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Current Evidence for Spinal Opioid Selection in Postoperative Pain

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Background:

Spinal opioid administration is an excellent option to separate the desirable analgesic effects of opioids from their expected dose-limiting side effects to improve postoperative analgesia. Therefore, physicians must better identify either specific opioids or adequate doses and routes of administration that result in a mainly spinal site of action rather than a cerebral analgesic one.

Methods:

The purpose of this topical review is to describe current available clinical evidence to determine what opioids reach high enough concentrations to produce spinally selective analgesia when given by epidural or intrathecal routes and also to make recommendations regarding their rational and safety use for the best management of postoperative pain. To this end, a search of Medline/Embase was conducted to identify all articles published up to December 2013 on this topic.

Results:

Recent advances in spinal opioid bioavailability, based on both animals and humans trials support the theory that spinal opioid bioavailability is inversely proportional to the drug lipid solubility, which is higher in hydrophilic opioids like morphine, diamorphine and hydromorphone than lipophilic ones like alfentanil, fentanyl and sufentanil.

Conclusions:

Results obtained from meta-analyses of RTCs is considered to be the 'highest' level and support their use. However, it´s a fact that meta-analyses based on studies about treatment of postoperative pain should explore clinical surgery heterogeneity to improve patient's outcome. This observation forces physicians to use of a specific procedure surgical-based practical guideline. A vigilance protocol is also needed to achieve a good postoperative analgesia in terms of efficacy and security. (Korean J Pain 2014; 27: 200-209)

Key Words:

epidural opioids, intrathecal opioids, postoperative pain, spinal analgesia.

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INTRODUCTION

The quality and quantity of evidence available for the treatment of acute pain has grown rapidly over recent years. Clinicians usually coping with pain, therefore, face an almost impossible task in keeping up to date with integrating all of the current evidence applicable to their personal practice. Fortunately, assistance in recording and organizing knowledge is also increasingly available and comes in a number of different forms, including systematic reviews, clinical guidelines, evidence summaries, expert reviews and analgesic "league" tables [1]. While a large amount of evidence related to acute pain treatment is available, limitations may exist in terms of its quality as well as clinical significance, especially in the areas of neuraxial anesthesia and spinal opioid selection for postoperative pain. The quality of evidence used in evidence summaries or guidelines is often graded, and in all cases evidence obtained from meta-analyses of randomized controlled trials (RCTs) is considered to be the 'highest' level [1]. However, it has been recently suggested that meta-analyses that evaluate studies about the treatment of postoperative pain can explore clinical heterogeneity associated with variable types of surgery to arrive at better implications for clinical practice [2]. This point implies the general use of a specific surgical practical guideline based on evidence to help physicians in their management of postoperative pain [3].

The principal purpose of this topical review is to describe currently available clinical evidence to determine what opioids reach high enough concentrations to produce spinally selective analgesia when administered through epidural or intrathecal routes in a perioperative setting. A secondary purpose is to make recommendations regarding their rational use for the best management of postoperative pain. To this end, a search of Medline/Embase was conducted to identify all articles published up to December of 2013 using the keywords "postoperative pain", "spinal analgesia", "epidural opioids", and "intrathecal opioids".

FACTORS AFFECTING SPINAL OPIOID BIOAVAILABILITY

Humans have administered opioids for hundreds of years to produce either analgesia or other clinical and recreational effects mediated by the central nervous system. In fact, it was not until the 1970s when it was demonstrated that the analgesic effects of these drugs are mediated by opioid binding to specific receptors located in the brain stem [4]. A forward step was taken in 1979, with the publication in The Lancet of the first article on the use of epidural morphine administered as a bolus of 2 mg for the treatment of either acute or chronic pain. It was suggested by the authors that the analgesic effect was directly mediated by morphine joining specific opioid receptors located in the posterior dorsal medullar horn (*Substancia Gelatinosa of Rolando*) [5].

