Alpha 2 Agonists and Magnesium As Adjuvants to Intrathecal Bupivacaine For Postoperative Analgesia

Essay

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Joseph Sobhy Yacoub Halaka

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List of Abbreviations

ACC	:	Anterior cingulate cortex
ACTH	:	Adrenocorticotrophic hormones
AF	:	Atrial fibrillation
BBB	:	Blood brain barrier
cAMP	:	Cyclic adenosine monophosphate
CGRP	:	Calcitonin gene-related peptide
CNS	:	Central nervous system
DEX	:	Dexmedetomidine hydrochloride
DNIC	:	Diffuse noxious inhibitory control
DRG	:	Dorsal root ganglion
ECG	:	Electrocardiogram
EDRF	:	Endothelium-derived relaxing factor
GDP	:	Guanyl di-phosphate
GTP	:	Guanyl tri-phosphate
GTPase	:	Guanyl tri phosphatase
IASP	:	International Association for the Study of Pain
IV	:	Intra-venous
MAC	:	Minimal alveolar concentration
Mg	:	Magnesium
MPQ	:	McGill Pain Questionnaire
NE	:	Norepinephrine
NMDA	:	N-methyl-$_{D-}$ aspartate
NRM	:	Nucleus raphe magnus
NS	:	Nociceptive specific
OPS	:	Objective Pain Score
PCA	:	Patient-controlled analgesia
PFC	:	Premotor cortices, prefrontal cortex
PTH	:	Parathyroid hormone
SAH	:	Subarachnoid Hemorrhage
SVR	:	Systemic vascular resistance
TDP	:	Torsades de pointes

List of Abbreviations (Con.)

TEG	:	Thromboelastography
TIH	:	Tourniquet-induced hypertension
TIVA	:	Total intravenous anesthesia
TNS	:	Transient neurological symptoms
VAS	:	Visual Analogue Scale
VF	:	Ventricular fibrillation
VRSs	:	Verbal Rating Scales
WDR	:	Wide dynamic range

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Introduction

Lower abdominal and lower limb surgeries may be performed under local, regional (spinal or epidural) or general anesthesia, but neuraxial blockade is the preferred mode of anesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, lower risk of infection as from catheter in situ, less failure rates and cost-effectiveness, but has the drawbacks of shorter duration of block and lack of postoperative analgesia ***(Deepika Shukla et al., 2011).***

In recent years, use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate, patient satisfaction, decreased resource utilization compared with general anesthesia and faster recovery. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly. The quality of the spinal anesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs [such as dexmedetomidine (DXM), clonidine, magnesium sulfate (Mg), neostigmine, ketamine and midazolam], but no drug to inhibit nociception is without associated adverse effects ***(Deepika Shukla et al., 2011).***

Bupivacaine, is a drug with long lasting local anesthetic effect, in neuraxial anesthesia, provides an effective and safe anesthesia ***(Coskuner et al., 2007)***.

Recently, Alpha 2-adrenoceptor agonists are being increasingly used in anesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery; but also cause sedation and analgesia; they are also used as adjuvants during regional anesthesia.

Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in human for analgesia and sedation ***(G. E. Kanazi et al., 2006)***.

Mg is a noncompetitive antagonist to NMDA receptors and has the potential to prevent central sensitization from peripheral nociceptive stimulation. Intravenous (i.v.) administration of Mg, even at high doses, is associated with limited passage across the blood-brain barrier ***(Hwang et al., 2010).***

The addition of intrathecal magnesium sulfate (MgSO4) to 10 mg bupivacaine plus 25μg fentanyl prolonged spinal anesthesia in patients undergoing lower extremity surgery ***(M.B. Khezri et al., 2012).***

Antinociceptive effect of Mg appears to be relevant not only to chronic pain but it also determines, in part, the duration and intensity of postoperative pain. These effects are primarily based on the regulation of calcium influx into the cell, i.e. natural physiological calcium antagonism ***(Hwang et al., 2010).***

Aim of the Work

To discuss the best drugs that achieve maximum post operative analgesic effects when used as adjuvants to intrathecal bupivacaine as regard efficacy and duration of the analgesic effect.

Anatomy and Physiology of Pain

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience that is primarily associated with tissue damage. It is a protective mechanism that occurs whenever tissues are being damaged, and it causes the individual to react to remove the pain stimulus **(Tenti and Hauri, 2004).**

Pain pathway

Specificity theory states that there is a specific pain system that transfers information about potential or actual tissue damage to the place of perception (the brain). Nociceptive energy is transduced into electrophysiological signals that are transmitted to perceptive apparatus. However, the pain pathway is not 'hard wired', but undergoes profound functional changes and modulation under certain conditions, such as tissue damage and inflammation (e.g. postoperative pain). This plasticity is mediated by many mechanisms, including peripheral/primary and central/secondary sensitization. The substrate for these changes is a plethora of chemical mediators peripherally and spinally, comparable in complexity to neurotransmitters in the brain **(Smith, 2007).**

