,2].

Though dexmedetomidine was initially approved by FDA for short term sedation in critical care, its unique pharmacodynamic profile has render it suitable for perioperative care during general or regional anaesthesia. Dexmedetomidine is increasingly used as an adjunct to various regional techniques [3-8]. There are studies on its successful use to facilitate laryngoscopic endotracheal intubation without using muscle relaxant [9,10], and fiber optic guided intubation [11].

The different potential role of intravenous dexmedetomidine in neuraxial anaesthesia has not been evaluated fully, few studies have shown that it prolong the sensory-motor blockade and provide better intraoperative and postoperative analgesia [12,13]. Apart from prolonging analgesia, it has been used for prevention and treatment of shivering [14-23].

A systemic review is done to evaluate and provide update on the use of intravenous dexmedetomidine on spinal anaesthesia block quality, duration of postoperative analgesia, intraoperative sedation following spinal anaesthesia and also to highlight its potential advantages and risk associated with its use.

Pharmacodynamic of Dexmedetomidine

Dexmedetomidine is an imidazole compound, dextroisomer of medetomidine and is 7-8 times selective alpha 2 agonist than clonidine. Alpha 2 agonist inhibits adenyl cyclase activity, reduces brain stem vasmotor center-mediated CNS activation producing sympatholysis, anxiolysis, sedation and posses some analgesic properties [15,16].

Alpha 2 receptor have been found in the peripheral and central nervous system, platelets, liver, pancreas, kidney and eyes [16,17]. The physiological responses regulated by alpha 2 receptor vary depending on their location. Brain and spinal alpha 2 receptor activation inhibit neuronal firing, which leads to hypo tension, bradycardia, sedation and analgesia. Apart from action in nervous system, extraneuronal alpha 2 activation leads to decrease in salivation and secretions, decrease gastric motility, inhibit renin release, increased glomerular filtration rate; decreased intraocular pressure and decrease insulin secretion from the pancreas [18,19]. There are various sub classification of alpha 2 receptor, alpha 2 A, B and C [16]. Analytical effects is manly mediated by alpha 2 C and alpha 2 A receptors present on the neurons of superficial dorsal horn in lamina II, when activated, it inhibits the release of pro-nociceptive transmitters namely substance P and glutamate and hyperpolarize spinal inter-neurons inhibiting signal transmission [20,21] whereas the sedative action of dexmedetomidine has been postulated as hyper-polarization in locus ceruleus neurons on the pons and lower brain stem (alpha 2A) resulting in inhibition of noradrenaline release and inhibiting activity in descending medullospinal noradrenergic pathways [22,23]. Alpha 2 B-agonism suppresses shivering centrally, promote analgesia spinal and induces vasoconstriction in peripheral arteries. The alpha 2C receptor is also...
associated with sensory processing, mood and stimulant induced locomotor activity, modulation of cognition and regulation of adrenaline outflow from the adrenal medulla [20,24].

Pharmacokinetics

Dexmedetomidine undergo first pass metabolism, so has very poor bio-availability if administered orally. Intravenous dexmedetomidine in the dose range of 0.2-0.7 mcg/kg/hr exhibits linear pharmacokinetics. Being lipophilic it is distributed widely, crosses blood brain barrier, volume of distribution 118 L, it is 94% protein bound and as such does not displace most protein bound drug commonly used in anaesthesia and intensive care. After I V administration, dexmedetomidine has a rapid distribution phase with a half-life of 6 min and the elimination half-life of 2 hrs with a clearance rate of 39 l/hr. Context-sensitive-half-life varies from 4 min for 10 min infusion to 250 min for 8 hr infusion. Dexmedetomidine undergoes complete bio-Transformation by glucuronidation and by cytochrome P-450 mediated aliphatic hydroxylation to inactive water soluble metabolites, 95% of which is excreted in urine and the remaining in faeces. The dose need to be adjusted in patients with hepatic failure owing to lower rate of metabolism [25,26].

Intravenous dexmedetomidine and spinal anaesthesia

Use of intravenous dexmedetomidine before or just after spinal block is not a new concept. The intent of using intravenous dexmedetomidine is either to (1. increase the quality and duration of sensory-motor block, (2. to provide prolong postoperative analgesia, (3. to provide sedation and or as (4. anti-shivering prophylaxis. The timing and dosing method of intravenous dexmedetomidine in spinal anaesthesia varies in different study. Commonly used method of intravenous dexmedetomidine is either as loading dose just before or after spinal anaesthesia [12,27-32], loading dose followed by continuous infusion [11,33-36]. Most commonly used loading dose is 0.5 mcg/kg to 1 mcg/kg over 10 min and infusion dose range from 0.2 mcg/kg/hr to 1 mcg/kg/hr [25,26].