All currently available opioids are expected to produce analgesia by the same molecular mechanism, which involves decreasing the excitability of nerve cells. To achieve this purpose, all of them bind to the G-protein, produce an inhibition of the enzyme adenylate cyclase, and finally stimulate the activation of potassium channels as well as the inhibition of voltage-dependent calcium ones. Due to this common action, it is a legitimate scientific undertaking to investigate why many differences appear among opioids in terms of their pharmacokinetic and pharmacodynamic characteristics, and whether this fact implies a change in our clinical practices with regard to the selection of the optimal postoperative drug regimen [6]. For many years, it has been assumed that, epidurally or intrathecally, opioids would in all cases produce better analgesic effects than the use of parenteral routes, and that fewer systemic negative effects would ensue. In contrast with the results we expected, many opioids can reach higher brain centers through the cerebrospinal fluid (CSF) or the blood, or can be retained in adverse environments such as epidural fat while their spinal bioavailability remains very low [7]. Experiments in both animals and humans strongly support the hypothesis that bioavailability at the spinal cord is inversely proportional to the degree of drug lipid solubility, which is higher in hydrophilic opioids (e.g., morphine and hydromorphone) than in the lipophilic types (e.g., alfentanil, fentanyl and sufentanil) [7,8]. Diamorphine is a purified derivative of heroin (diacetylmorphine) and is considered to be a prodrug that lacks intrinsic opioid activity, but is quickly metabolized by esterases into neural tissue and subsequently transformed into the active ingredients 6-cetylmorphine and morphine (about 77 %), which act on opioid spinal cord receptors [8]. In light of this, morphine could indeed be considered as the opioid with the best overall profile for spinal administration due to having the

best opioid bioavailability, but this does not imply that morphine is an ideal drug in all clinical situations. It should not be used in ambulatory surgery or in patients with high cardio-respiratory risk as it can cause dose-dependent delayed supraspinal effects (either analgesic or side effects), meaning that patients have to be carefully selected [8].

It has been reported that epidural morphine requires between 5 to 10 hours to reach a high enough drug concentration in the brain stem to produce measurable trigeminal anesthesia [9], which is in direct relation to the timing of delayed respiratory depression found after an epidural morphine administration [10]. On the other hand, it has also been reported from cervical CSF samples of volunteers that peak fentanyl concentrations were reached in only 10 to 30 min [11]. This great disparity cannot be explained either by the energy obtained from the cardiac systole and diastole, which contract and expand the brain and the spinal cord, or by the simple laws of the diffusion of drugs; the resulting motion of the CSF is homogeneous both in terms of its velocity and direction for all comparably sized opioid molecules. These differences, then, can only be understood in terms of the variations in the clearance rate from the CSF. Therefore, if a drug is rapidly cleared into the plasma or the epidural space, there will be little left to produce spinal analgesia [6-8]. It has been determined that both opioids [intrathecal injections of 50 μg of fentanyl (F) together with the same dose of morphine (M) injected into the lowest palpable interspace (L5-S1)] reach their peak CSF concentration at the lumbar cephalic site at the same time. Fentanyl achieved this first after 41 ± 13 min, followed by morphine after 57 ± 12 min. Moreover, the M : F concentration ratio increased from 2 : 1 to 4 : 1 after a period of 36 to 103 minutes. The distance between the needles, the CSF volume, the patient height, or the patient weight did not correlate with the individual model parameters determined previously by the authors, and these results were explained using a simple pharmacokinetic model with high individual variability. The authors' conclusion was that fentanyl was more quickly removed than morphine from the CSF with lower spinal bioavailability over time; however, no differences were found after the first hour of the trial in relation to the spread of the two compared opioids [12]. In fact, in humans, the clearance rate of morphine (2.8 μg/kg/min) is almost 10-fold lower than that of sufentanil (27 μg/kg/min), which could explain the longer clinical analgesic effect observed for morphine after spinal administration [6-8]. It has also been suggested that lipophilic opioids have greater affinity for white matter compared to water-soluble drugs, which had greater affinity for gray matter [6-8]. This fact was measured in an experimental animal model, with intrathecal injections of different opioids (morphine, fentanyl, sufentanil and alfentanil) at equimolar doses, with subsequent measurements of the concentrations of drugs in the extracellular compartment around the spinal cord. The exposure to morphine was higher than it was in all of the lipophilic opioids, with morphine having as much as a three-fold higher concentration and also slower clearance, both at the thoracic-level injection (T11) and the lumbar site (L2 to L3) [13].

