Remifentanil as Analgesia for Labor

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Background and objectives: The neuraxial techniques currently represent the most effective methods for pain control during labor and the epidural block using ultradiluted anesthetic solutions is considered the gold standard promoting adequate pain relief with minimum side effects. In some situations however the use of these techniques is limited by the existence of maternal contraindications, or structural or material obstacles. In these cases, the alternatives are still precarious and scarce offering little optimistic results and of dubious effectiveness.

Content: This article presents through a literature review the available information on the use of remifentanil as an alternative technique for analgesia during labor discussing aspects of pharmacokinetics, analgesia efficacy, maternal satisfaction and maternal/fetal side effects.

Conclusions: The initial data show that remifentanil is a promising option to be employed in situations where the parturient cannot or does not want to receive the neuraxial analgesia.

Keywords: ANALGESIA, Opioids: remifentanil; ANALGESIA, Obstetrics.

INTRODUCTION

The neuraxial techniques currently represent the most effective methods for pain control during labor 1 and the epidural anesthsia using ultradiluted anesthetic solutions is considered the gold standard promoting adequate pain relief with minimal side effects 2. These techniques however do not apply to all obstetric patients 1,3,4. In some cases, they are impossible to be used due to absolute or relative maternal contraindications or by the unavailability of structure, material or adequate number of professionals trained at the institution. In addition to all these questions, there is the fact that the neuraxial techniques are not risk-free 5. Important complications such as lumbar pain, post-dural puncture headache and neurological damage can appear due to the use of the technique, the medications and the materials employed. Immediate complications caused by the inadvertent injection of anesthetic solutions in the subarachnoid, subdural and intra-vascular space can also occur at low incidences, but not negligible (1:2,900, 1:4,200 and 1:5,000, respectively) 5. Such complications must not, in practice, represent a limitation to the use of neuraxial techniques, but in some situations they generate anxiety or even refusal on the part of the patient to accept the procedure.

In cases where it is not possible to perform the neuraxial analgesia the therapeutic options are scarce and precarious and are usually restricted to systemic analgesia with opioids or inhaled anesthetics (using mainly nitrous oxide). Such techniques however offer little optimistic results and some publications have raised serious doubts regarding its analgesic effectiveness 6-8. Therefore, the development of an alternative technique to the neuraxial block for use during labor has been much sought after. This article aimed at assessing based on a literature review the role of remifentanil as an option for situations where the parturient cannot or does not want to receive the neuraxial analgesia.

Use of opioids in labor analgesia

The association between obstetric anesthesia and opioids throughout time has not been an easy one. The reports of sedation, nausea, vomiting, delayed gastric emptying and respiratory depression (in both the mother and the newborn) combined with a doubtful analgesic effectiveness has limited its use during labor 4. An ideal intravenous opioid should result in adequate analgesia without interfering with the pattern of uterine contractions, fetal cardiography and its effect on the respiratory pattern of mother and fetus should be minimal so that the administration could be maintained until the end of the expulsion phase 4.
Among the currently employed opioids the meperidine is the most commonly used and studied. Most studies have shown that meperidine results in a certain degree of analgesia, but with inconsistent or insufficient response in a large number of cases, leading some authors to suggest that it acts more like a sedative than an analgesic agent. The prolonged fetal depression associated with its use is a well-documented effect. It is caused by the drug’s prolonged half-life (2.5 to 3 hours in the mother and 18 to 23 hours in the neonate) and the accumulation of active metabolites. Normeperidine, for instance, has a half-life of 60 hours and can be responsible for persistent neonatal respiratory depression for up to 3 to 5 days after the birth, even after low doses of meperidine. In addition to these problems, meperidine affects the maternal gastric motility, modifies the cardiotocography and is related to fetal acidosis at the analysis of umbilical cord blood.

Fentanyl, a highly liposoluble opioid with high protein-binding capacity and 800 times more potent than meperidine, presents better analgesia performance with a peak of action 3 to 4 minutes after the infusion in bolus. However, fentanyl presents several adverse effects in the neonate, with a high incidence of naloxone at birth, low neurobehavioral scores up to 7 days after birth and an adverse dose-dependent impact on the capacity to breastfeed soon after the birth. The use of alfentanil has also been assessed and the drug has shown worse analgesia results when compared to fentanyl, with lower neurobehavioral scores than the patients that received meperidine. Sufentanil is largely used in neuraxial analgesia with good results, but its venous use is very limited due to the potential effects of placental deposition and respiratory depression in the newborn.

