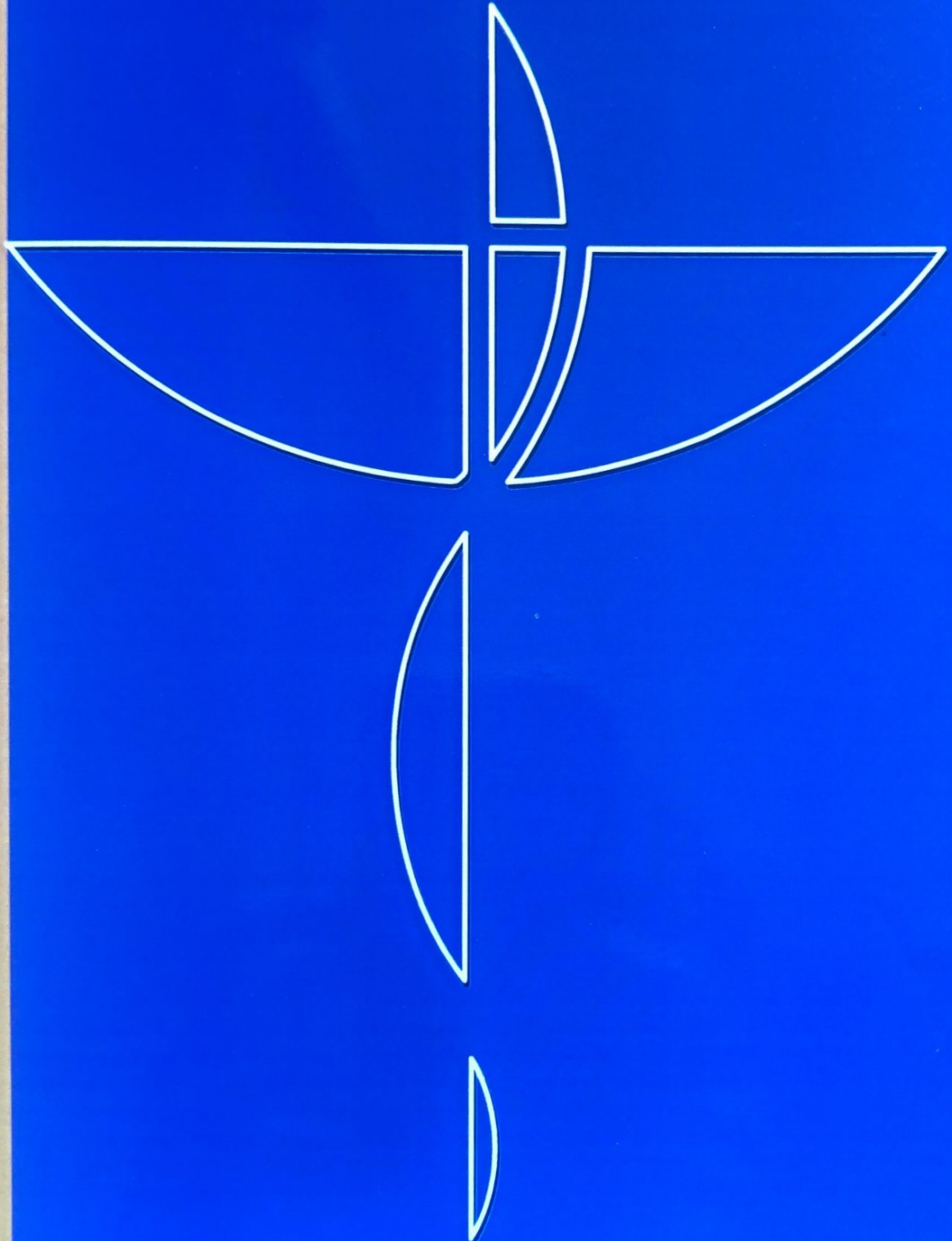




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Guidelines for authors

INTRAVENOUS REMIFENTANIL FOR LABOR ANALGESIA – A Review

Karadjova D¹, Shosholcheva M², Ivanov E¹, Sivevski A¹, Kjaev I¹, Spasovski S¹, Kartalov A³, Kuzmanovska B³, Zlatkova M¹, Samardziski I¹, Spasova R¹, Kochovski G¹

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Abstract

In modern obstetrics there has been a need for safe, efficient, and easy-to-use systemic analgesia with a rapid and short onset, and without an effect on either mother or fetus. Although epidural analgesia remains the gold standard for labor analgesia, opioids applied intravenously can be very useful in cases when epidural analgesia is contraindicated, refused by the patient, or in the absence of a skilled anesthesiologist. Closest to the ideal for systemic analgesia is remifentanil: a potent, ultra short-acting $\mu 1$ agonist, which is rapidly metabolized in both mother and fetus. This article, through a literature review, will present the efficacy of remifentanil, its pharmacokinetics, the most effective dose, the safety for both mother and fetus, and the satisfaction for the mother. The results available show that remifentanil can be quite a satisfactory alternative to neuraxial analgesia, hence taking its deserved place in modern obstetrics. A low number of reported side effects from mother and child are enough to open a field for future research.

Key words: remifentanil, painless labor analgesia, obstetrics.

ИНТРАВЕНСКИ РЕМИФЕНТАНИЛ ЗА БЕЗБОЛНО ПОРОДУВАЊЕ

Апстракт

Во модерното акушерство се појавува потреба од безбедно, ефикасно и лесно за апликација системско обезболување кое брзо и кратко дејствува без да го компромитира фетусот. Иако епидуралната аналгезија останува златен стандард за обезболување, интравенски опиоиди можат да бидат многу корисни во случаи кога епидуралната аналгезија е контраиндицирана, мајката не сака или едноставно нема доволно искусен анестезиолог. Најблиску до идеален лек за системско обезболување е ремифентанилот, потентен кратко делувачки $\mu 1$ агонист кој брзо се метаболизира и кај мајката и кај бебето. Во овој ревиски преглед преку разгледување на литературата ќе ја прикажеме ефикасноста на ремифентанилот, неговата фармакокинетика, дозволеното дозирање, безбедноста на мајката и плодот како и задоволството на мајката. Достапните резултати ни покажуваат дека ремифентанилот може да биде сосема задоволителна алтернатива на неврооксијалната анестезија и си обезбедува место во модерното акушерство. Мал број на пријавени несакани ефекти од страна на мајката и детето се доволни за отварање на поле за понатамошни истражувања.

Клучни зборови: ремифентанил, безболно породување, акушерство

Introduction

In modern obstetrics the possibility to obtain pain relief during labor is one of the most important goals in women's satisfaction related to medical care. The neuraxial techniques are the most effective methods for labor analgesia¹, while epidural analgesia using ultradiluted anesthetics is considered the gold standard in obstetric anesthesia, promoting excellent analgesia with minimal side effects². However, these techniques are not always applicable for every patient. In some cases they are impossible because of the existence of maternal absolute and relative contraindications (coagulopathies, infections, a high risk of thrombosis, long-term use of prophylactic anticoagulants, spine abnormalities, etc.), or the unavailability of a skilled anesthesiologist. The fact that neuraxial anesthesia has minimal side effects does not imply no risk at all. The complications can be very serious: from lumbar pain, to post-dural puncture headaches, even to serious neurological damages³. These complications should not present an obstacle or limitation for the use of neuraxial techniques, but it should be taken into consideration that for some previously well-informed patients, discomfort towards and even refusal of such invasive procedures is a possibility. In addition, the unavailability of professionals should not be overlooked. In fact, smaller hospitals do not have anesthesiologists who can perform an epidural analgesia for labor at any time of day.

Opioids for intravenous analgesia

In the search for alternative methods for pain relief during labor, obstetric anesthesiologists are more and more directed towards systemic opioids⁴ and finding an ideal opioid for intravenous analgesia. Opioids have been used in obstetrics for more than 100 years, and their beginnings are characterized with a mixture of morphine and skopolamine, while in the year 1950 meperidine (pethidine) was introduced, being the most frequently used opioid. In smaller hospitals this opioid is a drug of choice for labor analgesia⁵. In the USA the incidences of opioid use varies between 30 and 56%, in England it is on average 38%⁶, while in the Nordic countries (more precisely, Norway) according to the study in 2009 the usage of meperidine is noted in almost 77% of all deliveries, while the percentage of epidural analgesia is only 26%⁷. Although meperidine is widely used, its side effects are commonly known (sedation, insufficient analgesia, respiratory depression of the newborn, breastfeeding problems in the newborn), and they are the result of its quite slow metabolism as well as accumulation of active metabolites – norpethidine, whose half-life varies from 20 to 60 hours⁸. New opioids like fentanyl and alfentanil have been shown to be not good enough mainly because of insufficient analgesia and prolonged respiratory depression in the newborn⁹. The introduction of remifentanil in the pharmacological market in the 90-ies provides the possibility for intravenous analgesia. It was used in obstetrics for the first time in 1998, when it was given to 19 patients as a supplement to epidural analgesia during a cesarean section with epidural anesthesia¹⁰, initially demonstrating its pharmacokinetic profile with pregnant patients and neonates. After this study a series of isolated cases appeared, while 2001 saw the first clinical trial with remifentanil for labor analgesia for 21 healthy patients¹¹. In the last 10 years the reported number of studies with remifentanil is increasing, thus opening more opportunities related to the potential of remifentanil in labor analgesia.

Pharmacokinetics of remifentanil

Remifentanil is an ultra-short acting, μ -1 opioid receptor agonist, metabolized to an inactive metabolite by plasma and tissue esterases. Its metabolites, all inactive, are eliminated through urine. Blood-brain equilibrium occurs in 1.2-1.4 minutes. The fast onset of analgesia (30-60 seconds), with a maximum effect in 2.5 minutes and analgesic half-life of

3.5-6 minutes, makes remifentanyl ideal for labor analgesia^{12,13}. Plasma concentrations of remifentanyl in pregnant women are approximately half of those found in women not pregnant due to the greater volume of distribution and higher clearance. Remifentanyl crosses the placenta very quickly, with a concentration ratio umbilical vein/maternal artery of 0.88. The concentration ratio umbilical artery/umbilical vein is 0.29, demonstrating that the drug is rapidly metabolized and redistributed in the fetus¹⁰. This pharmacokinetic profile gives remifentanyl a head advantage in comparison with other opioids that are used for labor analgesia.

Optimal dosing

The efficacy of remifentanyl depends on the dosage as well as the manner of administration. It is usually administered through intermittent patient-controlled boluses - PCA (through patient-controlled pump) with a locked interval, with or without continuous background infusion. Dosing is probably most important in achieving adequate analgesia and it is a point of interest in many studies. Different studies use different boluses, starting from 0.15 and going up to 1 µg/kg, most commonly with a fixed dosing of 0.5 µg/kg. In Table 1 different studies are shown, with different remifentanyl dosing^{11,14,15,16,17,18}. The largest number of the studies have shown wide variation in boluses, which are needed to achieve adequate analgesia. Moreover, these variations in boluses show that fixed dosing can subdose the patient and lead to insufficient analgesia, or can overdose the patient and lead to side effects (respiratory depression/desaturation). Furthermore, the PCA boluses should be titrated for the needs of the patients¹⁹. In his study in 2013¹⁹ on 41 patients, Tveit started the PCA boluses with 0.15 µg/kg and increased it slowly in regards to the needs of the patient. 93% of the patients were satisfied, showing no serious side effects.

Another important aspect in achieving adequate analgesia is as well the moment of application of the boluses. Pharmacodynamic studies in the non-obstetric population have shown that maximum effect of the bolus dose in the central nervous system is achieved between 1 and 3 minutes after the intravenous bolus, thus the best moment for the bolus would be at the start of the contraction, having maximum effect most probably during the next contraction^{20,21}. The lock-out interval varies between 1 and 3, most commonly being 2 minutes.

Additionally, continuous background infusion has been the subject of many studies. Although Balki et al.²¹ demonstrated excellent results with a fixed bolus of 0.25 µg/kg and a continuous background infusion of 0.025-0.1 µg/kg/min, a larger number of the studies^{11,27} demonstrate that continuous background infusion only increases the maternal side effects.

Analgesic efficacy

According to the meta-analysis of 2012, which includes several studies, remifentanyl is more efficient in pain relief during labor than meperidine, nitrous oxide and fentanyl²³. Regarding epidural analgesia there is no doubt that epidural analgesia provides better analgesia. In almost all of the studies in which intravenous analgesia is compared with remifentanyl and epidural analgesia, remifentanyl is associated with considerably higher pain scores^{17,18,24-26}. Yet what is interesting to note is that aside from lower pain in epidural analgesia, the satisfaction scores did not show significant differences with both groups^{17,25,26}. The latest study by Freeman et al., finished in 2015¹⁸, which includes 1.358 patients and primarily focuses on the patients' satisfaction, shows visibly lower satisfaction scores in the remifentanyl group, as compared to the epidural analgesia group (but the study was performed with fixed remifentanyl boluses). To analyze the pain, which is one of the main aims of every study, the authors used a visual analogue scale (VAS) with different ratings (the older VA scales are between 0 and 10 mm, while the newer ones are between 0 and 100

mm). Table number 1 exhibits different studies with different bolus dosing and middle pain score results according to VAS.

Table 1 . Studies for clinical efficacy of remifentanil for labor analgesia

References	Number	Bolus (µg/kg)	Lock-out interval (minutes)	Compared with	Middle pain score results (VAS) (0-100 mm)
Blair ¹¹	21	0.25-0.5	2	None	50mm
Volikas ¹⁴	50	0.5	2	None	46mm
Evron ¹⁵	88	0.27-0.93	3	Meperidine	R:35.8mm M:58.8mm
Ng ¹⁶	68	0.37-0.44	3.75-4.5	Meperidine	R:20mm M:36mm
Ismail ¹⁷	1140	0.1-0.9	1	EA CSE	R:34mm EA:36mm CSE:23mm
Volmanen ²	45	0.3-0.7	1	EA	R:73mm EA:52mm

R - intravenous remifentanil group
M - intravenous meperidine group
EA - epidural analgesia group
CSE - combined spinal-epidural group
VAS - visual analogue scale

Maternal side effects

The biggest concern when using intravenous opioids are the maternal side effects, such as: sedation, oxygen desaturation, hypoventilation, pruritus, nausea, and vomiting. A large number of studies have shown that maternal sedation and respiratory depression which needs oxygen substitution is short-term and without undesirable consequences. In the literature there have been only few isolated cases reported^{27,28,29,30} on obstetric patients who developed apnea during analgesia with remifentanil. One case report was while continuous remifentanil infusion²⁷ was used, while the others were with parallel use of more methods of analgesia^{29,30}. All of the side effects were short-term and ended well, but these cases state further required caution and readiness for the whole duration of the analgesia.

Compared to epidural analgesia, intravenous analgesia with remifentanil is connected to substantially lower values of oxygen saturation, which needs substitution (from 10 to 65%)^{25,31}, while compared with other systemic opioids it shows a similar incidence of desaturation³² or better results¹⁵.

Moreover, remifentanil compared with other possibilities for labor analgesia is safe and tolerated well. The main concern remains the possibility for oxygen desaturation, which according to all available studies up to now is short-term and easily correctable with nasal oxygen, further implying that monitoring of saturation in patients receiving remifentanil is obligatory as well as availability of oxygen if needed.

Maternal sedation also represents an important side effect of opioid intravenous analgesia³¹. Occasional monitoring and assessment of the score of the sedation is obligatory.

Some studies have exhibited pruritus, with low to medium intensity, without the need for therapy¹⁴.

Nausea and vomiting are well-known side effects of opioid analgesia, and their incidence with remifentanil is in the range of 0 to 60%²². These symptoms develop during childbirth,

even when there is no analgesia, so it is necessary to determine the incidence of nausea and vomiting directly associated with opioids. In a large number of previous studies there is no significant connection between nausea and vomiting and the use of opioids^{14,24}, but Volmanen in his study in 2008 showed that incidences of nausea decrease in the group with remifentanil analgesia².

Effects on the fetus and newborn

Just as with any other use of opioids, either intravenously or in central blocks, some abnormalities in fetal heart rate can appear, which are manifested through abnormalities on the cardiotocograph (CTG) and neonatal depression. In all of the studies the incidence of CTG abnormalities are low and short-term. However, the use of the cardiotocograph in every patient receiving an opioid is obligatory. In every available study the Apgar scores and the values of umbilical cord measured gases have all been within the normal limits after remifentanil administration^{2,10,11,14}. No neonate has needed naloxane (an opioid antagonist) after delivery, hence confirming the rapid metabolism of remifentanil and its redistribution in the neonate after placental transfer. Table 2 shows some of the maternal and neonatal side effects and their incidence in percentages in the studies.

Table 2 Reported maternal and neonatal side effects during labor analgesia with remifentanil

References	Bolus (µg/kg)	Maternal sedation	Number of episodes of respiratory desaturation	Apgar scores in 1 and 5 minutes (middle value)	Abnormalities in fetal heart rate
Blair ¹¹	0.25-0.5	9.5%	23.8%	8/9	9.5%
Volikas ¹⁴	0.5	44%	0	9/9	20%
Evron ¹⁵	0.27-0.93	0	0	>7	7.8%
Ng ¹⁶	0.37-0.44	0	0	8/9	3%
Ismail ¹⁷	0.1-0.9	0	0	/	/
Volmanen ²	0.3-0.7	29%	54%	9/9	54%
Douma ²⁶	0.5	10%	5%	/	/
Volmanen ²⁴	0.2-0.8	100%	59%	9/9	29%

Monitoring

The more serious maternal, fetal and neonatal side effects imply the need for obligatory monitoring during intravenous analgesia with remifentanil. In this context, the highest importance is placed on continuous measurement of oxygen saturation and maternal heart frequency with pulse oxymetry, as well as continuous cardiotocographic monitoring for fetal heart rate. Occasional measurement of non-invasive blood pressure, number of respirations, and occasional assessment (in 30 minutes) of the maternal sedation score are all included in obligatory monitoring.

Future research

In all the available literature there is insufficient information regarding maternal and neonatal side effects, which can thus misrepresent the safety of using remifentanil in labor. The fact that a very low number of side effects is reported does not mean that they do not

exist. Future research is mandatory for more information and for the creation of reasonable recommendations for monitoring, since this method of pain relief is very promising.

Conclusion

Remifentanil is a viable alternative to neuraxial anesthesia in cases when neuraxial block is contraindicated, unavailable, or simply unwanted by the patients. Bolus dosing with a PCA pump, with a gradual increase of the dose according to patient needs, leads to acceptable and clinically satisfactory results in reference to the pain scores during labor. Although pain score results are much higher in the patients with remifentanil than in the patients with neuraxial analgesia, the mothers' satisfaction scores are almost identical. The use of remifentanil should always be accompanied with appropriate monitoring and the existing possibility to intervene in case of eventual respiratory complications. Future research is mandatory in order to determine the safety of the mother and the neonate, as well as to establish the optimal dose of remifentanil for effective analgesia.

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