Introduction

Regional anesthesia has become more popular in cesarean deliveries because most of the parturients prefer being awake during the birth process. In addition, regional anesthesia may be a safer method than general **(*Jawad, 2011*).**

In spinal anesthesia, local anesthetics alone may not be enough for an effective postoperative analgesia and hemodynamic stability of the patient which is crucial during Cesarean section. So far many adjuncts have been used to augment the analgesia produced by intrathecal local anesthetics and to reduce their adverse effects ***(Yu et al., 2002).***

Low dose fentanyl added to Bupivacaine provided spinal anesthesia for cesarean delivery with less hypotension, vasopressor requirements, and nausea. However intrathecal fentanyl frequently produces pruritus which is unfortunately difficult to be prevented by prophylactic medications ***(Korhonen et al., 2003).***

Dexmedetomidine is a highly selective α2 Adrenergic agonist which has both analgesic and sedative properties when used as an adjuvant in regional anaesthesia. Dexmedetomidine can be titrated to the desired level of

sedation without significant respiratory depression. Dexmedetomidine has an analgesic-sparing effect, significantly reducing opioid requirements both during and after surgery. In addition, dexmedetomidine has a sympatholytic effect that can attenuate the stress response to surgery; thus mitigating tachycardia and hypertension. Because of its analgesic properties "cooperative sedation" and lack of respiratory depression, dexmedetomidine is increasingly being used as a sedative and adjuvant in anesthesia ***(Martin et al., 2003).***

Intrathecal Dexmedetomidine are found to have antinociceptive action for both somatic and visceral pain. Experimental study on acute exposure of rats to dexmedetomidine at the anticipated delivery time recorded absence of any adverse effects on their perinatal morphology ***(****Gupta et al., 2011).*

Aim of the work

The purpose of this study is to compare effects of single dose intrathecal Bupivacaine with Dexmedetomidine versus Bupivacaine with Fentanyl on labor outcome in spinal anesthesia for uncomplicated cesarean delivery.

Pharmacology of Dexmedetomidine

Introduction

Dexmedetomidine is a highly selective alpha-2 agonist (α2-AR) that provides anxiolysis and cooperative sedation without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose-dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence that dexmedetomidine has organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection, and renoprotection (***Scheinin et al., 2008).***

Dexmedetomidine is a relatively new drug approved at the end of 1999 by the Food and Drug Administration (FDA) for humans use for short-term sedation and analgesia (<24 hours) in the intensive care unit (ICU). Dexmedetomidine is a useful sedative agent with analgesic properties, hemodynamic stability and ability to recover respiratory function in mechanically ventilated patients facilitating early weaning ***(Takrouri et al., 2002)***.

Besides being a new modality of sedation and analgesia in ICU patient management, it has been studied in several other perioperative settings ***(Takrouri et al., 2002)***.

Receptor Pharmacology

Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine. Its specificity for the alpha-2 receptor is seven times that of clonidine, with an alpha-2/alpha-1 binding affinity ratio of 1620:1, and its effects are dose-dependently reversed by administration of a selective alpha-2 antagonist such as atipamezole (**Ma et al., 2004).**

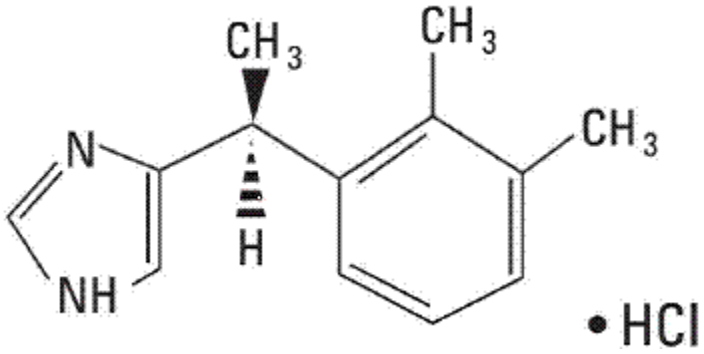

Fig. (1): Structural formula of dexmedetomidine hydrochloride **(Karol& Maze, 2000).**

α2-AR agonists produce clinical effects after binding to G-Protein-coupled α2-AR, of which there are three subtypes (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found in the central, peripheral, and autonomic nervous systems, as well as in vital organs and blood vessels ***(Moura et al., 2006).***

Distribution of alpha-2 adrenoceptors:

Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve ending and noradrenergic neurons in the central nervous system where they inhibit the release of noradrenaline. Postsynaptic alpha-2 adrenoceptors exist in a number of tissues where they have a distinct physiological function: these include the liver, pancreas, platelets, kidney, adipose tissue and the eye ***(Langer, 2005)***.