Intravenous dexmedetomidine on quality of sensory-motor blockade

Several clinical studies have been published on the effect of intravenous dexmedetomidine on spinal anaesthesia. Most of these studies and meta-analysis has shown that intravenous dexmedetomidine given just before or after spinal anaesthesia improved the quality and duration of spinal block [12,27-33]. There are many variation in the dosing and method of administration, so it challenging to reliably translate the result into clinical practice. Spinal anaesthesia might shorten the onset of sensory-motor block due to alpha-2 receptor activation induced inhibition of nociceptive impulse transmission [11]. Dexmedetomidine has been reported to potentiate the effects of intrathecal local anaesthetics. The mechanism of synergistic action of dexmedetomidine on spinal local anaesthesia is still not clear. However, supra-spinal, spinal or direct analgesia and or vasoconstriction activities are involved [32,37-43]. More-over, dexmedetomidine produces a greater degree of differential blockade by preferentially blocking the myelinated A alpha-fibers involved in motor Conduction [27].

Block Characteristics

Onset of sensory/motor blockade

Few studies have evaluated the onset time of sensory block after spinal anaesthesia, Readdy et al. have compared intravenous dexmedetomidine with clonidine reported that dexmedetomidine shortened onset of sensory-motor block [41] but other studies are not supporting the faster onset of sensory/motor block [12,13,27-30]. Few study have reported intravenous dexmedetomidine shortened the onset time by 30-60 sec, which might be clinically significant but it was insignificant statistically [11,33,35].

Block height

There are limited studies on effect of intravenous dexmedetomidine on sensory-motor block height. Some studies have reported higher level of sensory-motor blockade of hyperbaric bupivacaine by the use intravenous dexmedetomidine [30,31,33,35,43] whereas, in study using low dose intravenous dexmedetomidine as sedative agent after spinal anaesthesia reported no difference in block characteristic by dexmedetomidine [36]. Lee et al. [12] using two different dose of dexmedetomidine (0.5 mcg/kg Vs 1 mcg/kg) reported higher level of sensory block in both group of dexmedetomidine in comparison to placebo. Abdallah et al. [27] did quantitative analysis in a meta-analysis after collecting data from the studies showing higher sensory block, but they failed to see any statistically significant increase in height of block by use of dexmedetomidine.

Duration of block

Most of the studies on intravenous dexmedetomidine were to assess the duration of sensory/ motor blockade. Sensory block duration -though there are too much variation in method and dose of intravenous dexmedetomidine and duration of sensory blockade-but most of the studies has reported significantly increased duration of sensory blockade by use of intravenous dexmedetomidine [11-13,28-35,37,38,42]. Only one study did not find any difference in block quality with the use of low dose dexmedetomidine infusion that was used solely for the purpose of intraoperative sedation [36]. Few studies has observed differences in sensory and motor blockade, compared with the prolongation of sensory block, the duration of motor block was not affected use of intravenous dexmedetomidine [30,32,35]. In a recent meta-analysis on use of intravenous dexmedetomidine on the duration of spinal anesthesia, 7 moderate to high quality studies were analyzed. Sensory block duration was prolonged by at least 34% (CI limit, Point estimate 38%) and motor blockade by at least 17% (CI limit, point estimate 21%) [27]. Another meta-analysis on the effects of intravenous and intrathecal dexmedetomidine in spinal Anaesthesia found that whatever route of administration, dexmedetomidine could prolonged the sensory and motor blockade, although there was significant heterogeneity in the duration of sensory and motor in intravenous route, such results were not found consistently in intrathecal route [39]. Several studies reported prolonged duration of motor block following use of intravenous dexmedetomidine bolus followed by infusion. However, in a study by Kaya et al. [35] use of single dose of 0.5 mcg/kg of dexmedetomidine did not affect the duration of motor block.

