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Evaluation of Intravenous Dexmedetomidine on Duration of Bupivicaine Spinal Anesthesia

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Presented By:

Wael Samir Mohamed Amin Maher
M.B.B.Ch.- M.Sc. in Anesthesiology
Faculty of Medicine,
Ain Shams University

Supervised by:

Prof. Dr. AmrEssam El-Din El-Hennamy
Professor of anesthesia and intensive care
Faculty of medicine, Ain Shams university

Prof. Dr. Hesham Mohamed Mahmoud El-Azzazi
Assistant Professor of anesthesia and intensive care
Faculty of medicine, Ain Shams university

Dr. Assem Adel Moharram
Lecturer of anesthesia and intensive care
Faculty of medicine, Ain Shams university

Ain Shams University
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INTRODUCTION

Spinal anesthesia has several advantages, for example spared spontaneous respiration, low cost, reduced risk of pulmonary aspiration secondary to vomiting in patients with full stomach, facilitated surgery via provision of relaxation in the intestines and abdominal wall, elimination of the need for intubation, minimal disruption of blood chemistry, reduced surgical hemorrhage, and earlier return of intestinal motility ***(Brown, 2009)***. Spinal anesthesia also has complications and contraindications, for example refusal by the patient, inability to estimate the duration of surgery, post-dural puncture headache (PDPH), urinary retention, and waist and back pain ***(Bernard, 2001).***

Despite the many advantages of spinal anesthesia, the relatively short duration of the local anesthetic during prolonged surgery can be a problem. Prolonging the duration of spinal anesthesia would allow longer surgical interventions. Various additives have been used in order to prolong the duration of spinal anesthesia, including vasoconstrictive agents such as epinephrine, phenylephrine, and clonidine. Agents such as opioids and neostigmine have also been used ***(Almeida et al., 2003)***.

Alpha 2-adrenoceptor agonists are being increasingly used in critical care and anesthesia. Beside sedation and analgesia, they also decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery. In addition, they are used as adjuvant drugs during regional and general anesthesia ***(Kaabachi et al., 2007).*** Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation in the intubated patients at the intensive care settings ***(Kanazi et al., 2006).***

Different adjuvants have been used to prolong spinal anesthesia, with the possible advantages of delayed-onset of postoperative pain and reduced analgesic requirements. Dexmedetomidine, a highly selective alpha 2-adrenoreceptor agonist, has been used for premedication and as an adjunct to general anesthesia. Intravenous dexmedetomidine premedication before general anesthesia provides preoperative sedation, analgesia, and hemodynamic stability and reduces requirements for intraoperative inhalational agents and postoperative analgesics ***(Basar et al., 2008).***

AIM OF THE WORK

The aim of this study is to evaluate the effect of intravenous dexmedetomidine administration on the duration of bupivicaine spinal anesthesia, and to assess the level of sedation and any hemodynamic changes after its administration.

PHARMACOLOGY OF DEXMEDETOMIDINE

Alpha 2-adrenergic receptor (α2-AR) agonists have been successfully used in several clinical settings in view of diverse actions which include sedation, analgesia, anxiolysis, perioperative sympatholysis, cardiovascular stabilizing effects, reduced anesthetic requirements, and preservation of respiratory function ***(Kemp 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, 2002)***.

Molecular Pharmacology:

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 ***(Afsani, 2010)***.

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, 2001)***.

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 substantiagelatinosa. 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***(Nakamura and Ferreira, 2002).***

The substantiagelatinosa 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 ***(Tamsen and Gordh, 2001).***

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) ***(Hunter et al., 2003)***

Pharmacokinetics:

Absorption and distribution:

Dexmedetomidine exhibits linear pharmacokinetics inthe recommended dose range of 0.2 to 0.7 μg/ kg/ hradministered 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

ofdistribution 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***(Gertler et al., 2001)***.

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 potentialrole 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., 2000)***.

Dexmedetomidine pharmacokinetics were not significantly different in subjects with severe renal impairment (creatinine clearance <30 L/min) compared to healthy subjects ***(Khan et al., 2006).***

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 ***(Ralph et al., 2001).***

Pharmacodynamics

Central nervous system 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 ***(Yazbek-Karam and Aouad, 2006)***.

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***(Guo et al., 1996)***.

The spinal level of antinociceptive action seems to be through the substantiagelatinosa (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 ***(Jaokola et al., 1991)***.

Respiratory system effects:

Dexmedetomidine effect on respiration appears to be similar in order of magnitude to those seen in the heavy sleep state ***(Venn et al., 2000)***. In humans, respiratory rate and oxygen saturation remain within normal limits and there is no evidence of respiratory depression following treatment with dexmedetomidine, within the recommended dose range of 0.2 to 0.7 µg/kg/hour, or significant effect on hypoxic and hypercapnicventilatory drive ***(Joseph et al., 2000).***

The combination of alpha-2 adrenoceptor agonists with opioids does not lead to further ventilatory depression ***(Jarvis et al., 2002)***. At clinicly effective doses, dexmedetomidine has been

shown to cause much less respiratory depression than other sedatives ***(Belleville et al., 2003.)***

Cardiovascular system effects:

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 ***(Philipp et al., 2002)***.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 ***(Bloor et al., 2002).***

The incidence of postoperative bradycardia has been reported in healthy surgical patients who received dexmedetomidine, especially high doses. Usually, these temporary effects were successfully treated with atropine or ephedrine and volume infusions ***(Jalonen et al., 2002).***

Endocrine and renal effects:

Dexmedetomidine activates peripheral presynaptic α2- AR which reduces the release of catecholamines, and hence reduces sympathetic response to surgery ***(Elbert et al., 2006)***. Stimulation of alpha-2 adrenoceptors has a number of effects that promote diuresis and natriuresis. They decrease the secretion of vasopressin and antagonize its action on renal tubules and are also thought to inhibit the release of renin ***(Chen et al., 2002).***

Skeletal muscle effect:

Dexmedetomidine can reduce the incidence of postoperative shivering. That happens in 40% of post-operative cases with general anesthesia. The mechanism of this action is not established firmly yet ***(Takahiko and Mervyn, 2000).***

Clinical uses of Dexmedetomidine:

Premedication:

Indications to the use of dexmedetomidine as premedication include patients susceptible to preoperative and peri-operative stress, drug addicts and alcoholics, chronic opioid users and hypertensive patients. Dexmedetomidine when given as a premedication, it decreases oxygen consumption intraoperatively by 8% and post-operatively by 17% ***(Yazbek-Karam and Aouad, 2006)***.