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PATIENT-CONTROLLED ANALGESIA (PCA) WITH REMIFENTANIL VERSUS INTERMITTENT EPIDURAL BOLUSES FOR LABOR ANALGESIA

ПАЦИЕНТ-КОНТРОЛИРАНА АНАЛГЕЗИЈА СО РЕМИФЕНТАНИЛ НАСПРОТИ ИНТЕРМИТЕНТНИ ЕПИДУРАЛНИ БОЛУСИ ЗА БЕЗБОЛНО ПОРОДУВАЊЕ

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Апстракт

Вовед. Ремифентанилот станува се популарен за безболно породување како алтернатива на невроаксијалната аналгезија. Во оваа студија јаспоредуваме јачината на болката, задоволството на родилките и несаканите ефекти од страна на мајката.
Методи. 80 пациентки АСА 1 или 2, прворотки, во термин за раѓање, беа вклучени во студијата и поделени во 2 групи. Првата група (35 пациентки) добија интравенски ремифентанил на пумпа за пациент-контролирана аналгезија (ПКА) во болус дози. Втората група (45 пациентки) добија интермитентни епидурални болуси со силно дилуиран локален анестетик и опиоид (Bupivacain и Fentanil). Анализиравме пулсна оксиметрија (SpO_2), број на респирации, крвен притисок, пулс, седација, гадење и повраќање како и скоровите за болка и задоволството на родилките преку 2 различни VAS скали.
Резултати. Средната SpO_2 беше значително пониска во групата на ПКА со ремифентанил 96.2%±1.6 наспроти 98.2±1.2 во епидуралната група. Респираторна депресија (број на респирации <9 или SpO_2<90%) не беше најдена во двете групи. Скоровите на седација беа значително повисоки во групата наПКА со ремифентанил, P<0.05. Инциденцата на гадење и повраќање беше иста во двете групи, без сигнификантна разлика. Во однос на скоровите за болка ПКА со ремифентанил беше инфериорна во однос на епидуралната аналгезија во сите временски точки, но без сигнификантна разлика измеѓу двете групи во задоволството на родилките.
Заклучок. Интравенска пациент контролирана аналгезија со ремифентанил обезбедува задоволително ниво на обезболување, со понизок SpO_2 и повеќе седација. Може да биде одлична алтернатива на епидуралната аналгезија, но континуиран мониторинг и достапност на кислород е задолжително.

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Клучни зборови: ремифентанил, епидурална аналгезија, безболно породување

Abstract

Introduction. Remifentanil is becoming more and more popular for labor analgesia as an alternative for neuroaxial anesthesia. In this study we comparedthe severity of pain, patient satisfaction and side effects between two different types of labor analgesia.
Methods. Eightyprimiparous patients ASA I or II, atterm pregnancy, were included in the study and divided in two groups. The first group (35 patients) received intravenous remifentanil on patient control pump in bolus doses. The second group (45 patients) received intermittent epidural boluses with highly diluted local anesthetic and opioid (Bupivacain and Fentanil). We analyzed oxygen saturation (SpO_2), respiration rate, heart rate, blood pressure, sedation, nausea and vomiting as well as patient pain scores and satisfaction scores through 2 different VAS.
Results. Mean SpO_2 was significantly lower in the PCA remifentanil group 96.2%±1.6 versus 98.2±1.2 in the epidural group. Respiratory depression (RR<9 or SpO2 <90%) was not found in both groups. Sedation scores were significantly higher in the PCA remifentanil group, P<0.05. Incidence of nausea and vomiting was similar between the two groups, without significant difference. PCA remifentanil was inferior to epidural analgesia with respect to pain scores at all time points, but without significant difference in patient satisfaction between the two groups.
Conclusion. Intravenous patient-controlled analgesia with remifentanil provides satisfactory level of labor analgesia, with lower SpO_2 and more sedation. It could be an excellent alternative to epidural analgesia but continuous monitoring and oxygen supply is mandatory.