Lee et al. conducted a study using two different dosing of dexmedetomidine 0.5 mcg/kg and 1 mck/kg bolus without any infusion, observed that the duration of spinal anaesthesia (sensory-motor block) was prolonged by dexmedetomidine in comparison to placebo. There was no difference in block quality between the two different dosing of dexmedetomidine [12] which also match with the observation by Jaakola et al. [40] where there is ceiling effect on analgesia at 0.5 mcg/kg.

A recent double blind study with intrathecal (3 mcg) and intravenous (0.5 mcg/Kg) dexmedetomidine against placebo (saline) reported prolonged duration of spinal anaesthesia (sensory-motor)
which was more longer in intrathecal route. There was no effect on the block onset or maximum block height [41].

Postoperative Analgesia

Different method or techniques were used to evaluate the Postoperative analgesia, some studies it was evaluated as pain score or time for first analgesic request whereas some studies it was used as additional opioid requirement or opioid sparing effect. In a meta-analysis by Abdulla et al. revealed that use of intravenous dexmedetomidine resulted in 61% reduction in pain score at 6 hrs and 53% prolongation of the time of first analgesic request [27]. Annamalai et al. [30] has used 1 mcg/kg dexmedetomidine as slow bolus over 10 min, either 10 min before or 30 min after the spinal anaesthesia with bupivacaine reported reduced pain score and longer duration of postoperative analgesia by dexmedetomidine. The timing of dexmedetomidine injection did not make any difference in the postoperative analgesia or other block characteristics.

Recent double blind study by Dinesh et al. reported prolongation of first analgesic request and 24 hrs mean analgesic requirement was significantly less in the dexmedetomidine group compared to control group [33]. Reddy et al. compared intravenous dexmedetomidine (0.5 mcg/kg) with clonidine (1 mcg/kg) as premedication before giving the spinal anaesthesia with bupivacaine [31] observed significantly longer interval for the first analgesic request in dexmedetomidine group.

Sedation under spinal anaesthesia

Though regional anaesthesia confer many benefit and patient satisfaction in terms of staying awake during the procedure, early family contact and early food intake, [44,45] from anaesthesiology point of view, rapid postoperative recovery and preservation of protective airway reflexes are the most important advantages of regional anaesthesia. But many patients don’t like to be awake to remember or recall the intraoperative procedure [46] and request for some form of sedation. The aim of sedation in regional anaesthesia technique include general patient comfort, freedom from specific discomfort and some amnesia for entire procedure [47]. proper sedation has shown to improve the patient satisfaction during regional anaesthesia [48,49] and may be considered as a mean to increase the patient acceptance for regional anaesthesia technique, sedation not only increases the patient acceptance for regional anaesthesia, it sometime cover up some inadequate or insufficient block and can help to reduce the requirement of opioid angesic and indirectly contribute to reduction in postoperative nausea vomiting [50-52]. The sedative action of dexmedetomidine differs from other agents (benzodiazepine and propofol) that act through GABA receptor and produces clouding of consciousness and at times patient co-operation may be lost, the sedation produced by dexmedetomidine is like that of natural sleep as it act on the locus ceruleus of the brain, which induces sedation resembling natural sleep by means of sleep modulation and maintaining respiratory control [53-55]. moreover dexmedetomidine has no or minimal effect on respiratory rate and tidal volume [56,57]. Most of the studies on intravenous dexmedetomidine have used either a loading dose or loading dose followed by infusion and sedation was a secondary outcome measure. Few study has been done on intravenous dexmedetomidine where sedation was the primary measure [58-60]. Adequate sedation has been reported with lower dose of dexmedetomidine (0.5 mcg/kg with or without infusion) [1,11,12,61]. excessive sedation has been reported when intravenous dexmedetomidine (1 mcg/kg) was given as bolus dose [1,12,29,30,34,37,60,61].

Ok et al. conducted a study on intravenous dexmedetomidine to find out the optimal dose for sedation after spinal anaesthesia. After a loading dose of dexmedetomidine 1 mcg/kg over 10 min, patients were divided into three group, one group to receive 0.2 mcg/kg/hr, another group 0.4 mcg/kg/hr and third group saline as placebo [1]. All patient had good sedation till 60 min, after that the saline treated group had less sedation, whereas, 0.2 mcg/kg/hr infusion group sedation was prolonged for 80 min and 0.4 mcg/kg/hr infusion group by 120 min. Tekin et al. also found significant sedation with 0.4 mcg/kg/hr infusion for 50 min after a loading dose of 1 mcg/kg over 10 min following spinal anaesthesia [37]. Lee et al. using two different dose of 0.5 mcg/kg and 1 mcg/kg dexmedetomidine as loading dose without any infusion observed deeper sedation for about 60 min in 1 mcg/kg group without compromising the cardio-respiratory functions [12]. Similarly Annamalai et al. using 1 mcg/kg intravenous dexmedetomidine 10 min before or 30 min after block reported higher sedation with 1 mcg/kg dexmedetomidine [30]