Therefore, none of the traditionally used and studied opioids presents the efficacy and pharmacokinetic profile that make them the ideal opioid for use during labor. Remifentanil, introduced in the market in the beginning of the 1990s, represents an actual possibility in the development of this alternative. For more than one decade, the properties of remifentanil have been explored in studies of surgical anesthesia, sedation and postoperative analgesia in non-obstetric populations. Its use in obstetric anesthesia was only started in 1998, when a study established the pharmacokinetic profile of the drug in pregnant patients and neonates. After this study, a series of case reports and clinical trials were performed and showed the potential of remifentanil to become a new option for the analgesia in labor.

Remifentanil in obstetrics
Pharmacokinetics and pharmacodynamics

Remifentanil is a synthetic opioid chemically related to fentanyl, which presents unique characteristics due to the presence of ester-type radicals in its chemical structure. It is a μ selective agonist, with pKa = 7.07 (weak base), little liposoluble and high protein-binding capacity (∼70%, mainly to alpha-1 acid glycoprotein). It is a fast-action drug (± 60 seconds) and it is metabolized through hydrolysis by nonspecific plasma and tissue esterases, which results in rapid metabolism and ultra-short action (half-life sensitive to the context of 3 to 5 minutes) and prevents the accumulation of the drug after prolonged administration. Its metabolites, all inactive, are eliminated in the urine and it is antagonized by naloxone. Remifentanil crosses the placental barrier, but it is rapidly redistributed and metabolized by the neonate, who already has sufficient plasma and tissue esterases for its degradation. The concentration ratio of remifentanil in the umbilical cord/uterine artery is 0.88, showing that there is a fast exchange of maternal blood to the fetus, whereas the concentration ratios in umbilical artery and umbilical vein is 0.29, suggesting significant metabolism and redistribution. The clearance of remifentanin in pregnant patients seems to be two-fold higher than in non-pregnant patients, showing that the physiological alterations of pregnancy might be responsible for this difference due to the change in the volume of distribution, lower concentration of plasma proteins and increased nonspecific esterase activity.

The administration of remifentanil is simple, being necessary to obtain a venous access and a continuous-infusion pump with IV-drip support and compatible syringes. The main adverse effects observed in pregnant patients were nausea, vomiting, pruritus, sedation and respiratory depression. The incidence of nausea and vomiting was variable being as high as 48% in one of the studies. However, as these symptoms occur rather often during labor even without any analgesia it is necessary to estimate and distinguish the incidence directly associated with the use of opioids. The association between the increase in the incidence of nausea and the use of remifentanil in the analgesia for labor was not statistically significant in previously published studies. In a randomized, controlled and double-blind study comparing remifentanil and epidural analgesia controlled by the patient the presence of nausea was observed in some patients before the start of the analgesic technique and the final results showed that, differently from what was expected, the incidence of nausea decreased after the start of the analgesia in the group that received remifentanil.

Some studies have shown the occurrence of pruritus, normally of mild to moderate intensity and without report of the need for treatment. There has been a report on the use of the drug in a patient that presented pruritus secondary to gestational cholestasis and in this case there was no increase in the symptom after the opioid was administered. A preliminary study using patient-controlled analgesia (PCA) with remifentanil reported a patient with generalized pruritus, in whom the drug was discontinued.

Sedation has been described in several cases, but it is always mild and rarely associated with apnea. There have been very few reports of excessive sedation with the need for assisted ventilation. Practically all studies that...
have been published showed episodes of alteration in the respiratory pattern and desaturation (without apnea and with SpO₂ values > 90%). These effects, however, were transient and easily corrected with the use of supplementary nasal oxygen and decrease in the dose used. Due to such reports, however, remifentanil must be used in patients who are under constant follow-up and continuous monitoring of oxygen saturation and the professional must have at his/her disposal a supplementary source of oxygen for use in nasal catheter or facial mask and adequate equipment for assisted ventilation and resuscitation.

There has been no evidence of hemodynamic instability with the use of remifentanil. The development of acute tolerance has been observed with several opioids. However, studies in volunteers and observation of patients in intensive care maintained with a continuous infusion of remifentanil (to aid mechanical ventilation) have not shown the occurrence of acute tolerance.

Some authors studied the effects of the different opioids (including remifentanil) and local anesthetics in the isolated uterine muscle of pregnant rats. The results showed that these two groups of medications reduce the contractility of the uterine muscle fiber. Such medications, when used through epidural or spinal anesthesia, do not reach sufficient plasma concentrations to induce the effects described above, but when they are used intravenously, they can reach the concentrations used in the experiments. However, there have been no clinical studies that showed in vivo results that were similar to the ones observed in vitro.

There has been no association between the infusion of remifentanil and any deterioration in cardiotocography that would indicate intervention or investigation, as well as in the fetal blood samples. A transient variability in the tracing has been noticed, but these effects are much less frequent than the ones observed with the systemic administration of other opioids. The Apgar scores and blood pH of the umbilical cord did not present abnormal results. None of the studies in analgesia demonstrated the need for neonatal use of naloxone or an unexpectedly low Apgar score (without other reasons involved in it), which leads us to conclude that the dose used in the analgesia is rapidly metabolized also by the neonate. In the reports in which naloxone was necessary for neonatal resuscitation, remifentanil was used to supplement the general anesthesia in infusions > 0.1 μg.kg⁻¹.min⁻¹ and associated to other drugs.

The pharmacokinetic profile of remifentanil in neonates is similar to that of older children and adults, and remifentanil is used in the neonatal ICU in patients undergoing mechanical ventilation and surfactant administration. Remifentanil does not bind to NMDA and GABA receptors and therefore it is not associated with apoptotic neurodegeneration and persistent deficits of memory and learning by the newborn when used in pregnant patients.

### Remifentanil in analgesia for labor effectiveness and maternal satisfaction

The first reports on the use of remifentanil for analgesia during labor involved pregnant patients that presented some type of absolute contraindication to neuraxial analgesia and agreed to receive an alternative analgesic technique. The first study that reported the use of the drug in healthy patients was published in 2000. The pharmacokinetic profile of remifentanil suggested the possibility of its use in bolus, thus matching the peak of the action with the peak of the pain produced by the uterine contractions. In this study, the drug was administered to four parturients as manual bolus at the start of the contractions perceived by the uterine dynamics. The results showed that there was a delay in the start of the action in relation to the contractions and the peak of the analgesic action occurred during the interval between them. The final conclusion was that remifentanil was not effective as an analgesic technique for labor. Computerized simulations of the concentration in an effector site had already predicted a half-life of equilibrium (blood-site effector) of 1.3-1.6 minutes and a study that analyzed the effect on the ventilator pattern in healthy volunteers with a bolus of 0.5 μg.kg⁻¹ showed that the start of the effect occurred in 30 seconds with a peak in 2.5 minutes. These data suggested that the bolus infusion in the beginning of the uterine dynamics would make it difficult to match to the peak effect with the peak of the pain.

In 2001, Blair et al. investigated the effectiveness and safety of PCA with remifentanil in 21 parturients. The drug was used in an initial bolus of 0.25 μg.kg⁻¹, with a minimum interval (lockout time) of 2 minutes, gradual increase up to a maximum dose of 1 μg.kg⁻¹ and in association or not with a continuous infusion of 0.025 to 0.05 μg.kg⁻¹.min⁻¹. There was a considerable decrease in the pain score in 90% of the patients, without the need to administrate an associated continuous infusion. There were no significant decreases in the fetal cardiotography and the Apgar scores and blood pH values of the umbilical cord remained within normal ranges. The authors concluded, then, that the technique was safe and resulted in analgesia that in spite of being incomplete was acceptable during labor.

In a case report published in 2002, Owen et al. reported the use of remifentanil in a morbidly obese patient with antiphospholipid syndrome, severe thrombocytopenia, kidney failure, preeclampsia and epigastric pain (with normal liver function and abdominal ultrasound results). Remifentanil was used as a continuous infusion at doses that varied from 0.05 μg.kg⁻¹.min⁻¹ and 0.2 μg.kg⁻¹.min⁻¹. This case report stood apart from others due to fact that the infusion was maintained for 34 consecutive hours. The mean pain score obtained was 4 in 10 and although the total pain control (score < 2 in 10) was not obtained, the researchers reported that the patient, family members and obstetric team were satisfied with the degree of analgesia attained.
In the same year, Volmanen et al. 15 used remifentanil as PCA infusion for a period of 60 minutes while evaluating 17 healthy pregnant patients. In this study, an initial bolus of 0.2 μg.kg⁻¹ was used (lockout of 1 minute), which was administered as soon as the patient perceived the first signs of uterine contraction, with an increase of 0.2 μg.kg⁻¹ per dose when the analgesia was ineffective (up to a maximum of 0.8 μg.kg⁻¹). All patients reported adequate pain relief (scores varying from 3.1 to 5.2 in a scale of 10), with a mean bolus of 0.4 μg.kg⁻¹ and a maximum bolus of 0.8 μg.kg⁻¹.