Keywords: remifentanil, epidural analgesia, labor analgesia

Introduction

Epidural analgesia provides reliable and effective analgesia during labor and it is considered a gold standard in obstetric anesthesia [1]. However,there are conditions that limit the use of epidural analgesia: when it is contraindicated (coagulopathies, long term use of anticoagulants, infections on the place of the punction, spine abnormalities) or when the parturient simply does not wantit because it is an invasive procedure as well as due to side effects, which although rare, can be very serious. But, it is clear that effective and safe alternative should be established.

Remifentanil with its pharmacokinetic capacities can be an ideal medicine for labor analgesia. It is an ultrashort acting, μ-1 opioid receptor agonist, metabolized to an inactive metabolite by plasma and tissue esterases. It is characterized with fast onset of analgesia (30-60 seconds), with a maximum effect in 2.5 minutes, analgesic half-life of 3.5-6 minutes and without accumulation effect after long-term use. Plasma concentrations of remifentanil in pregnant women are approximately half of those found in women not pregnant due to the greater volume of distribution and higher clearance. It crosses the placenta very quickly, but it is rapidly metabolized and redistributed in the fetus [2]. All these characteristics make remifentanil ideal for labor analgesia [3,4].

In recent years many studies have been published examining remifentanil in terms of efficacy and safety. One large multicenter randomized study conducted by Freeman *et al.* [5] from 2015 was specifically focused on the satisfaction of patients, while another large retrospective study by Lin *et al*. [6] from 2014 as well as the meta-analysis of Stourac *et al.* [7] from 2015 were focused on the effectiveness and maternal and neonatal side effects. Many issues still remain insufficiently clarified and leave space for much more research before we can carelessly use it for pain relief. It was the aim of our study to compare the analgesic efficacy of patient-controlled analgesia (PCA) with remifentanil to epidural analgesia with bupivacain/fentanil and to analyze any maternal side effects.

Materials and methods

This was a prospective randomized clinical study performed at the University Clinic for Gynecology and Obstetrics in the period from 09.2015 to 03.2016. The study was approved by the Ethics Committee of the Medical Faculty in Skopje.

Inclusion criteria for the study were: primiparous, patients older than 18 years, healthy or with mild systemic disease (ASA 1 or 2) and at term for birth (gestational age> 34 weeks). Eighty patients that matched the inclusion criteria were included in the study. All patients after admission to hospital for childbirth signed an informed consent and were randomly assigned into two groups, remifentanil intravenous PCA group (RG) and epidural analgesia group (EG). Parturients in both groups were adequately prepared by placing a peripheral venous line and basic monitoring (non-invasive blood pressure, pulse oximetry, respiratory rate). We began with pain relief at 4-5 cm cervical dilatation, always in agreement with the gynecologist-obstetrician.

Thirty-five patients were included in the remifentanil group (RG) and they received intravenous remifentanil in bolus doses on a pump for patient-controlled analgesia in 2 minutes locked interval. We started the remifentanil analgesia with smaller doses and increased them gradually. We started with 0.15 μg/kg remifentanil (solution 20 μg/ml), gradually increased for 0.1 μg/kg up to the maximum bolus dose of 1 μg/kg. All patients were explained how to operate the pump and when to give the bolus dose. We advise all patients to apply the bolus when they feel pain is coming. Few labor pains are enough and patients know when to give the bolus. Analgesia was stopped 10 minutes before the expected expulsion of the newborn.

Forty-five patients were distributed in the epidural group (EG) and they received epidural analgesia with intermittent bolus dosing. After placement of the epidural catheter and negative test dose all patients received a bolus dose of 10 ml 0.1% Bupivacain with Fentanil 0.05 mg. Further on, all patients hourly received epidural bolus of 10 ml 0.0625% Bupivacain with Fentanyl 2 μg/ml. The last bolus dose patients received at least 30 minutes before the expected completion of the birth.

At all times during labor analgesia parturients were monitored: oxygen saturation and heart rate continuously, respiratory rate and noninvasive blood pressure every 15 minutes, continuous cardiotocograph recording for fetal monitoring. The level of sedation was evaluated every 30 minutes by Ramsey sedation score - RSS (0- alert; 1- anxious, restless; 2- cooperative, oriented; 3- responding to commands; 4- brisk response to stimulus; 5- weak and slow response to stimuli; 6- does not respond to strong painful stimuli). The incidence of nausea, vomiting and itching was also recorded.

If oxygen saturation of the parturient fell <95%, a nasal catheter with $O_2$2-3 l/min was immediately placed. If the parturient SaO_2fell <92% or respiratory rate (RR) decreased <9 or RSS was 4 or greater than 4, then we temporarily stopped with analgesia. After normalization of physiological parameters the analgesia was started again with one step lower doses.

During the birth both groups of patients were asked to answer two separate questions. First they were asked to determine the level of pain on a specially designed scale for pain (visual analogue scale-VAS) from 0 (no pain) to 100 (highest possible pain) of "how strong pain is during contraction" in every 30 minutes during childbirth starting with the first question before starting analgesia. The second question was designed to determine the patient satisfaction with analgesia. Parturients

were asked to determine their satisfaction with labor analgesia on different VAS scale from 0 (extremely dissatisfied) to 100 (very satisfied) with the answer to the question "are you satisfied with the analgesia".

Results

Between 09.2015 and 03.2016 eighty (80) patients were randomized to receive either intravenous PCA remifentanil (35 patients) or epidural analgesia (45 patients) for painless delivery. Sixty-five patients were ASA 1 (76.5%), while 15 patients were with mild systemic disease, ASA 2 (23.5%).

The average $SpO_2$was significantly lower in the PCA remifentanil group 96.2%±1.6 versus 98.2±1.2 in the epidural group (Figure 1), with statistically significant difference ($p<0.01$). Nasal catheter with O_2 2-3 L/min was set only if SpO_2 fell less than 95%. Nineteen patients (54%) from the RG needed O_2 support, while only 3 patients (7%) from the EG neededO_2. None of the patients in both groups had a drop in saturation less than 92% or respiratory rate less than 9.

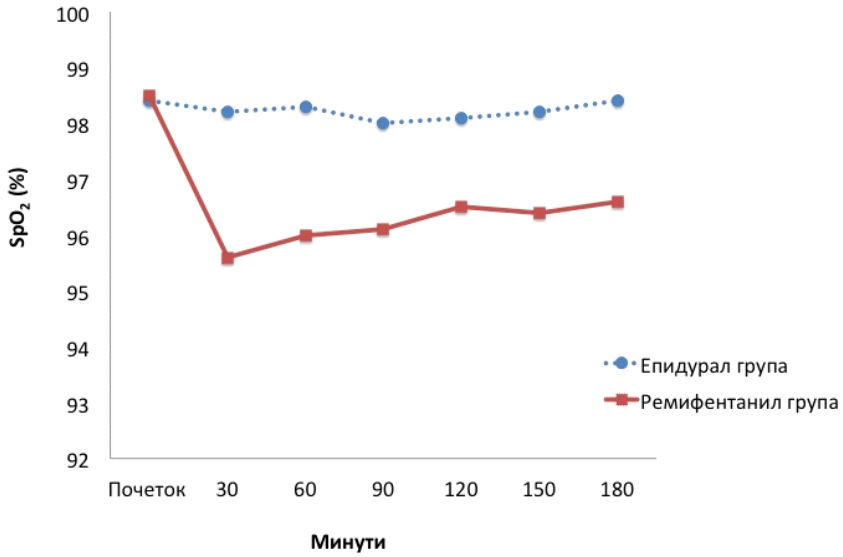

Fig. 1. Comparison of SpO_2 between the two groups of patients
Start-Minutes; Epidural group-Remifentanil group

Noninvasive blood pressure, measured in every 15 minutes was all the time stable in both groups of patients during birth. Mild hypotension appeared in 2 patients from the EG, but without need for vasopressors.

Sedation was significantly higher in the RG at all times during birth ($p<0.05$). Four patients from the RG reached the sedation score 3 according to RSS, while only 1 patient in the RG reached score 4. Remifentanil was stopped temporary and after 3 minutes the analgesia was proceeded with one step lower doses.