Pain and genetics is currently an interesting field in that findings in that area are relevant to opioid clinical efficacy levels. There are three major G-protein-coupled opioid receptors which are essential for functional analgesic properties throughout the body (μ, δ and κ) as well as several minor subtypes, which imply broad inter-individual variability. The μ-opioid receptor (MOR) is the primary one and is encoded by the opioid receptor μ 1 gene (PORM1) located in chromosome 6. Alterations in the alleles of PORM1 could significantly vary the dosage requirements of exogenous opioids. It has been suggested that around 15% of Caucasians are carriers of the most common polymorphism of this gene, defined as A118G substitution, in which an adenine is substituted for a guanine in position 40D in exon 1, exhibiting a decreased response to opioids and subsequently an increased drug requirement to manage pain [14].

CLINICAL PHARMACOLOGY OF SPINAL OPIOIDS ALONE AND WITH LOCAL ANESTHETICS

It is well recognized that the spinal administration of local anesthetics (LA) will always produce segmental analgesia by direct spinal action, blocking sodium channels and inhibiting the crossing of 7000 ions per 1/1000 of a second to produce cell membrane depolarization. However, the most commonly used practice for spinal analgesia is often a mixture of LA and opioids because a supra-additive effect in the spinal cord posterior horn pain transmission mechanism is observed between opioids and

sub-anesthetic concentrations of LA. Moreover, this practice improves and maintains the overall analgesic effect over time and with fewer adverse effects [15]. In a review of combinations of opioid analgesics, it was suggested that the combination of LA and opioids improves analgesic efficacy with fewer side effects due to the interaction with the GPT-mediated signal transduction between calcium channels and opioid receptors [16].

A meta-analysis [17] (3338 patients, 1932 of whom received opioids) based on studies of opioids added to LA for single-shot intrathecal anesthesia in patients undergoing minor surgery showed that the most frequently tested drugs were morphine (0.05-2 mg) and fentanyl (10-50 μg) added to bupivacaine. The overall postoperative analgesia duration was longer either with fentanyl (60 to 168 min) or morphine (315 to 641 min). Further, morphine increased the risk of vomiting (number needed to harm [NNH] 10), nausea (NNH 9.9), urinary retention (NNH 6.5), and pruritus (NNH 4.4).On the other hand, fentanyl only increased the risk of pruritus (NNH 3.3).

In another recent meta-analysis performed by the same group [18], the authors systematically searched for RCT while comparing a reduced dose of intrathecal LA with an opioid to a standard dose of LA alone in adults undergoing surgery with only neuraxial anesthesia (28 trials and 1393 patients were included). The overall conclusion was that the addition of an opioid to LA decreased LA-related adverse effects and improved recovery from the spinal blockade without compromising intraoperative anesthesia.

The combination of continuous intrathecal morphine plus bupivacaine in the management of cancer pain resulted in a minor progression of the morphine dose during the initial phase of controlling analgesia due to a synergistic effect of the LA on the morphine-induced antinociception [19]. Mercadante et al. [20] found that intrathecal opioids in combination with LA provided long-term improvement of analgesia in cancer patients who were unresponsive to multiple adequate trials of systemic opioids, with a decrease in either the adverse effects or rescue opioid consumption until death. Moreover, in a postoperative setting involving more than 4227 cancer patients, a four-year study demonstrated that continuous epidural analgesia with 0.05-0.1% bupivacaine and 0.01% morphine was an effective means of perioperative analgesia with a low incidence of side effects. It can also be safely utilized on surgical wards [21].

Morphine can be considered as the "gold standard" of spinal drugs because it shows the best spinal bioavailability among opioid drugs. The clinical dose required is lower for epidural than for intravenous administration (1/5-1/10) due to its good spinal cord selectivity [8]. In clinical practice, morphine can be administered either as an epidural bolus (30-100 μg/kg) or a continuous infusion (0.2-0.4 mg/h), which seems to produce a better quality of analgesia. This drug can be administered either alone or together with LA, as the synergy between the drugs is assumed to increase the overall analgesic effect [8,15,22,23]. Controlled studies [24-26] have also demonstrated that a single-dose extended release of epidural morphine (EREM) administered before surgery at the lumbar level without LA provides a good quality of perioperative analgesia over 48 hours with a predictable side effect profile. However, a higher risk of respiratory depression has been estimated for EREM compared to intravenous (IV) morphine in patient-controlled analgesia (PCA), [odds ratio (OR) of 5.80 (95% CI 1.05-31.93; P = 0.04] [27].