Choi and Lee has compared two different loading dose 0.6 mcg/kg and 1 mcg/kg of dexmedetomidine after spinal anaesthesia, similar sedation level were observed 5 min after the loading dose, but there was more hypotension and bradycardia incidences in 1 mcg/kg group [58].

A comparative study between dexmedetomidine and remifentanil infusion as sedation technique for arthroscopic knee surgery under spinal anaesthesia by Kirman et al. [59] observed higher sedation in dexmedetomidine (1 mcg/kg bolus followed by 0.2 mcg/kg/hr infusion) group than remifentanil (0.5 mcg/kg bolus followed by 3 mcg/kg/hr). Although dexmedetomidine treated group exhibited deeper sedation, there was no haemodynamic or respiratory depression. Whereas remifentanil treated group had lighter sedation with short recovery time but exhibited higher incidences of respiratory depression.

Dexmedetomidine has linear pharmacokinetics and dose dependent sedative action, [57] when a loading dose of dexmedetomidine 1 mcg/kg administered over 10 min, the average peak concentration was reached in 17 min with terminal half life of 2 hr 10 min. So a single bolus dose might be sufficient for procedure lasting less than 60 min whereas continuous infusion is needed for longer procedure. The recommended dose of dexmedetomidine for sedation is 1 mcg/kg bolus followed by 0.2-0.7 mcg/kg/hr for conscious sedation or procedural sedation [25] however the optimal sedative dose of after spinal anaesthesia has not been defined, spinal anaesthesia as such have some sedative action because of blockade of ascending somato-sensory transmission that depress the excitability of reticulo-thalamo-cortical arousal mechanism [60]. Because of this patients under spinal anaesthesia require much lower dose of any sedative drug.

Use of dexmedetomidine as anti-shivering

Incidences of shivering under spinal anaesthesia has been reported as high as 40-60% [61-64]. Shivering not only cause discomfort to the patient, it increases the oxygen consumption, increases catecholamine level subjecting the patient to a higher risk of cardiovascular complications [63-65]. The Alpha-2 receptor agonists are known to possess anti-shivering property by lowering shivering and vasoconstriction threshold without increasing respiratory depression, nausea-vomiting unlike the other anti-shivering drugs like meperidine [61,62]. In addition, it has central hypothalamic thermoregulatory effects [66-69].

Intravenous Dexmedetomidine in dose range of 0.5 to 1 mcg/kg has been used successfully used either for prevention [14,67-69] or treatment [70-72] of shivering after general or regional anaesthesia. Intravenous dexmedetomidine 0.5 mcg/kg as loading dose was found 100% effective in treatment of post anaesthesia shivering following
general anaesthesia in children [72]. Gupta et al. using tramadol vs. dexmedetomidine, observed that dexmedetomidine was equally effective, but was associated with favorable outcome such as shorter time for complete cessation of shivering and less incidences of nausea-vomiting [73].

### Intravenous dexmedetomidine and adverse outcome

Most commonly reported adverse effects after intravenous dexmedetomidine is Bradycardia requiring atropine and hypotension. Hypotension and bradycardia are common physiological response to spinal anaesthesia due to blockade of sympathetic system. The primary physiologic alteration are decrease preload and cardiac volume, which combine with bradycardia to reduce arterial blood pressure and cardiac output. Mild to moderate hypotension and bradycardia may be treated with volume loading, epinephrine or atropine [74-76].

#### Hypotension

As we all know, hypotension occurs easily with spinal anaesthesia and it can be treated with either fluid loading, epinephrine or phentolamine [77,78]. The incidence of hypo-tension requiring intervention after spinal anaesthesia remained same despite use of intravenous dexmedetomidine. None of the studies so far has shown that dexmedetomidine increases the hypotension after spinal anaesthesia [27,40].