I-Primary afferent neurons:

There are three classes of primary afferent fibers in skin that may be activated by a given cutaneous stimulus. The fibers that are largest and have the fastest conduction velocity are the large-diameter myelinated (Aβ) fibers. These fibers, when activated, do not normally result in a sensation of pain, but rather of light touch, pressure, or hair movement. The axons of the nociceptive neurons are generally unmyelinated (C fibers) or thinly myelinated (Aδ fibers) **(Dubner, 1994).**

Unmyelinated C polymodal nociceptors are activated by many potentially tissue-damaging modalities, are associated

with prolonged 'burning' pain, and are slowly conducting (0.5-2.0 m/s). Some may have a differential sensitivity to heat or mechanical stimuli **(Smith, 2007).**

The Aδ is thinly myelinated, mechano-heat receptors that thought to mediate a briefer 'sharp' pain. These larger fibers are more rapidly conducting (5-20 m/s). Aδ fibers are also delineated into two types, depending on their differential responsiveness to intense heat. A final group of nociceptors do not appear to exhibit sensitivity to noxious stimuli. These 'silent' nociceptors develop novel sensitivity usually after tissue injury or inflammation. Silent nociceptors have been well characterized in the visceral domain, although there is some evidence to support the existence of somatic counterparts **(Smith, 2007).**

II-Spinal cord to brain:

Secondary afferents decussate and pass up the spinal cord to the midbrain via the spinothalamic, spinoreticular and spinomesencephalic tracts to the thalamus and to sensory cortex, but also have many other links, such as to reticular formations, limbic and hippocampus areas, Fig.(1). The different pathways may have functional correlates involving memory, cognition and emotion, which contribute to the neural network of overall pain perception. Moreover, neurons that project from these areas of the brain provide descending modulation of spinal cord processing. **(Brooks and Tracey, 2005)**

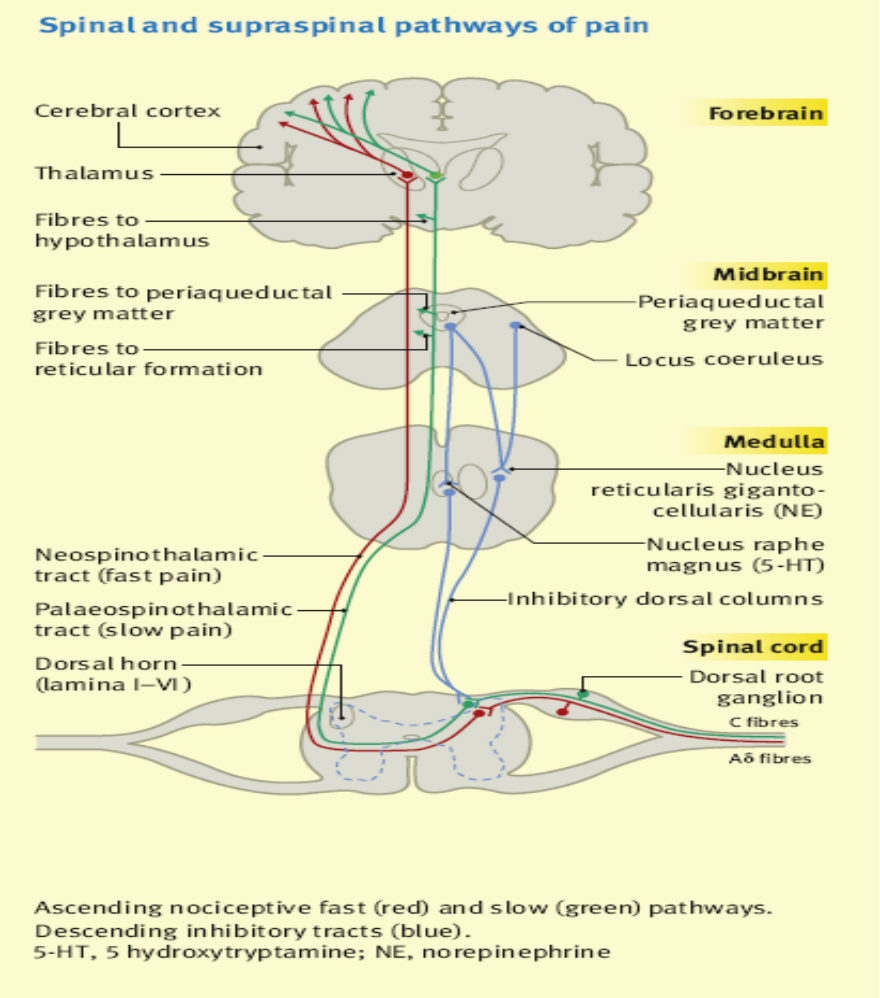

Fig.(1): Spinal and supraspinal pathways of pain **(Smith, 2007)**

The first synapse in somatosensory signaling occurs either at the spinal dorsal horn or in the dorsal column nuclei at the spinal cord-brain stem junction. Evidence has accumulated to indicate that both nociceptive and non nociceptive fibers provide input to both of these initial targets. However, under normal circumstances, the dorsal column nuclei can be considered to selectively process inputs from the large myelinated fiber classes related to light touch, whereas the spinal dorsal horn primarily processes inputs of the nociceptive primary afferent fibers **(Pockett, 1995).**

