Facilitatory Effects of Perineural Dexmedetomidine on Neuraxial and Peripheral Nerve Block

A Meta-Analysis

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List of Abbreviations

Abb.	Full term

ASRA ..... The American Society of Regional Anesthesia and Pain Medicine

BP..... Blood Pressure

BS..... Bromage score

CI..... Confidence Interval

CNS..... Central Nervous System

CSF ..... Cerebrospinal Fluid

DXM..... Dexmedetomidine

DOA ..... Duration of Analgesia

FDA..... Food and Drug Administration

HR……Heart Rate

ICU..... Intensive Care Unit

LA..... Local Anesthetic

LAST……Local Anesthetic Systemic Toxicity

MD ..... Mean difference

NE ..... Norepinephrine

OR..... Odds Ratio

SCM ..... Sternocleidomastoid

SD..... Standard Deviation

SNS ..... Sympathetic Nervous System

US ..... Ultrasound

INTRODUCTION

Dexmedetomidine (DXM) is an anxiety reducing, sedative, and pain medication. It has been used as adjunct to local anesthetics (LAs) to improve the quality of perioperative analgesia and prolong its duration ***(Cormack et al., 2005)***.

Alpha$_2$-adrenergic agonists have expanded the horizons of regional anesthesia. DXM is a highly selective α-2 agonist similar to clonidine but with a greater affinity for the α-2 receptor. It is the pharmacologically active d-isomer of medetomidine, a full agonist of α-2 adrenergic receptors ***(Gertler et al., 2001).***

In general, presynaptic activation of the $\alpha_2$adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate (HR). Combined, these effects can produce analgesia, sedation, and anxiolysis. DXM combines all these effects, thus avoiding some of the side effects of multiagent therapies ***(Virtanen et al., 1988).***

DXM was approved in 1999 by the US Food and Drug Administration (FDA) as a short-term sedative and analgesic (<24 hours) for critically ill or injured people on mechanical ventilation in the intensive care unit (ICU). The rationale for its

short-term use was due to concerns over withdrawal side effects such as rebound high blood pressure. However, these effects have not been consistently observed in research studies ***(Shehabi et al., 2004)***. Since 2004, when it was first used as a LA adjuvant in IV regional anaesthesia, the use of DXM in peripheral nerve blocks have evolved ***(Memis et al., 2004)***.

DXM is highly lipophilic and thus is rapidly distributed in neural tissues and produces its antinociceptive effects by binding to α^{-2} receptors in spinal dorsal horn when used neuraxially ***(Bajwa et al., 2013).***

One of the highest densities of α_2 receptors has been detected in the locus coeruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The hypnotic and sedative effects of α_2-adrenoceptor activation have been attributed to this site in the CNS. The locus coeruleus is also the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. In this region of the brain, α_2-adrenergic and opioidergic systems have common effector mechanisms, indicating that DXM has a supraspinal site of action ***(MacDonald and Scheinin, 1995).***

In addition to DXM's action in the locus coeruleus of the brain stem, it has been shown to stimulate α_2 receptors directly in the spinal cord, thus inhibiting the firing of nociceptive neurons. The substantia gelatinosa of the dorsal horn of the

spinal cord contains receptors which, when stimulated, inhibit the firing of nociceptive neurons stimulated by peripheral Aδ and C fibers and also inhibit the release of the nociceptive neurotransmitter substance P. This spinal mechanism is most likely why DXM is now being used epidurally and intrathecally in addition to its primary use as an intravenous drug ***(Tamsen and Gordh, 1984).***

The mechanism by which DXM mediates peripheral nerve blocks is not fully defined. However, there are several hypotheses. It blocks Aδ and C fibers and increases potassium conductance in isolated neurons, thus intensifying the LA conduction block. It may also cause local vasoconstriction, thus decreasing LA spread and removal around neural structures. In addition to its α2A adrenoceptor ***(Yoshitomi et al., 2014)***.

AIM OF THE WORK

The aim of this study is to evaluate the efficacy of DXM as an adjuvant to local anesthetics for intrathecal and supraclavicular blocks compared to LA alone.

Chapter 1

ANATOMY

Anatomy relevant to subarachnoid blockade:

The spinal cord is continous with the brain stem proximally and terminates distally in the conus medullaris as the filum terminale (fibrous extension) and the cauda equina (neural extension). This distal termination varies from L3 in infants to the lower border of L1 in adults due to the differential growth rates between the bony vertebral canal and the central nervous system (CNS) ***(Miller et al., 2014).***

The spinal canal has a protective sheath composed of three layers. From the outside to the inside they are: dura mater, arachnoid and pia mater ***(Figure 1)***. These membranes concentrically divide the vertebral canal into three distinct compartments: the epidural, subdural, and subarachnoid spaces ***(Snell, 2007).***

The epidural space contains fat, epidural veins, spinal nerve roots, and connective tissue. The subdural space is a potential space between the dura and the arachnoid and contains a serous fluid. The subarachnoid space is traversed by threads of connective tissue extending from the arachnoid mater to the pia mater. It contains the spinal cord, dorsal and ventral nerve roots,

and cerebrospinal fluid (CSF). The subarachnoid space ends at the S2 vertebral level ***(Reina et al., 1988).***

Lumbosacral CSF has a constant pressure of approximately 15 cm H2O, but its volume varies according to the patient because of differences in body habitus and weight. It is estimated that CSF volume accounts for 80% of the variability in peak block height and regression of sensory and motor blockade ***(Miller et al., 2014).***

The nerve root is the main site of action for spinal anesthesia. In spinal anesthesia the concentration of LA in CSF is thought to have minimal effect on the spinal cord itself ***(Mulroy, 2002).***

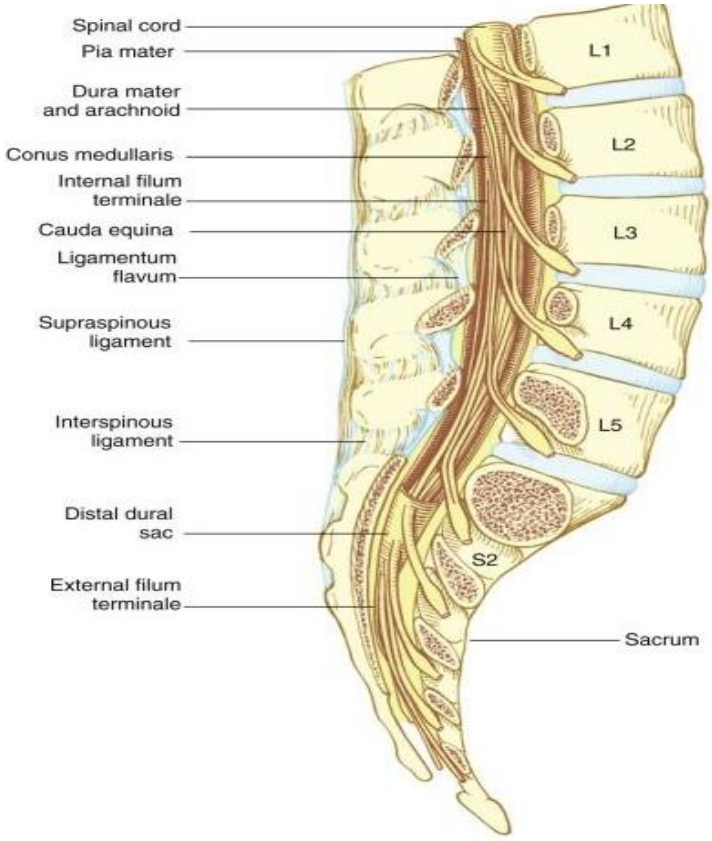

Fig. (1): Longitudinal section of spinal cord ***(Reina et al., 2000).***

Anatomy relevant to supraclavicular blockade:

The brachial plexus is formed by the ventral rami of C5-C6-C7-C8-T1, occasionally with small contributions by C4 and T2. The block is performed at the level of the distal trunks and origin of the divisions ***(Figure 2)***, where the brachial plexus is confined to its smallest surface area ***(Leffert and Robert, 1985)***.

The three trunks carry the entire sensory, motor, and sympathetic innervations of the upper extremity, with the exception of the uppermost part of the medial side of the arm (T2). The densely packed divisions, in contrast, carry a similar