#### Bradycardia

Haemodynamic response in the form of transient hypertension and reflex bradycardia followed by hypotension and bradycardia has been described with the use of higher dose and rapid infusion of dexmedetomidine [74,75]. Most studies on intravenous dexmedetomidine with dose of 1 mcg/kg loading dose over 5-10 min had bradycardia as one of the prominent side effect with incident up to 30-40% [29,32-34,37,71].

Meta-analysis on the intravenous dexmedetomidine and spinal anaesthesia by Abdallah et al. [27] has found that there was 3.7 fold increase in bradycardia incidence and it was more significant where dexmedetomidine initial loading dose was infused over a shorter period such as over 5 [29] to 10 [32-34] min, compared with those studies where initial loading dose was administered over 20 min [38]. Similarly Niu et al. in a meta-analysis found that use of dexmedetomidine has either intravenously or intrathecally resulted increase incidence of bradycardia requiring atropine [39]. The reported bradycardia in all these studies was transient and were easily reversed with intravenous atropine.

#### Other adverse events

There are no reports of increase incidences of headache, pruritus, urinary retention that has been directly attributed by dexmedetomidine.

### Dexmedetomidine and organ protection

Dexmedetomidine has been shown to have organ protective effects in animal models particularly in modulation of cytokine and inflammatory mediators in variety of ischaemia and ischemic-reperfusion injury in animal [78-83]. However, such protective effects are not evident in human studies. Bostankulu et al. conducted a study to define the effects of dexmedetomidine on the tourniquet ischemia-reperfusion injury during general anaesthesia, use of dexmedetomidine did not alter the total antioxidant capacity or metabolites of lipid peroxidation indicating it has no additional organ protective effects under general anaesthesia. One study has demonstrated that use of dexmedetomidine in post-bypass period in coronary bypass surgery had lower incidence of acute kidney injury [84]. Few other animal experimental study has shown organ protective effects of dexmedetomidine on myocardial protection [82,85] neuronal protection in spinal cord injury [86-89], reduction in cerebral vasospasm after sub-arachnoid haemorrhage, [89] prevention of retinal apoptosis in retinal ischaemia [90], preventive effects in Acute lung injury [91], visceral and renal protection in ischemic-reperfusion injury [81-84,92,93]. The ability to protect against organ dysfunction, notably myocardial, renal and neuronal, may yet to be the defining characteristic of this class of drug in human being. Dexmedetomidine pre-treatment delayed the onset of bupivacaine induced cardiotoxicity in rat model [85]. Further clinical and preclinical studies are required to inform us about the diversity of therapeutic application of dexmedetomidine.

### Summary

Intravenous dexmedetomidine in context of spinal anaesthesia has a definite role in providing adequate intraoperative sedation, good quality of block and prolonging the postoperative analgesia. It definitely prolong the duration of sensory block as shown by various studies, the duration of motor block has inconsistent report and it is difficult to come to any conclusion till this moment. Similarly the onset of block, height of block has conflicting results in different study and there is no strong evidence to prove that intravenous dexmedetomidine really help in reducing onset time or increasing the level of sensory- motor block. The timing of dexmedetomidine injection did not make any difference in the postoperative analgesia or other block characteristics. The prolongation of postoperative analgesia though consistent in many study it has a plateau effect at around 0.5 mcg/kg, given as either isolated bolus or bolus followed by infusion. Increasing the loading dose beyond 0.5 mcg/kg, there is proportionate increase in side effects notably bradycardia requiring atropine and excessive sedation. More adverse effects were also reported when loading dose of 1 mcg/kg was infused over short period (5-10 min).

Optimal dosing of intravenous dexmedetomidine has not been defined yet. Similar postoperative analgesia has been achieved without using the loading infusion also. No loading or low loading dose of 0.25 to 0.5 mcg/kg or loading over longer period (more than15 min) followed by infusion might be more safer and appropriate provide the adequate intraoperative sedation, good quality of block with prolong postoperative analgesia. Future studies using different dosing regime such as isolated bolus bolus followed by infusion or isolated infusion alone might clear our knowledge and understanding of the proper dosing of intravenous dexmedetomidine in patients under spinal anaesthesia.

### Conclusion

Intravenous dexmedetomidine provide adequate intraoperative sedation, increases patient comfort, improves spinal block quality and prolong the postoperative analgesia. The optimal dosing is yet to be defined. More incidences of bradycardia and excessive sedation is warranted with higher dose approaching 1 mck/kg.

### References