At the spinal level, nociceptive afferent fibers from the periphery terminate in a highly ordered way in the dorsal horn of the spinal cord on the same side of the body as the dorsal root ganglion (DRG), where the primary sensory neurons are located. The dorsal horn is anatomically organized in the form of lamina (Rexed's) (Fig.2).

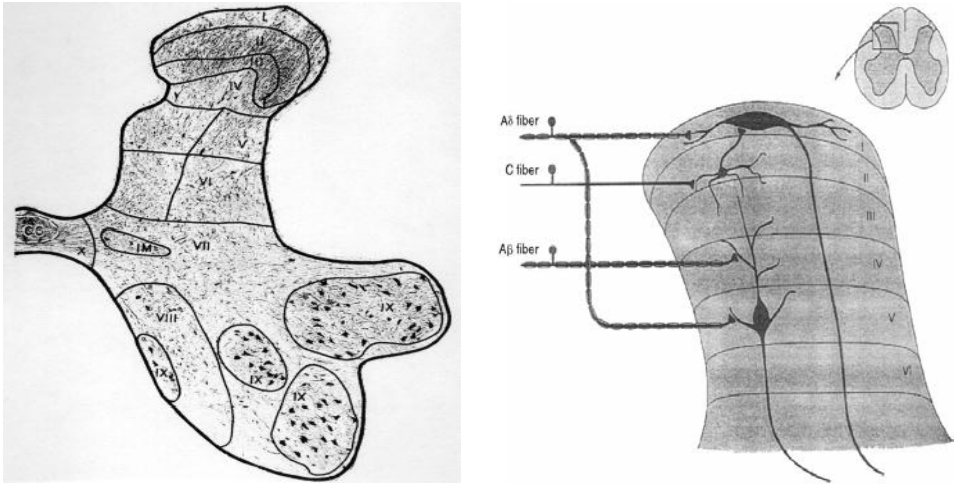

Fig.(2): Location of Rexed'slaminae at the L5 level of the spinal cord **(Dubner, 1994).**

The unmyelinated C fibers terminate primarily in lamina II, whereas the thinly myelinated Aδ fibers end in lamina I and in laminae III to V. The collaterals of the large myelinated fibers (Aβ) that terminate in the dorsal horn do so in laminae III to V **(Dubner, 1994).**

Two predominant types of second-order nociceptive spinal projection neurons have been identified in the spinal cord: wide dynamic range (WDR) neurons and nociceptive specific (NS) neurons. WDR cells are especially concentrated in the deeper laminae of the dorsal horn (laminae III to V) where they receive input from both low-threshold (Aβ) and nociceptive afferent fibers, and, hence, are activated by both non-noxious and noxious stimuli. However, the responses of WDR cells to these stimuli are graded so that noxious stimuli

evoke a greater response than non-noxious stimuli **(Dubner, 1994)**.

In contrast to WDR cells, NS projection cells respond only to noxious stimuli under physiologic conditions. The majority of NS cells are found in the superficial laminae of the dorsal horn (I and outer II). These cells have a lower rate of spontaneous activity than WDR cells, averaging about 3 to 5 Hz. The discharge rates to the noxious stimuli of NS cells are comparable to those of WDR cells, averaging about 50 Hz. **(McMahon, 1992).**

The axons of both WDR neurons and NS second-order neurons cross the midline near the spinal level of the cell body, gather into a bundle of ascending fibers in the contralateral anterolateral spinal region, and then ascend toward targets in the brain stem and diencephalon. The conduction velocity of the WDR cells is usually faster than that of the NS cells (approximately 30m/second versus. 12 m/second. Additionally, the axons of the NS cells, which largely arise from lamina I of the dorsal horn, and those of the WDR cells, which primarily arise from laminae III to V, tend to run in slightly different positions in the anterolateral spinal funiculus. In the anterolateral spinal column the NS cell axons are found in the dorsal medial region, whereas axons of WDR cells are more concentrated in the ventrolateral region **(McMahon, 1992).**

III- The pain matrix:

Usually pain experience is described along 2 main axes: the sensory discriminative dimension, comprising spatial, temporal, and intensity properties, and the affective-motivational dimension related to the unpleasantness of pain. Consistent with the multidimensional concept of pain, multiple brain regions, which composite the pain matrix, have been demonstrated to be involved in representing both the