The locus coeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and has a high density of alpha-2 receptors. A high density of alpha-2 adrenoceptors has also been demonstrated in the vagus nerve, intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains alpha-2a subtype adrenoceptors, while the primary sensory neurons contain both alpha-2a and alpha-2c subtypes of adrenoceptors ***(Scheinin and Schwinn, 2004).***

Mechanism of Action:

Dexmedetomidine, an imidazole compound, is the active pharmacologically dextroisomer of medetomidine that displays specific and selective alpha 2-adrenoceptor agonism. The mechanism of action is unique and differs from those of currently used sedatives agents, including clonidine.

Activation of the imidazoline receptors in the brain and alpha-2 adrenoceptors in the spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the alpha-2 adrenoceptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract, contraction of vascular and other smooth muscle, inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in kidney, decreased intraocular pressure and decreased insulin release from the pancreas ***(Ralph et al., 2001).***

The mechanism of the analgesic actions of alpha-2 agonists has not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral alpha-2 adrenoceptors may mediate antinociception ***(Kauppila et al., 2009).***

The substantia gelatinosa of the dorsal horn of the spinal cord contains alpha-2 receptors which, when stimulated, inhibit the firing of nociceptive neurons stimulated by peripheral A-delta and C fibers and also inhibit the release of the nociceptive neurotransmitter substance P. The spinal mechanism explain why anesthesiologists have found success in using clonidine as an epidurally

administered agent in addition to its primary use as an intravenous drug ***(Arain et al. 2004).***

The improved specificity of dexmedetomidine for the alpha-2 receptor, especially for the 2A subtype of this receptor, causes it to be a much more effective sedative and analgesic agent than clonidine. Studies have shown that dexmedetomidine is 8 times more specific for alpha-2 adrenoceptors than clonidine (ratios of alpha 2 to alpha 1 activity, 1620:1 for dexmedetomidine, and 201:1 for clonidine) ***(Nelson et al., 2006).***

Pharmacokinetics:

Absorption and distribution:

Dexmedetomidine exhibits linear pharmacokinetics in the recommended dose range of 0.2 to 0.7 μg/ kg/ hr administered as intravenous infusion up to 24 hours. The distribution phase is rapid, with a half-life of distribution of approximately 6 minutes and elimination half-life of 2 hours. The steady-state volume of distribution is 118 Litres. The average protein binding is 94% and is constant across the different plasma concentrations and also similar in males and females. It has negligible protein binding displacement by drugs commonly used during anesthesia and in the ICU like fentanyl, ketorolac, theophylline, digoxin, and lidocaine

(Kivisto et al., 2004). Context-sensitive half-life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Oral bioavailability is poor because of extensive first-pass metabolism. However, bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication ***(Anttila et al., 2003)***.

Metabolism and excretion:

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation to produce inactive metabolites involves both direct glucuronidation as well as cytochrome P450 mediated metabolism ***(Dutta et al., 2008)***.

Dexmedetomidine pharmacokinetics were not significantly different in subjects with severe renal impairment (creatinine clearance <30 L/min) compared to healthy subjects ***(De Wolf et al., 2005).***

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subject. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those

observed in the normal healthy subjects, respectively. It may be necessary to consider dose reduction in patients with hepatic impairment ***(De Wolf et al., 2005).***

Pharmacodynamics

Sedative and analgesic effects:

Dexmedetomidine induces sedation resembling physiological sleep maintaining reusability without causing respiratory depression. It produces analgesia by central, spinal and peripheral mechanisms. Net result is neither the nerve/ terminal are allowed to get stimulated, nor it can transmit/ propagate the signal forwards ***(Langsjo et al, 2010)***.

The supra-spinal level of analgesia and sedation may be due to modulation of descending noradrenergic pathway originating in the main noradrenergic nucleus/center locus coeruleus. This supraspinal action could explain the prolongation of spinal analgesia after intravenous administration of dexmedetomidine ***(Nelson et al., 2006)***.

The spinal level of antinociceptive action seems to be through the substantia gelatinosa (Lamina II of Rexed in grey matter of spinal cord). It closes the gate at the dorsal horn to stimuli coming from peripheral Aδ and C fibers and also inhibits release of nociceptive humoral transmitters like substance P. It produces hyperpolarization of cell membrane.

These mechanisms effectively suppress, both neuronal firing, as well as, release of neurotransmitter noradrenaline at the nerve terminals. This anti-nociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics ***(Kohli et al., 2010*)**.

