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Essay

Intrathecal opioids and respiratory depression: Is it myth in obstetrics?☆

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ABSTRACT

The addition of opioids to bupivacaine for spinal anesthesia has been shown to improve quality of anesthesia by the action of fentanyl, and extend postoperative analgesia by the effect of morphine. Side effects, particularly respiratory depression, have prevented their widespread use. Studies are not consistent regarding the incidence of respiratory depression due to the variety of definitions of this complication and the doses of opioids used. Low dose regimens currently used do not produce further respiratory depression than parenteral opioids. The high levels of progesterone, a potent respiratory stimulant, makes safe the use of neuroaxial opioids in scenarios such as obstetrical anesthesia or analgesia, hence their use should not be overlooked.

Opioides intratecales y depresión respiratoria: ¿un mito en obstetricia?

Palabras clave:
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RESUMEN

La adición de opioides a la bupivacaína para la anestesia raquídea ha demostrado mejorar la calidad de ésta por la acción del fentanilo y prolongar la analgesia postoperatoria por el efecto de la morfina. Los efectos secundarios, en particular la depresión respiratoria, han impedido la generalización de su uso. Los estudios no son consistentes en cuanto a la incidencia de depresión respiratoria por la variedad de definiciones sobre esta complicación y las dosis de opiáceos empleadas. Las bajas dosis utilizadas actualmente no producen mayor depresión respiratoria que los opiáceos parenterales. Los altos niveles de progesterona, un potente estimulante respiratorio, hacen seguro el empleo de opiáceos neuroaxiales en escenarios como la anestesia o la analgesia obstétricas, por lo que no deberían omitirse.

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Introduction

Neuraxial techniques are commonly used in obstetric analgesia and anesthesia. These techniques have been modified as new anesthetic agents and adjuvants prove their superiority against their predecessors. The discovery of opioid receptors in the dorsal horn laminae in the sixties[1] encouraged the study and administration of these drugs into the neuraxis, a growing practice that represents one of the most effective measures in the treatment of acute, obstetric, postsurgical and even chronic pain.[2] The likelihood of respiratory depression frequently discourages the use of these drugs, although its incidence at the current doses is extremely low. This article analyzes the use of neuraxial opiates in obstetric patients, emphasizing their considerable higher safety as compared to the general population, because high progesterone levels provide a protective effect (progesterone is a potent stimulant of the respiratory system).[3–5]

The addition of opioids to spinal anesthetic solutions is aimed at improving the quality of intraoperative anesthesia and extending postoperative analgesia. Fentanyl and morphine, respectively, are the most commonly used opioids for this purpose. Fentanyl, at the current recommended doses below 20 μg, improves the quality of anesthesia and reduces the dose of the local anesthetic but has a very short analgesic effect – around 60 min – while morphine, because of its hydro solubility, has a late onset of action at approximately 60 min, but its effects last for about 11–29 h.[2]

Physiology of neuraxial opioids and respiratory depression

The opioid receptors of the posterior horn of the spinal cord play a key role in pain modulation and the direct administration of small amounts of opioids into the anterolateral chemosensitive surface of the spinal cord, into the fourth ventricle, the lateral ventricles or the pontine region cause respiratory depression. The pre-Bötzinger complex, located in the spinal cord, has been recently identified as the structure responsible for the drop in respiratory rate following the systemic administration of opioids.[6]

Animal and human trials have indicated that hydrophilic opioids, such as hydromorphone or morphine, bind more strongly to the specific receptors than the lipophilic opioids such as alfentanyl, fentanyl and sufentanyl. This can be explained by the spinal cord selectivity and the bioavailability of such compounds. These differences can be attributed to pharmacokinetic and pharmacodynamic differences between the two groups of opioids. It is easier for the lipophilic opioids to reach and maintain sufficient concentration at the action site due its binding to epidural fat and rapid plasmatic clearance at the epidural and intrathecal spaces. Moreover, its supraspinal effects are early.[7] In contrast, the opposite properties of morphine make it the drug of choice for the treatment of acute postoperative pain.

Progesterone and other steroid hormones act as chemical messengers in a broad range of target tissues to elicit a slow genomic response via the activation of nuclear receptors, or a rapid response due to its action on the cell membrane receptors.[4] The high levels of progesterone during pregnancy stimulate the respiratory system, increase the minute ventilation, decrease the $PaCO_2$ and cause a mild respiratory alkalosis.[8] Progesterone levels drop abruptly upon removal of the placenta and reach pre-conception levels at around the fifth day post-delivery.[9]

Experimental tests suggest that progesterone and other steroid hormones may be involved in the central neural control of respiration by acting on the center responsible for the respiratory rate, through a direct effect on GABA, and indirectly on the modulation of the respiratory motor neurons, acting over some neuromodulator systems, particularly on the serotoninergic system.[4,10]

Neuraxial morphine in the general population

In the opinion of the American Society of Anesthesiology (ASA), respiratory depression following the administration of opioids may be defined as a respiratory rate below 10 bpm, arterial oxygen saturation below 90%, hypercapnia above 50 mmHg or clinical signs such as dizziness, sedation, periodic apnea or cyanosis.[11] The lack of a universally accepted definition and the variability of the doses used have prevented us from establishing the true incidence of respiratory depression.[12] A single 100–250 μg dose of morphine could cause depression between 0.01% and 7%, and between 0.08% and 3%, with the epidural administration of 3 mg.[11,13–15]

Shapiro et al. studied the records of 1524 patients treated with morphine between 1.999 and 2.002, to establish the incidence of respiratory depression defined as 10 bpm or less, based on three scenarios: 700 patients of which 46% received PCA-IV morphine; 680 patients – 45% – received epidural morphine, and 144 patients – 9%, received intrathecal single dose morphine. Within the subgroup of 700 PCA-IV-treated patients, there were 3 cases (1.86%) of respiratory depression. Among the 680 patients treated with daily epidural morphine, there were 4 cases (0.59%) of respiratory depression. Finally, only one (0.69%) of the 144 patients receiving a single dose of intrathecal morphine developed a respiratory rate below 10 bpm.[16]

Obstetrics

The time to the first administration of the analgesic agent when spinal anesthesia was used with local anesthetic was of 2 h only (range 1–4 h), in contrast to 27 h with 100 μg and 200 μg of morphine (range from 11 to 29 h).[2,17] In the case of fentanyl, the time to analgesia is proportional to the dose; 6–8 h with 60 μg, but with these amounts the side effects, particularly pruritus, nausea, and vomiting, are intolerable.

The spinal anesthesia techniques using local anesthetic agents only do not provide the same level of analgesia for labor or post-cesarean section as the additional use of neuraxial opioids. In our environment, 43% of babies are born through cesarean section[18] and most of these procedures are done with spinal anesthesia, while the number is considerably lower for

epidural. Less than 30% of pregnant women in Colombia[19] receive neuraxial analgesia during labor and delivery.

Caldwell and Rosen in 1994 compared the efficacy of analgesia and the adverse effects of spinal or epidural opioids in a group of obstetric patients. The epidural group showed a longer effect of analgesia, while the spinal group required more treatment for nausea, vomiting, and pruritus. No cases of respiratory depression were reported.[20]

Palmer et al. compared the analgesic efficacy of increasing doses of intrathecal morphine (25, 50, 75, 100, 200, 300, 400 and 500 μg) for managing acute pain following cesarean section but no significant improvement was found at doses above 75 μg. Another trial with the same type of patients used intrathecal morphine at doses of 50, 100 and 200 μg, and concluded that 100 and 200 μg provide effective and comparable levels of analgesia, while the 50 μg dose was less effective. However, the incidence of adverse effects was higher with the 200 μg dose. Milner et al. reported that 0.1 mg of intrathecal morphine provided post-cesarean section analgesia similar to 200 μg. No cases of respiratory depression were reported, but the lowest dose resulted in lower incidence of nausea and vomiting.[6]

The risk factors for respiratory depression in the obstetric population include: high BMI, prior opioid use, magnesium sulfate infusion and the presence of respiratory co-morbidities. Special consideration may be granted for the administration of neuraxial opioids to this group of patients.

Conclusions

Wang in 1979 was the first to study intrathecal morphine using a 2 mg dose that caused a high percentage of side effects. In the 35 years that elapsed since then, a large number of trials have been completed with varying and decreasing doses, and for diverse situations. This experience provides the foundation to say that at the currently used low doses – 50–150 μg, there is no difference in the incidence of respiratory depression when comparing neuraxial versus parenteral opioids. This statement is also made in the ASA guidelines on this topic. However, there is a group of patients that could be "protected" against respiratory depression as a result of the high levels of progesterone – a potent respiratory stimulant – and these are the obstetric patients. In obstetric patients spinal or epidural anesthesia or analgesia should be accompanied with the administration of the well-established doses of morphine, as a way to contribute to the solution of the postpartum pain affecting over one-third of women.

The time of administration of the local anesthetic agent into the subarachnoid or epidural space is an invaluable opportunity to add morphine and fentanyl to the anesthetic solution, since the benefits of this practice during the postpartum, the transoperative and postoperative period are unquestionable.

Conflicts of interest

The authors have no conflicts of interest to declare.

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