Nausea, vomiting and itching were approximately the same in both groups, with no statistically significant difference.

VAS pain scores with starting mean value of 92±8.1 immediately after initiation of analgesia were significantly reduced in both groups, but still remained higher in the RG. As the labor continued pain scores were elevated in both groups, more in the RG, but still far from initial scores (Figure 2). Mean values of the VAS pain scores after onset of analgesia in the remifentanil group were 45±4.3 and in the epidural group 30±3.9, with statistically significant difference of $p<0.01$.

On the other hand, satisfaction scores were all the time almost the same in both groups (Figure 3). Mean VAS satisfaction scores in the remifentanil group were 89± 7.8 and in the epidural group 90±9.2, with no statistically significant difference in both groups ($p=0.6$).

Table 1. Side effects and complications

		RG (n = 35)	EG (n = 45)
Hypotension		/	2 (4.4%)
Nausea		4 (11.4%)	5 (11%)
Vomiting		3 (8.6%)	3 (6.7%)
Itching		1 (2.8%)	2 (4.4%)
Sedation according to RSS	1	15 (42.8%)	35 (77.8%)
	2	16 (45.7%)	10 (22.2%)
	3	3 (8.6%)	0
	4	1 (2.9%)	0

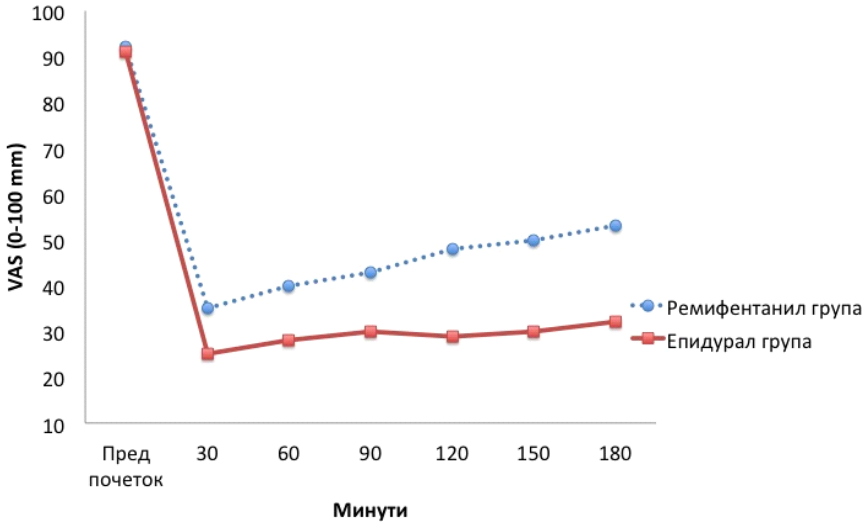

Fig. 2. Comparisonof VAS pain scores between the two groups of patients
before start-Minutes
Epidural group-Remifentanil group

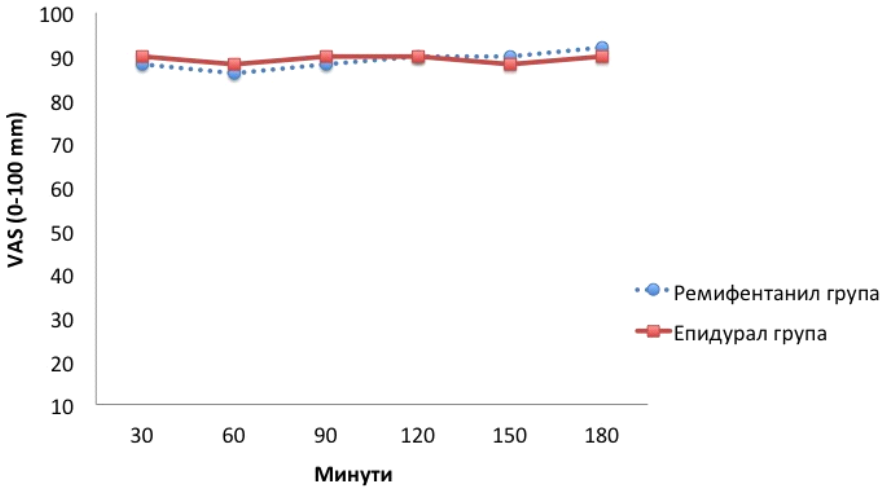

Fig. 3. Comparison of VAS satisfaction scores between patients in remifentanil and epidural group
Minutes
Epidural group-Remifentanil group