Cardiovascular system effects:

All subtypes of α2-adrenoceptors are present in blood vessels, and they play important roles in the regulation of the cardiovascular system, as they regulate vasoconstriction and inhibit noradrenaline release from sympathetic nerve endings. Additionally, α2-adrenoceptor activation results in reduced sympathetic tone and augmentation of cardiac-vagal activity, with consequent cardiovascular effects ***(Toader et al., 2009).***

Dexmedetomidine evokes a biphasic blood pressure response. A short hypertensive phase 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 ***(Kurnik et al., 2011).*** This initial response lasts for 5 to 10 minutes and is followed by a decrease in blood pressure of approximately 10% to 20% below baseline and a stabilization of the heart rate, also

below baseline values; both of these effects are caused by the inhibition of the central sympathetic outflow This is followed by a longer lasting decrease in heart rate and blood pressure due to a centrally mediated decrease in sympathetic tone and an increase in vagal activity ***(Snapir et al., 2006).***

In healthy subjects, dexmedetomidine reduces myocardial perfusion in parallel with reduced myocardial oxygen demand estimated by rate-pressure product. Dexmedetomidine did not appear to reduce myocardial perfusion in a dose-dependent manner, as the effects were similar at low (0.5 ng/ml) and high (5 ng/ml) plasma dexmedetomidine concentrations. Importantly, the attenuated myocardial perfusion did not result in myocardial ischaemia in healthy volunteers as assessed by ECG and echocardiography ***(Snapir et al. 2006).***

Cerebral vascular effects:

Dexmedetomidine has also been shown to have neuroprotective qualities ***(Ma et al. 2004).*** A recent study in healthy volunteers, however, reported that both cerebral blood flow and cerebral metabolic rate were decreased by dexmedetomidine in a dose-related manner, preserving the coupling of cerebral blood flow and cerebral metabolic rate ***(Drummond et al. 2008).*** It is not known whether this result

is valid also in patients with neurological injuries, even though a small study employing brain tissue oxygen partial pressure measurement in surgical patients with neurovascular injuries suggests it ***(Drummond and Sturaitis 2010).***

Respiratory effects:

In healthy volunteers, even very high dexmedetomidine doses (measured mean plasma dexmedetomidine concentration of 14.7 ng/ml) do not impair arterial oxygenation. Still, small decreases in blood pH and gradual increases in arterial carbon dioxide levels and respiratory rate follow administration of dexmedetomidine in increasing doses ***(Ebert et al., 2000).*** The lack of clinically significant adverse effects on respiration has been confirmed in further studies in healthy volunteers and patients ***(Cooper et al., 2011).***

The combination of alpha-2 adrenoceptor agonists with opioids does not lead to further ventilatory depression. At clinically effective doses, dexmedetomidine has been shown to cause much less respiratory depression than other sedatives. It has been expected that the lack of respiratory depressant effects of Dexmedetomidine would shorten the time needed for mechanical ventilation ***(Riker et al., 2011).***

Gastrointestinal effects:

Generally, α2-agonists have inhibitory effects on gastric emptying and motility .When α2-agonists are used as premedication, decreased salivary flow is one of the advantages. Previous reports have suggested that dexmedetomidine inhibits gastric emptying and gastrointestinal transit in rats ***(Fulop et al., 2005).*** In a previous study, dexmedetomidine did not significantly inhibit gastric emptying compared with propofol in intensive care patients ***(Memis et al., 2006).***

Skeletal muscle effect:

Dexmedetomidine can reduce the incidence of postoperative shivering. It has decreased the incidence of shivering after general and spinal anesthesia and been used to treat shivering during therapeutic hypothermia ***(Venn et al., 2001).***

Miscellaneous effects:

As an imidazole compound, dexmedetomidine has the potential to have inhibitory effects on cortisol synthesis similar to etomidate. However, hypocortisolism has not been an issue after clinically relevant dexmedetomidine doses in healthy volunteers, surgical patients or patients needing post-operative intensive care ***(Venn et al., 2001).***

α2A-adrenoceptors are involved in the regulation of blood glucose homeostasis, and dexmedetomidine lowers insulin and elevates glucose levels in mice .It has been shown that there is a tendency for low insulin concentration in postoperative intensive care patients and hyperglycemia in intensive care patients after dexmedetomidine administration ***(Riker et al. 2009).***

It has been shown in mice that clonidine and dexmedetomidine protect against contrast medium-induced nephropathy by preserving outer medullary renal blood flow as quantified using laser-Doppler flow probes ***(Billings et al., 2008).*** Additionally, dexmedetomidine inhibits vasopressin secretion, causing water diuresis, which might be beneficial during ischemic events. The increasing effect of dexmedetomidine on urinary output has been observed in thoracotomy and heart surgery patients, but no clear clinical renal benefit has been shown (***Leino et al., 2011).***

Therapeutic uses of dexmedetomidine

Sedation: