

Which epidural opioid is more suitable for postoperative pain management?

Abstract

Opioids have always been considered the best option in clinical practice for the treatment of severe postoperative pain. However, the spinal administration of an opioid drug does not always guarantee selective action and segmental analgesia in the spine. This fact is due to partial reuptake to blood systemic circulation reaching brain receptors. Recent evidence from clinical studies indicates that bioavailability in the spinal cord biophase is negatively correlated with liposolubility, which is higher for hydrophilic opioids, than for lipophilic ones. Actually, clinical guidelines recommend using a mixture of local anesthetic plus a strong opioid to improve the global analgesic effect, minimize adverse effects and improve the overall patient's satisfaction. Moreover, an opioid alone like morphine can be administered to provide a long period of postoperative analgesia for 24h, or even 48h when an extended release epidural formulation is used. In this narrative review, practical information for correct spinal opioid selection is provided to help the physicians a better choice for postoperative epidural analgesia.

Keywords: spinal analgesia, epidural opioids, intrathecal opioids, postoperative pain, multimodal analgesia

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Introduction

Opioids have been considered by clinical physicians the strongest option in clinical practice for the treatment of postoperative pain. Humans have been administering opioids for many years in an effort to produce either analgesia or other clinical and recreational effects mediated by the central nervous system. Spinal opioids have become a current and extended practice for the treatment of acute postoperative pain, obstetric analgesia and also cancer-related pain due to its great effectiveness. However, the spinal administration of an opioid drug does not always guarantee segmental analgesia and also selective action in the spine. Evidence from experimental studies indicates that the bioavailability in the spinal cord biophase correlates negatively with liposolubility. This one is higher for hydrophilic opioids, such as morphine than lipophilic opioids, such as fentanyl, sufentanil and alfentanil.¹ In this review from Ovid/Medline until December 2016, a historical journey from the past to current clinical guidelines on spinal opioids has been made.

The historical use of opium

The use of the opium plant itself (*Papaver somniferum*) has a long human history and probably predates history. "Poppy tears" (*lachrymal papaveris*) is the dried latex obtained from the opium poppy. It is widely believed that cultivation of these opium poppies was used for ritual purposes and dates back to at least the Neolithic New Stone Age. It was also known to be cultivated in lower Mesopotamia and the Sumerians referred to it as Hul Gil, the "joy plant," and passed its secrets to the Assyrians who, in turn, passed it on to the Babylonians, who, in turn, would pass their knowledge onto the Egyptians. Opium was first mentioned at Luxor-Thebes in the winter of 1873–1874 BC by Georg Ebers into the book "*Ebers Papyrus*". Further, the writings of Pedanius Dioscorides (40–90 AD), a Greek botanist, pharmacologist and physician, who authored a five-volume encyclopedia about herbal medicine and related medicinal substances, mentioned opium plant. Opium was also mentioned by the great luminaries Claudius Galenus (129–199 AD) and Avicenna in the Middle Ages as a textbook of medicine (*The Canon of Medicine*). An opium-based elixir has been ascribed to Roman Byzantium and

around 1522, Paracelsus made reference to an opium-based elixir that he called *laudanum* from the Latin word *laudare*, meaning, "to praise". In the late 18th century, when the East India Company gained a direct interest in the opium trade, another opiate recipe called *laudanum* became very popular among physicians and their patients. Widespread medical use of unprocessed opium continued through the American Civil War before giving way to morphine, which was first discovered in 1804 by Friedrich Sertürner (1783–1841), a German pharmacist, first distributed by the same person in 1817, and first commercially sold by the pharmaceutical company Merck in 1827.² August Bier, a surgeon, and his assistant Hiselbrandt, made history using intrathecal cocaine on each other, at the Royal Chirurgical Clinic in Kiel in 1898. They used 5mg of intrathecal cocaine and complete loss from legs sensations lasted almost 45minutes. In the United States the first surgeons to utilize spinal anesthesia were Tait and Cuglieri in San Francisco on 1899, which performed an osteotomy of tibia under regional anesthesia. The Romanian surgeon Racoviceanu-Pitesti, who reported his experience using a mixture of cocaine and morphine in Paris in 1901, made the first publication concerning the use of opioids in spinal anesthesia.³ The field was plagued with problems that were overcome in the 1970s when spinal opioid receptors were discovered, and it was proven that direct application of morphine into the spine produced analgesia.⁴ This became a tangible reality when Wang et al.,⁵ successfully used intrathecal morphine bolus dose injection in humans, and with the publication by Behar et al.,⁶ in *The Lancet* in 1979, the first paper on the use of epidural morphine at 2mg doses for the treatment of acute and chronic pain.⁶ The latter authors reported achieving pain relief for between 6 and 24hours in 10 patients and suggested that there was a direct spinal effect on the specific receptors in the gelatinous substance of the posterior horn of the spinal cord. Therefore, more than a century passed until it became routine to use opioids via the spinal cord for intra and postoperative analgesia and in labor, as well as for chronic pain, in particular that associated with cancer. It is striking that in the first 50years of the history of spinal anesthesia the main role was played by the surgeons themselves, and then over time they became less involved, the field now being exclusively the domain of anesthesiologists.^{7,8}

The pharmacokinetics of spinal opioids

The physicochemical properties of neuraxial opioids determine their onset time, duration of action, and potency. High lipid solubility and low pKa results in a highly potent opioid with a rapid onset of effect, but limited duration of action, whereas decreasing lipophilicity increases the duration of action. Lipid soluble opioids also resemble local anesthetics in terms of their pKa, molecular weight, and partition coefficients that may explain some of the analgesic effects of CSF opioids. At physiological pH (7.4), the tertiary amine groups of the opioids are ionized rendering them water-soluble. However, it is the hydroxyl groups on the morphine molecule that are responsible for its greater water solubility compared with other opioids. Increased water solubility is responsible for slow onset of effect and long duration of action. Potency of spinal opioids increases with increasing hydrophobicity.⁹

The pharmacokinetics of intrathecal opioids is complex, follows a multi-compartmental model, and is determined by the opioid physicochemical properties and the CSF dynamics. In the systemic circulation, the calculation of pharmacokinetic data such as volume of distribution assumes adequate mixing and equilibration of drug across all compartments. However, the CSF is a poorly mixed compartment with established cephalic-caudal gradients for opioids after administered into the lumbar CSF. The clinical characteristics of each opioid will be the consequence of the sum of all these types of distribution as they define its bioavailability and its spinal effect. Cephalic movement of opioids injected into the CSF is the result of Bulk flow of drug in a caudal-cephalic direction, fluctuating pressure changes within the thorax as a result of respiration, facilitating cephalic flow of CSF, expansion on systole and relaxation on diastole of the brain, occurring as a result of the cardiac cycle. This helps to create a backward and a forward motion of CSF with a net transfer of opioid in a cephalic direction.¹⁰

After epidural injection, Lipophilic opioids, such as fentanyl and sufentanil, are able to rapidly cross the blood brain barrier, have a high degree of sequestration in the epidural fat and good vascular uptake, and bind similarly well to the receptors in the spinal white and grey matter. Clinically this would result in a short latency, limited rostral diffusion and, therefore, spinal analgesia at the level of the injection site, short duration of action and a risk of early respiratory depression due to diffusion in the blood. By contrast, hydrophilic opioid, such as morphine, cross the blood brain barrier more slowly, bind to the epidural fat to a lesser extent, and more strongly to specific receptors in the grey matter, as well as having a slow plasma reuptake, maintaining concentrations in the CSF higher and for longer. This leads to a later onset of action, a greater area of effect in the spine and longer duration of action together with a potential delayed respiratory depression.^{9,10}