Discussion

Desaturation is the main side effect during intravenous analgesia with remifentanil. Incidence of maternal desaturation in analgesia with remifentanil beneath 95% was observedin 25-75% of cases [8-12]. It is not higher than desaturation during analgesia with meperidine or Entonox, but is far higher than with epidural analgesia. In our study 19 patients (54%) from the RG and only 3 patients (7%) from the EG showeddecrease in the saturation less than 95%. Episodes of desaturation associated with remifentanil are usually short-termed and easily correctable with application of nasal oxygen and stimulation of the mother. In our study all patients immediately normalized SpO_2 with nasal oxygen 2 L/min, without the need for temporary stop of the remifentanil pump. There are several case reports [13-16] of obstetric patients that showedvery serious cases of desaturation resulting in apnea, all of them started as remifentanil labor analgesia. These cases required further caution, continuous SpO_2 monitoring and the possibility of application of oxygen during intravenous analgesia with remifentanil.

Sedation also appears as a frequent side effect of remifentanil analgesia. Different levels of maternal sedation are common [12,18,19], while in some studies [20,21] incidence of sedation of nearly 100% has been observed. In our study there was a significantly higher level of sedation in the RG than in the EG, which was expected. Fourpatients in the RG reached score 3 according to RSS, and only 1 patient in the RG reached RSS score 4, which meant suspension of analgesia and return to 1 step lower doses. All this was short-lived, easily corrected, but again implying the need for continuous and obligatory monitoring.

The incidence of nausea, vomiting and itching were similar in both groups, shown in many previous studies [6,12,19]. As it is already known the use of opioids whether given by intrathecal, intravenous or epidural administration can lead to nausea, vomiting and itching. But these symptoms may develop during childbirth, even when there is no analgesia.

The difference in analgesic efficacy between PCA with remifentanil and epidural analgesia at all times during childbirth was visible and statistically significant ($p < 0.01$). It has been proven in many older and recent scientific papers [5,6,8,22]. After initiation of analgesia pain scores decreased in both groups, but more in the epidural group. As the labor progressed pain scores in the RG increased. Remifentanil bolus dose in our study varied from 0.15 μg/kg up to 0.8 μg/kg. In 30 patients (85.6%) the bolus dose of remifentanil was increased up to maximum0.6 μg/kg, because the pain scores were really low or because the patients felt that the pain was reduced and that dose was sufficient. We did not reach the maximum bolus dose of 1 μg/kg in any patient. However, side effects are dose-dependant and increasing the dosage of remifentanil side effects (mostly sedation) increased. The only patient that reached RSS score 4 was run at the moment with 0.8 μg/kg PCA remifentanil.

Latest researches go towards improving the efficiency of bolus doses of remifentanil [23]. The overlap of pain with the peak of remifentanil can be improved by the prediction of contractions, but it is not known yet whether the technique will improve the safety.

On the other hand, satisfaction scores of the patients in our study were all the time almost the same in both groups, with no statistically significant difference ($p=0.6$). But, it is very important that many studies [18,20,24,25] found no significant difference in maternal satisfaction between these two groups of labor analgesia. This probably indicates that remifentanil provides weaker but highly acceptable maternal analgesia. One explanation may be opioid-induced euforia [12], or simply easy applicability.

Conclusion

Intravenous PCA analgesia with remifentanil provides a satisfactory level of pain relief with lower $SpO_2$and more sedation. It can be a great alternative to epidural analgesia, but continuous monitoring and availability of oxygen is mandatory.

Conflict of interest statement. None declared.

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