A meta-analysis [28] of 645 patients receiving intrathecal morphine and general anesthesia (27 studies concerning cardiothoracic, abdominal and spinal surgery) has demonstrated that the visual analogic scale (VAS) at rest was 2 cm lower at 4h and 1cm lower at 12h and 24h on a scale of 10cm; moreover, this effect was more pronounced with movement. Adverse effects such as respiratory depression, pruritus, and urine retention were higher in the intrathecal morphine group, with odds ratios of 7.8, 3.8, and 2.3 respectively. However, a higher rate of nausea or vomiting was not detected. The use of rescue IV morphine for the first day was significantly higher in the cardiothoracic surgery group (−9.7 mg) than in the abdominal group (−24.2 mg). This point could make the use of lumbar intrathecal morphine during thoracic surgery highly questionable because a similar reduction of IV morphine could be obtained with other perioperative strategies, such as IV paracetamol (−8 mg), IV ketamine (−16 mg) or IV NSAID (−10 to 20 mg) on the first day after surgery [29].

In a meta-analysis based on studies of morphine plus an LA for regional anesthesia [30], the rate of adverse effects was analyzed (n = 790) compared to a placebo (n = 524). A morphine group at a dose below 300 μg had a higher relative risk (RR) of pruritus (RR 1.8, CI 1.4-2.2), nausea (RR 1.4, CI 1.1-1.7), and vomiting (RR 3.1, CI 1.5-6.4). However, a morphine group at doses above 300

μg had similar values for these three parameters but a higher risk of pruritus (RR 5.0, CI 2.9–8.6) and a higher rate of respiratory depression events (7/80) than the low-dose group (2/247).

Fentanyl and sufentanil are the lipophilic opioids most widely used intrathecally in the context of postoperative pain. Both drugs present a quick onset (10–15 min) with a short clinical duration (2–5 h). Many studies have demonstrated the beneficial effect of the combination of these drugs with LA either during ambulatory surgery or obstetrics and labor pain [15,31]. The association between bupivacaine or lidocaine and sufentanil (5–7.5 μg) or fentanyl (20–30 μg) produces a faster blockade and better intraoperative and immediate postoperative analgesia with no increase in the degree of motor blockade or time until discharge [32]. This practice (using a mixture of LA plus a lipophilic opioid) has also been adopted in the epidural space for the management of postoperative pain, with fentanyl being the opioid on which most studies have focused, clarifying its direct spinal analgesic action. This discussion may in fact be obsolete because it was demonstrated 10 years ago how the method and level of administration affect the final result [33]. The authors argued that epidural bolus injections (>10 μg/ml) would cause a higher diffusion gradient across the meningeal membranes into the CSF, implying that spinal mediated analgesia should prevail over systemic administration. Continuous fentanyl infusion at high doses can reach the minimum effective analgesic concentration for fentanyl (0.63 ηg/ml), producing primary systemic analgesia, and is thus not recommended. Therefore, in clinical practice, a low dose of fentanyl (2–5 μg/ml) is commonly used with LA to improve global synergic analgesia because fentanyl alone cannot be recommended as a first choice to achieve spinal opioid-mediated analgesia [15,34], given that the spinal cord uptake of epidurally administered fentanyl will increase with an increase in the dose or an increase in the concentration of fentanyl placed in the epidural space. The systemic absorption and the supraspinal adverse effects will also increase [34]. Indeed, a meta-analysis found that both forms of epidural analgesia (continuous infusion and patient-controlled analgesia) provided significantly superior postoperative analgesia compared to IV-PCA for all types of surgery and pain assessments. Interestingly, the exceptions were epidural regimens based only on hydrophilic opioids [35]. Further, it was demonstrated that the combination of adrenaline (2 μg/ml) with a low dose of fentanyl (2 μg/ml) and bupivacaine (1 mg/ml) improves the overall synergic analgesic effect when administered at the thoracic epidural space (above the *conus medullaris*) coincident with the incision level. Therefore, this practice should become the gold standard for treating perioperative pain after major thoracic-abdominal surgery when epidural fentanyl plus LA are used [36,37].

In summary, morphine should be the most suitable opioid for neuraxial administration in the context of acute postoperative pain because it provides a very good quality of epidural and intrathecal analgesia, whereas its long elimination time and its potential to cause delayed adverse effects limit its routine use, thus compelling the careful selection of patients and vigilance protocols. Therefore, it is not recommended for ambulatory patients. Lipophilic opioids are a better choice in these cases and also in an obstetric setting [8,15,22].

EVIDENCE-BASED RECOMMENDATIONS FOR CORRECT OPIOID SELECTION

1. PROSPECT GROUP (Procedure-Specific Postoperative Pain Management: http://www.postoppain.org)

Current optimal analgesia should be based on clinical evidence of each surgical procedure. It should be combined with rehabilitation and physiotherapy programs in order to minimize the postoperative recovery period, the length of the hospital stay, and the overall convalescence experience of the patient [3].

The PROSPECT GROUP helps clinical physicians select the most adequate analgesic techniques and drug combination based on current medical published evidence.

This is the *modus operandi* of the Prospect Group:

1. Procedure-specific recommendations that take into consideration differences in the characteristics, location and severity of pain associated with different surgical procedures.
2. Evidence from a systematic review is supplemented with transferable evidence and expert knowledge from a Working Group of surgeons and anesthesiologists.
3. The Prospect Working Group formulates consensus recommendations using established methods for group decision-making (Delphi method, Nominal Group Process).

4. Recommendations are graded to indicate their strength (A–D).
5. Recommendations are provided with an explanation of the evidence on which they are based, including the level (LoE 1–4) and source of evidence (procedure-specific or transferable).
6. All evidence from systematic reviews, as well as transferable evidence, is summarized and abstracts of all references are provided.
7. Studies included in the reviews are assessed and assigned a level of evidence, with the study design, quality, consistency and directness taken into consideration.
8. Procedure-specific evidence, transferable evidence and clinical practice information (expert opinion) are clearly separated.
9. Benefits and damages of different interventions are indicated with a system of ticks and crosses, and the balance of benefits and damages is considered when formulating the recommendations.
10. Evidence and recommendations are freely accessible on the Internet at www.postoppain.org.

The following is an example on spinal opioids for postoperative pain. (Consult Table 1 and/or the original website for clarification of each level of evidence and/or recommendation.)

1) Recommendations for post-thoracotomy pain:

- Paravertebral blockade with LA and pre- and intraoperative thoracic epidural LA plus a strong opioid are recommended based on a reduction in pain compared with postoperative administration alone (Grade A).
- Thoracic epidural LA plus a strong opioid is recommended as a pre-operative bolus followed by an infusion continued for 2–3 days postoperatively based on a reduction in pain compared with systemic analgesia (Grade A).
- Thoracic epidural LA plus opioid is recommended in preference to a spinal strong opioid based on evidence that the analgesic effect of thoracic epidural analgesia has a longer duration than 24 h (Grade A).
- A pre-operative single bolus of a spinal strong opioid is recommended as part of a multi-analgesic regimen (Grade A) when epidural analgesia or para-

Table 1. Levels of Evidence and Grades of Recommendation in PROSPECT [3] (www.postoppain.org)

Level of evidence 1 (LoE1)	1-*Systematic review with homogeneous results* 2-*Randomised controlled trial (RCT):* -Statistics reported and >80% patients follow-up assessment and a, b or c. a) Allocation concealment assessment adequate (A) and JADAD score (1–5) b) Allocation concealment assessment unclear (B) and JADAD score (3–5) c) Allocation concealment assessment unclear (B) and JADAD score (1–2) and additional assessment of overall study quality required to judge LoE	Grade of recommendation: - Systematic reviews: Procedure-specific A Transferable B - RCT: Procedure-specific A (based on two or more studies or a single large, well-designed study) Transferable B
Level of evidence 2 (LoE2)	1-*Randomised controlled trial (RCT):* Statistics not reported or questionable or <80% follow-up and/or a, b, c a) Allocation concealment assessment unclear (B) and JADAD score (1–2) and additional assessment of overall study quality required to judge LoE b) Allocation concealment assessment inadequate (C) and JADAD score (1–5) c) Allocation concealment assessment not used (D) and JADAD score (1–5)	Grade of recommendation: - RCT: Procedure-specific B (or extrapolation from one procedure specific LoE 1 study) Transferable C
Level of evidence 3 (LoE3)	Non-systematic review, cohort study, case study; (e.g. some adverse effects evidence)	Grade of recommendation C
Level of evidence 4 (LoE4)	Clinical practice information (expert opinion); inconsistent evidence	Grade of recommendation D

vertebral block are not possible for any reason (Grade D). Repeated perioperative doses by the spinal route are not recommended because they are not considered to be safe or practical (Grade D).

- Spinal opioids are recommended in preference to intravenous PCA analgesia based on a greater decrease in pain for up to 24 hours, with no difference in respiratory function (Grade A).
- A lumbar epidural strong opioid is not recommended as the first choice based on evidence that the thoracic epidural route is more effective for pain relief (Grade A). However, there is procedure-specific evidence that a lumbar hydrophilic strong opioid reduces pain better compared to systemic analgesia.
- Epidural epinephrine is recommended if a low dose of epidural LA and/or an opioid is used (Grade B).

2. An updated report by the American Society of Anesthesiologist Task Force on Acute Pain Management

"Anesthesiologists who are currently coping with perioperative pain should use therapeutic options such as intrathecal or epidural opioids, systemic opioids by PCA, and regional blockade techniques after strongly considering the right balance between the risks and benefits. These strategies must be used instead of intramuscular opioids ordered by the patient. The consultants and the American Society of Anesthesia (ASA) members argue that the analgesic therapy selected should reflect the individual anesthesiologist's previous experience as well as the potential for the safe application of the analgesia regimen in each setting. Finally, when continuous infusion modalities are used, drug accumulation may contribute to vital adverse events. Hence, special caution must be taken [38]."

These are several examples of neuraxial regional opioid analgesia: (Consult Table 2 for a clarification of each level of evidence.)

- Meta-analyses of RTCs report either improved pain relief or an increased frequency of pruritus in comparisons of post-incision epidural morphine vs. a saline placebo (Category A1 evidence). Findings for

Table 2. Level of Scientific Evidence by the American Society of Anesthesiologists Task Force on Acute Pain Management [38]

CATEGORY A: Supportive literature Randomized controlled trials report statistically significant ($P < 0.01$) differences between clinical interventions for a specified clinical outcome.	Level 1: The literature contains multiple RCTs, and aggregated findings are supported by meta-analysis. Level 2: The literature contains multiple RCTs, but the number of studies is insufficient to conduct a viable meta-analysis Level 3: The literature contains a single randomized controlled trial.
CATEGORY B: Suggestive literature Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.	Level 1: The literature contains observational comparisons (e.g., cohort, case-control research designs) of clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome. Level 2: The literature contains non-comparative observational studies with associative (e.g., relative risk, correlation) or descriptive statistics. Level 3: The literature contains case-reports.
CATEGORY C: Equivocal literature The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.	Level 1: Meta-analysis did not find significant differences ($P < 0.01$) among groups or conditions. Level 2: The number of studies is insufficient to conduct meta-analysis, and (1) RCTs have not found significant differences among groups or conditions or (2) RCTs report inconsistent findings. Level 3: Observational studies report inconsistent findings or do not permit inference of beneficial or harmful relationships.
CATEGORY D: Insufficient evidence from literature The lack of scientific evidence in the literature is described by the following 2 terms.	Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes. The literature either does not meet the criteria for content as defined in the "Focus" of the Guidelines or does not permit a clear interpretation of findings due to methodological concerns (e.g., confounding in study design or implementation). Silent: No identified studies address the specified relationships among interventions and outcomes.

the frequency of vomiting and nausea were equivocal (Category C1 evidence).

- Meta-analyses of RTCs comparing post-incision IM morphine with epidural morphine report improved pain relief and a higher frequency of pruritus for the epidural route (Category A1 evidence).
- RCTs report improved pain relief when pre-incision epidural or intrathecal morphine is used compared with pre-incision oral, intravenous, or intramuscular (IM) morphine (Category A2 evidence).
- Meta-analyses of RTCs report improved pain scores and a higher frequency of either pruritus or urinary retention when postoperative epidural morphine is compared with IM morphine (Category A3 evidence). Findings with regard to the frequency of vomiting and nausea were equivocal (Category C2 evidence).