In 2005, Evron et al. 17 compared in a double-blind study PCA with remifentanil with intravenous meperidine in 88 parturients ASA I and II who did not wish initially to receive neuraxial analgesia. The dose in bolus of remifentanil was initially 20 μg (lockout of 3 minutes), with increases of 5 μg.kg⁻¹ per dose in case of insufficient analgesia up to a maximum of 1,500 μg.hour⁻¹. Meperidine was given as an initial dose of 75 mg per patient, with additional doses of 50 mg in case of insufficient analgesia up to a maximum of 200 mg. The doses of remifentanil ranged from 0.27 to 0.93 μg.kg⁻¹ per dose and were more effective than meperidine in the control of pain, with higher scores of maternal satisfaction and lower sedative effect. Blair et al. 27 also compared PCA with remifentanil (at doses of 40 μg.kg⁻¹ bolus with 2-minute intervals) with PCA using meperidine (5 mg with a minimum interval of 10 minutes). The pain scores were similar for both drugs, but the level of satisfaction with the analgesia was higher in the group that used remifentanil.

Volmanen et al. 16 conducted another randomized and double-blind study in 2005 using PCA with remifentanil, this time compared to nitrous oxide. In this study, 15 patients alternated remifentanil and nitrous for periods of 20 minutes with a wash-out of 20 minutes between techniques. Remifentanil was used as PCA in bolus of 0.4 μg.kg⁻¹ (lockout of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with consecutive increases (without a ceiling dose) and the nitrous oxide was offered through a mask of 1 minute) with 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The information presented here show that remifentanil has the potential to occupy an alternative position as analgesic technique during labor. Some questions discussed here, however, deserve attention and remain controversial with the data that have been published to date.

Table I – Use of Remifentanil (PCA Technique) during Labor

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose in bolus μg.kg⁻¹.dose</th>
<th>Lockout time</th>
<th>Pain score (in 100 mm)</th>
<th>Patients that chose conversion to epidural analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair (2001)</td>
<td>0.25-0.5</td>
<td>2 min</td>
<td>Mean = 50 mm</td>
<td>2 in 21 (9.5%)</td>
</tr>
<tr>
<td>Thurlow (2002)</td>
<td>0.20</td>
<td>2 min</td>
<td>Mean = 48 mm</td>
<td>7 in 18 (38%)</td>
</tr>
<tr>
<td>Volmanen (2005)</td>
<td>0.4</td>
<td>1 min</td>
<td>Decrease of 15 mm</td>
<td>-</td>
</tr>
<tr>
<td>Blair (2005)</td>
<td>40 μg (fixed)</td>
<td>2 min</td>
<td>Mean = 64 mm</td>
<td>2 in 20 (10%)</td>
</tr>
<tr>
<td>Volmanen (2002)</td>
<td>0.2-0.8</td>
<td>1 min</td>
<td>Decrease of 42 mm</td>
<td>-</td>
</tr>
<tr>
<td>Evron (2005)</td>
<td>0.27-0.93</td>
<td>3 min</td>
<td>Mean = 35 mm</td>
<td>8 in 88 (10.8%)</td>
</tr>
<tr>
<td>Volikas (2005)</td>
<td>0.5</td>
<td>2 min</td>
<td>Mean = 46 mm</td>
<td>5 in 50 (10%)</td>
</tr>
<tr>
<td>Balki (2007)</td>
<td>0.25 + CI</td>
<td>2 min</td>
<td>No information</td>
<td>1 in 20 (5%)</td>
</tr>
<tr>
<td>Volmanen (2008)</td>
<td>0.1-0.9</td>
<td>1 min</td>
<td>Mean = 73 mm</td>
<td>-</td>
</tr>
</tbody>
</table>

Cl – continuous infusion
loaned infusion pumps, supports, extensors and mean cost of the medication).

As it occurs with some drugs routinely employed in pregnant patients (such as fentanyl by spinal administration) remifentanil has not been released for use during pregnancy. This isolated fact does not represent an obstacle to its use, but the number of studies and patients that received this medication is still limited to justify the routine use of the technique.

CONCLUSION

Remifentanil as continuous infusion at a maximum dose of 0.15 μg.kg\(^{-1}\).min\(^{-1}\) associated or not to a bolus administered by PCA seems to result in an acceptable and clinically satisfactory mean decrease in pain scores during labor, apparently without interfering with its evolution. The described side effects are minimal and easily reversible in the mother and newborn and the technique does not affects the parturient’s capacity to experience the act of delivering. Although the available data do not allow the substitution of the neuraxial techniques by remifentanil, the drug is probably one of the best currently available alternatives for patients that for some reason do not wish to or cannot have a neuraxial block. In these cases, its better use is during analgesia for labor. However, the number of populations and studied patients is still low and further studies are necessary to confirm the initial data, to determine the most adequate doses and infusion regimens, cost assessment and maternal/fetal safety.