The best clinical evidence for the aforementioned statements is the decrease in the relative potency between opioids as a function of the route of administration. A 10-mg IV injection of morphine would be equivalent to 10µg of sufentanil intravenously, while to achieve the same degree of analgesia intradurally it would be necessary to use only 100µg of morphine; from this, it can be deduced that sufentanil has 100-fold lower potency administered at the spinal level, due to the low dose of drug that reaches the spinal cord biophase.¹¹

Current clinical use of epidural opioids

Clinical practice on spinal opioids from worldwide anesthesiologists varies very much in relation to the country selected. Although there is no "ideal analgesic" clinicians alike continue to

search for compounds with qualities which may approach this utopic idea. Regional anesthesia is now involved into the multimodal concept for the management of postoperative pain. To reach this objective, a spinal opioid is commonly used alone or plus local anesthetic (LA) to provide high degree analgesia associated to systemic drugs and also non-pharmacologic and rehabilitation programs.¹² Spinal analgesia is often provided using a mixture of LA and opioids, which yield analgesic synergy. In a review on combination opioid analgesics, the author concluded that this combination enhance and/or optimize analgesic efficacy and that this synergistic combination of agents provides better pain relief which is generally associated with fewer side effects than when either drug is given alone. Moreover, LA has been shown to alter signaling of other G protein-coupled receptors, but little is known about their effect on opioid receptor signaling. He also added that results from experimental studies suggest that LA decrease opioid inhibition of calcium channel activity by interfering with the GPT-mediated signal transduction between opioid receptors and calcium channels.¹³

Morphine was the first opioid approved by the US Food and Drugs Administration (FDA) for spinal administration and it's the epidural opioid that has been the most widely used and with which others are compared.⁹ Indeed, it could be considered the "gold standard" of spinal drugs, which does not always imply the ideal one, as due to its spinal cord-selectivity, the dose required is much lower for epidural than for parenteral administration based on it presents the best spinal bioavailability.⁹⁻¹¹ It can be administered as a bolus (30-100µg/kg) or as continuous infusion (0.2-0.4mg/h), which seems to induce better quality analgesia, and alone or together with local anesthetics, as synergy between the drugs increases the overall analgesic effect.^{11,14} In addition, controlled studies^{15,16} have demonstrated that a single-dose EREM (Extended Released Epidural Morphine) can provide up to 48hours very good quality of postoperative analgesia with an acceptable and predictable side effect profile (dose < 15mg). Prophylactic analgesia with EREM leads to a more satisfactory patient experience than IV PCA. In this review,¹⁶ there were three strong findings. Epidural morphine resulted in greater patient satisfaction, despite higher rates of adverse events. Those describing their analgesic medication as 'very good' or 'excellent' used IVPCA (intravenous patient controlled analgesia) opioid less and had pain scores significantly below the global mean, whereas those describing their medication as 'poor' or 'fair' had pain scores significantly above the mean. Epidural morphine meant less need for postoperative IVPCA opioid than epidural placebo. The therapeutic gain with EREM was lower pain scores with less IVPCA opioid. Moderate or severe pruritus was more common with IVPCA plus epidural morphine, whatever the formulation, compared with IVPCA plus placebo.

Morphine could be the most suitable opioid for neuraxial administration in the context of acute postoperative pain because provides a very good quality of epidural and intrathecal analgesia, but its long elimination time and its potential to cause delayed adverse effects, limit its routine use and require careful selection of patients and vigilance protocols, and it's not recommended for ambulatory patients.¹⁷ </p>

The most lipophilic opioids such as *fentanyl* and *sufentanil* are the opioids most studied and widely used epidural and intradurally in the context of postoperative pain given their rapid onset of action (10-15min) and their short duration (2-5h).¹⁸ Several studies have focused on demonstrating the beneficial effect of the combination of lipophilic opioids with LA in ambulatory surgery and in the field of obstetrics as analgesic agents for labor pain.¹⁰ In this way, the combination of spinal fentanyl (20-30µg) or sufentanil (5-7.5µg) with bupivacaine or

lidocaine leads to a faster onset of blockade and better intraoperative and immediate postoperative analgesia without increasing the degree of motor blockade or the time until discharge. It's a now widespread concept that epidural administration of lipophilic opioids, such as fentanyl and sufentanil, produce their analgesic action mainly by systemic uptake, and their stand-alone administration epidurally is not better than parenterally. Moreover, on the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route would appear to be marginal, or unproven in the case of upper abdominal or thoracic surgery, and in many situations it will not outweigh the risks of the a more invasive route of administration. However, their combination with LA achieve an enhancement of the analgesic effect, decreasing the total dose of each of the drugs used as well as the severity of the adverse effects and is the base of postoperative pain continuous epidural protocols.^{9,10}

Recently, it has been published a random-effects meta-analysis of randomized controlled trials that compared at least 2 continuous epidural infusions for acute postoperative analgesia over at least 24hours.¹⁹ Most trials (19/24) compared the clinically relevant opioids morphine, fentanyl, and sufentanil. Overall, there were no clinically significant differences in analgesia. There was an increased rate of postoperative nausea and vomiting PONV (OR = 1.91; 95% CI, 1.14–3.18; and NNT 9.6; 95% CI, 5.9–26.2) and pruritus (OR = 1.64; 95% CI, 0.98–2.76) among patients receiving morphine versus fentanyl. There were no other differences in opioid side effects detected, including respiratory depression, which had a low event rate. Limitations of this analysis included the heterogeneity in surgical populations, differences in outcome reporting among studies, and overall paucity of trials. Most common epidural opioids clinical dosages are summarized in Table 1.

Table 1 Recommended Dosages for Epidural Opioids

	Dilution	Bolus Dose	Infusion	Rescue Dose
Morphine*	20-40 µg/ml	2-5 mg	0.2-0.4 mg/h	0.1-0.2 mg/30 min
Hydromorphone	10 µg/ml	0.5-1.5 mg	0.1-0.2 mg/h	0.04 mg /10 min
Fentanyl**	2-5 µg/ml	50-100 µg	0.5-1 µg/kg/h	10-20 µg /10 min
Sufentanil**	0.2-0.35 µg/ml	20-40 µg	0.1-0.2 µg/kg/h	2-5 µg /10 min

*The FDA has also approved extended-release epidural morphine sulphate (EREM): 5-15mg/48 h without LA (local anesthetics).
**Usually used added to LA.

Conclusion

Opioids are the most potent centrally acting analgesic drugs for the treatment of any kind of pain. Since the discovery of spinal opioid receptors, the use of spinal opioids has been adopted in clinical practice in the hope of producing intense segmental analgesia that was devoid of the dose-limiting side effects associated with its systemic opioid administration. Either experimental or clinical studies have demonstrated that after neuraxial opioid administration, liposolubility is inversely proportional to their spinal selectivity, which is higher for morphine, than for other more lipophilic drugs, such as fentanyl and sufentanil.

In recent years, a great amount of information has been available regarding the use of spinal opioids alone or in combination with LA, which has helped physicians to define the clinical applicability and efficacy of these forms of therapy and has also contributed to the understanding of the disadvantages of their use. This knowledge must

be used to select a treatment based on patient's particular needs and personal clinical experience in the perioperative setting in order to produce a high quality pain control combined with a low incidence of adverse effects, but this decision should be pivot on published medicine evidence data. It can be considered, that epidural morphine is most suitable when administered alone or in EREM format, and fentanyl and sufentanil as continuous infusion associated to local anesthetics.

Finally, scientific community should reach a consensus on this topic and an international protocol should be adopted for proper patients monitoring after spinal opioids administration to avoid the feared respiratory depression and also other minor adverse effects such as pruritus, nausea and vomiting.²⁰

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Conflicts of interest

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