3. Practice guidelines for the management of respiratory depression associated with neuraxial opioid administration

"Respiratory depression is the worst complication of opioid administration expected in clinical practice. The prevalence is low for doses currently administered, but it is important to remember that it is dose-dependent for both lipophilic and hydrophilic opioids. The incidence ranges from 0.09 to 0.4 % based on data from large observational studies associated with continuous opioid epidural infusions. The estimated overall risk of respiratory depression after neuraxial opioids is less than 1%; therefore, limited data suggest that this risk is similar to that of opioids delivered via the parenteral route (0.25% IV-PCA bolus mode, 0.9% IM route, 1.65 % continuous IV infusion) [39]."

1) Prevention of respiratory depression after neuraxial opioid administration [39]:

- Careful attention is required with regard to a history of sleep apnea, coexisting diseases or conditions such as obesity or diabetes mellitus, as well as current medications, especially preoperative opioids, and adverse effects after previous opioid administration.
- Patients treated with non-invasive positive airway pressure for sleep apnea should bring their own equipment to the hospital.

• Drug selection:

- Single-shot neuraxial opioids could be safely used in place of parenteral opioids without increasing the risk of hypoxemia or respiratory depression.
- Single-shot neuraxial sufentanil or fentanyl could be safe alternatives to single-shot neuraxial morphine.
- If available, extended-release epidural morphine could be used in place of IV or immediate-release epidural morphine; however, extended monitoring is needed.
- Epidural opioids as a continuous infusion are a better choice than parenteral opioids for anesthesia and analgesia in terms of decreasing the risk of respiratory depression.
- If available, adequate doses of a continuous epidural infusion of fentanyl or sufentanil can be used in place of a continuous infusion of hydromorphone or morphine without increasing the risk of respiratory depression.
- Epidural or intrathecal hydromorphone or morphine should not be given to outpatient surgical patients.

• Dose selection:

- The first decision to minimize the risk of respiratory depression is to select the lowest efficacious dose of neuraxial opioids.
- Other drugs such as hypnotics and parenteral opioids should be administered with caution in the presence of neuraxial opioids.
- The concomitant administration of neuraxial opioids and either parenteral opioids, sedatives or magnesium requires an increased level of monitoring in terms of the duration, intensity or the use of additional methods.

2) Detection of respiratory depression: Every patient under treatment with neuraxial opioids should be monitored for adequacy of oxygenation, ventilation and their level of consciousness. For this purpose, the respiratory rate, depth of respiration assessed without disturbing a sleeping patient, and pulse-oximetry when appropriate, should be used. Monitoring should be performed at least once every hour for the first 12 hours if hydrophilic opioids are used as a bolus. Monitoring at least once every 2 hours for the next 12 hours should follow the vigilance period. After 24 hours from the initial administration, monitoring should be performed at least once every 4 hours for a minimum of 48 hours. On the other hand, when lipophilic opioids as a single bolus are used, monitoring should be performed

for the first 20 minutes after administration and followed at least once per hour until 2 hours have passed. Moreover, after 2 h for lipophilic opioids and 24 h for hydrophilic opioids, the frequency of monitoring should be dictated by the patient's overall clinical condition and by the use of any concurrent medications. Expert opinion agrees that monitoring should be performed during the entire time if an infusion of any opioid is in use [40].

CONCLUSIONS

Current clinical evidence-based recommendations conclude that spinal opioid procedures must be one of the most important skills to master for the treatment of postoperative pain, to be preferred to parenteral administration. This finding involves a broad type of surgical procedures that should benefit from the practice, ranging from minor or ambulatory surgery to major thoracic-abdominal procedures. The most commonly recommended practice is the association of a strong opioid with LA either by the epidural or the intrathecal routes, especially when a lipophilic drug (fentanyl or sufentanil) is used. Thoracic epidural adrenaline is the best coadjutant to LA plus fentanyl after major surgery. Morphine is the opioid that shows the best spinal bioavailability after a neuraxial injection. Indeed, its administration alone is a good choice in a perioperative setting, but careful patient selection is necessary. This general practice implies the expected incidence of adverse effects. Therefore, a vigilance protocol is also needed to achieve good postoperative analgesia in terms of efficacy and security. Finally, this procedure must be part of a multimodal analgesic approach and rehabilitation program to improve the outcome of postoperative patients.

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