CURRENT CONCEPTS IN NEURAXIAL ADMINSTRATION OF OPIOIDS AND NON-OPIOIDS

Essay

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ABBREVIATIONS

5-HT	: 5-hydroxytryptamine
CABG	: Coronary artery bypass grafting
CSE	: Combined spinal epidural
CSF	: Cerebrospinal fluid
ERPs	: Event-related potentials
ESRA	: European Society of Regional Anesthesia
ICU	: Intensive Care Unit
IT	: Intrathecal
LA	: Local anesthesia
MAC	: Minimal alveolar concentration
MAIOs	: Monoamine oxidase inhibitors
MAP	: Mean arterial pressure
MAG	: Magnesium
$MgSO_4$	: Magnesium sulphate
MPTP	: N-methyl-4-phenyl-1,2,3,6 tetrahydropyridine
M-re	: Muscarinic receptor
NMDA	: N-methyl-D-aspartate
NNH	: Number needed to harm
NNT	: Number needed to treat
NSAID	: Non steroidal-anti-inflammatory drugs
PACU	: Post Anesthesia Care Unit
PCA	: Patient controlled analgesia
SSRIs	: Selective serotonin reuptake inhibitors
ST-91	: 2,6-diethylphenylamine 2-imidazoline
VAPS	: Visual analogue pain scale
VAS	: Visual analogue scale

ABSTRACT

This study reviews in brief the introduction into clinical practice of opioids and non-opioids. This administration have achieved international popularity in various clinical settings. The use of augmentation strategies (neuraxial opioids or non-opioids) in the epidural and intrathecal analgesia and peripheral nerve blockade and ganglion blockade is wide spread and increasing for the marginal of intraoperative pain, postoperative pain, labour pain, chronic non malignant pain and cancer pain (using implantable, programmable intrathecal pump).

Keywords:

Acute pain
Chronic pain (malignant, non-malignant)
Neuraxial opioid
Neuraxial non-opioid

INTRODUCTION

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The identification of opioid receptors has opened new horizons in pain management, Yaksh and Rudy, in 1976, were the first investigators to demonstrate direct opioid analgesia at the spinal cord level[(1)]. Their study involved subarachnoid fentanyl and morphine in rats. However, the first application of neuraxial opioids can be traced to that in 1901, when a Japanese surgeon used 10 mg intrathecal (IT) morphine with the local anesthetic eucaine in two cancer patients[(2)].

In 1979, Wang *et al.*[(3)] observed significant analgesia with (0.5-1 mg) spinal morphine. The use of IT hydrophilic opioids (usually morphine) quickly spread to perioperative care with excellent postoperative analgesia in a wide array of surgical procedures.

In the context of "augmentation strategies" for epidural and intrathecal analgesia, the discovery of opioid receptors and the subsequent development of the technique of epidural and intrathecal opioid administration is undoubtedly one of the most significant advances in pain management in the last three decades. Plethora of studies has shown that spinal opioids can provide profound postoperative analgesia with fewer central and systemic adverse effects than with opioids administered systemically. A wide variety of non-opioids have also been used in epidural or subarachnoid space to achieve pain relief without the risk of respiratory depression. Segmental analgesia induced by spinal administration of opioids and non-opioids has been used successfully to treat intraoperative pain, postoperative pain, traumatic pain, obstetric pain, chronic pain and cancer pain[(4)].

This study was done to review current concepts of the physiologic processes underlying obstetric, postoperative, and chronic pain and their unique pharmacologies of analgesia, with emphasis on clinically available drugs and treatment techniques.

In 1979, Behar *et al.*[5] and Wang *et al.*[6] reported the first human use of epidural and intrathecal opioids to manage acute postoperative pain. Whereas epidural opioid analgesia has enjoyed widespread popularity, the intrathecal route is associated with inferior efficacy and safety, primarily due to relatively short duration of analgesia and incidence of respiratory depression and somnolence[7], especially when high doses were used. Combination of different drugs that prolong analgesia would therefore be advantageous. Diverse classes of drugs, such as local anesthetics[8], epinephrine[9], clonidine[10], and neostigmine[11], have been added to intrathecal opioids in attempts to prolong analgesia and reduce the incidence of adverse effects[7], observed when opioids are used alone.

PAIN PHYSIOLOGY AND PHARMACOLOGY

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Therapeutic application of neuraxial administration of opioid and non-opioid depend on the type of pain being treated (**Table 1**).

Table (1): Therapeutic applications of neuraxial administration of opioids and non-opioids[1,2]

I- Acute Pain: - Intraoperative pain - Postoperative pain - Trauma pain - Labour pain - Non-surgical pain (MI angina pectoris, herpes zoster, renal colic, thrombophlebitis, etc.)
II. Chronic non-malignant pain: - Post herpetic neuralgia - Complex regional pain syndromes (CRPS) - Back pain - Intractable angina pectoris - Ischaemic pain.
III. Cancer Pain: - Long term therapy with subcutaneous ports - Long term therapy with implantable, programmable pumps

The goal of this presentation is to review these different pain processes in order to provide a logical framework to better understand the unique approaches and responses to each.

Current understanding of all types of pain involve the concepts shown in the **(Fig. 1)**. A peripheral noxious stimulus (arrow on the far right) stimulates specialized receptors (nociceptors) on small myelinated and unmyelinated fibers, which release excitatory

molecules in the spinal cord dorsal horn. These excite a neuron which sends projections supraspinally, where sensory information is integrated and perceived as pain. They also excite various reflexes, including activation of the sympathetic nervous system.

The gain of this transmission is regulated by descending excitatory and inhibitory pathways, and on inhibitory receptors expressed on the fibers themselves.

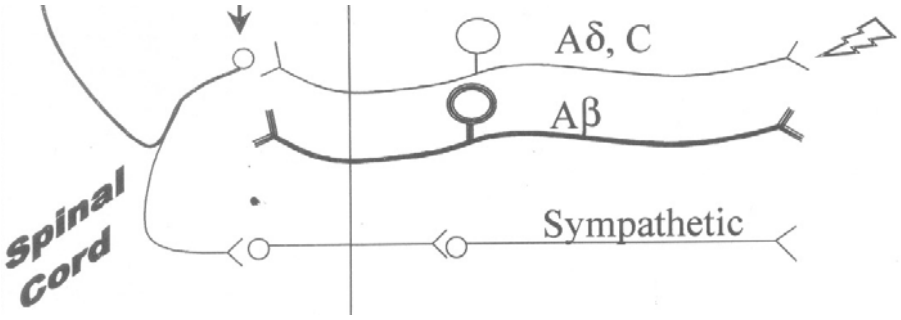

Fig . (1): Different types of pain[1,2] [a peripheral noxious stimulus (arrow on the far right) stimulates specialized receptors (nociceptors) on small myelinated and unmyelinated fibers]

Obstetric Pain:

A few characteristics of labor pain are Probably because of the limit in dose of systemic drugs administered to treat this pain (in order to avoid effects on the fetus and fetal heart rate), neither N_2O nor opioids are effective[12,13].

One could organize approaches to obstetric pain treatment from the periphery to central sites. Relatively little is known about the peripheral nociceptors in the lower uterine segment and the cervix. Only in gross detail do we know the types of stimuli which excite

them, and there is very little knowledge regarding inhibitory mechanisms on these afferent endings[14].

However, other visceral afferents studied in the gastrointestinal system express opioid receptors of the kappa subtype which powerfully inhibit their excitation[15].

It is conceivable that selective kappa opioid agonists could therefore treat labor pain at its source. Moving centrally from the afferent endings, blockade of nerve conduction by paracervical block or by lumbar sympathetic block relieves labor pain (and interestingly also speeds the progress of labor)[16].

However, these blocks are not practical, since they are short lived, require many needle passes and can therefore be painful, and can result in fetal bradycardia (paracervical block). More centrally still is blockade of conduction or neurotransmission through neuraxial techniques epidural and spinal injection of local anesthetics. This remains the mainstay of treatment of obstetric pain, since it is effective and addresses the main concern (lack of fetal effects). Adjunctive agents, such as opioids and alpha$_2$-adrenergic agonists can intensify the effects of local anesthetics and may improve analgesia or reduce local anesthetic-induced side effects.

A curious and unexplained observation in treatment of obstetric pain is the poor efficacy of spinal morphine. Very large doses (>1 mg) are required, and are not nearly as effective as local anesthetics. In contrast, relatively small doses of sufentanil (5 μg) or fentanyl (20 μg) are as effective as local anesthetics[17].