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Respiratory Side-Effects: Intravenous Patient-Controlled Remifentanyl Versus Inttermitent Epidural Boluses for Labor Analgesia

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Introduction: Birth is one of the vital aspects of human existence and the birth pain is probably the strongest pain that any woman will experience in her lifetime.
Remifentanil is an ultra-short acting, μ-1 opioid receptor agonist, characterized with a fast onset of analgesia and without an accumulation effect after its long-term use. Plasma concentrations of remifentanil in pregnant women are approximately half of those found in women not pregnant. It crosses the placenta very quickly, but it is rapidly metabolized and redistributed in the fetus. [1]
In the last few years many studies have been discussing and debating the respiratory side effects associated with remifentanil analgesia. So, in this study we analyze the side effects of intravenous patient-controlled analgesia with remifentanil compared with epidural analgesia.

Materials and methods: This is a prospective, randomized clinical study performed in the period from January 2016 to June 2017. The study was approved by the Ethic Committee for Human Research on 09.12.2015. Patients were randomized into two groups: remifentanil intravenous analgesia group, and epidural analgesia group.
Patients in the remifentanil group (RG) received intravenous remifentanil in bolus doses on a pump for patient-controlled analgesia (PCA) with 2 minutes locked interval. We started with 0,2 μg/kg remifentanil (solution 20 μg/ml), gradually increased for 0.1 μg/kg up to the maximum bolus dose of 1 μg/kg. The whole time during the analgesia with remifentanil, the anesthesiologist or experienced nurse remained in the delivery box with the laboring parturient.

Patients distributed in the epidural group (EG) received epidural analgesia with programmed intermittent bolus dosing. After the placement of the epidural catheter and a negative test dose all patients received a bolus dose of 10 ml 0.1% Bupivacain with Fentanil 0.05 mg. Further on, all patients received an epidural bolus of 10 ml 0.0625% Bupivacain with Fentanil 2 μg/ml every 60 minutes, starting 60 minutes after the initial dose. If needed, extra boluses of 5ml 0.1% Bupivacain were given for the treatment of breakthrough pain.
At all times during labor analgesia, the parturients were monitored: oxygen saturation and heart rate continuously; respiratory rate and noninvasive blood pressure every 15 minutes.
If oxygen saturation of the mother fell <95%, a nasal catheter with O2 2-3 l/min was immediately placed, while if the mother's SaO2 fell <92%, or the respiratory rate (RR) decreased <9 we temporarily stopped with analgesia. After the normalization of the physiological parameters, the analgesia was started again with one step lower doses.

Results: 155 patients were randomized to receive either PCA with remifentanil (80 patients) or intermittent epidural analgesia (75 patients) for painless delivery.
Table 1 shows the average SpO2 and the mean RR in different time points in patients in both groups. The results present a significantly lower SpO2 in the remifentanil group and significantly more respirations per minute in the epidural analgesic group (p<0.0001) at all time points after the start of analgesia.
A nasal catheter with O2 2-3 l/min was set only if SpO2 fell less

SaO2	Remifentanil group			Epidural group			p value
	N	mean ± SD	min – max	N	mean ± SD	min – max	
Before start	80	98.35±0.9 22.22±0.7	96-100 21-24	75	98.55±0.8 22.36±1.5	96–100 14-26	0.646ns 0.5 ns
15min	80	98.35±0.9 22.22±0.7	96-100 21-24	75	98.08±0.9 20.91±1.6	96-100 12-23	<0.0001** 0.00006**
30 min	79	96.78±1.2 18.51±1.6	93-100 9-21	75	98.12±0.8 20.71±1.8	96-100 12-24	<0.0001** <0.0001**
60 min	70	96.88±1.4 18.29±1.6	93-100 9-21	70	98.09±0.8 20.61±1.8	95-99 12-24	<0.0001** <0.0001**
120 min	50	96.54±1.2 17.59±1.6	93-100 9-21	61	98.03±0.8 20.56±1.9	97-98 11-24	<0.0001** <0.0001**
240 min	90	96.57±0.9 17.1±2.	95-98 12-19	12	98.3±0.8 21.07±0.8	97-99 20-23	0.0013** <0.00001**
Average	80	96.95 ± 1.4 18.67 ± 0.9	89-100 7-24	75	98.3±0.8 21.07±0.8	95-100 11-26	<0.0001** <0.0001**

**sig<0.01

p(Student t-test)

Table 1. Average saturation with oxygen and mean respiratory rate before start and in different time points after the start of analgesia in patients in the remifentanil group and in the epidural group

than 95%. 42 patients (52.5%) from the remifentanil group needed O2 support, while only 2 patients (2.67%) from the epidural group needed O2 (p <0.0001). On average, patients in the remifentanil group received oxygen for 78 minutes. Only 1 patient in RG had a drop in saturation less than 92%. The remifentanil analgesia was stopped, and after 5 minutes, the analgesia was continued with 1 step lower dose.

Discussion: Desaturation is the main side effect during intravenous analgesia with remifentanil. Compared to epidural analgesia, intravenous analgesia with remifentanil is associated with significantly lower values of oxygen saturation.[2] [3] [4] [5] The incidence of maternal desaturation under 95% in remifentanil analgesia was published in 25-75% of cases. [3] [4] [5] The largest number of studies that investigate remifentanil as labor analgesia at delivery show that respiratory depression with desaturation requiring oxygen substitution is short-lived, with no side effects, and as indicated in a study, ventilatory depression is self-limiting because frequent and painful uterine contractions stimulate ventilation. [4] [6] In the observational study of Messmer et al from 2016 on 61 patients receiving remifentanil for pain relief, the authors show that the patients using PCA with remifentanil often desaturate, on average once in every 50 minutes, with a mean duration of 16 seconds and that 70% of the patients desaturated at least once during PCA with remifentanil. [7] But although desaturation is much more common in patients who receive analgesia with remifentanil, several studies have also described desaturation in patients with epidural analgesia. [2] [5] [6] It is known that episodes of desaturation occur during normal delivery. Some studies have shown a decrease in saturation and below 90% during childbirth, and this is getting worse with receiving opioids. [8]

In recent years many studies have discussed the respiratory side effects associated with remifentanil analgesia. Stocki et al analyzing ETCO2, report 27 cases of apnea in 9 patients during PCA with remifentanil.[3] What is interesting in these cases is that in only 6 cases of apnea, SpO2 dropped below 94%. Another recent study of Weiniger et al from 2017 also emphasizes the moment that monitoring only of SpO2 can overlook the apnea.[9] Using RR and ETCO2 they counted 62 apneas in 10 of 19 patients using remifentanil for labor analgesia. New studies can generate fear and resistance to analgesia with remifentanil, but if we followed the recommendations and protocols, we should not be scared.

Aspiring to a safer PCA with remifentanil, Leong et al designed an interactive feedback system for continuous monitoring of side effects, for greater safety and better titration of doses. [10] The authors work on the improvement of the system so that it can respond to the reduction of respiratory frequency or connect it with a capnograph or with a cardiotocograph.

Respiratory depression is defined as a reduced respiratory rate, less than 8-9 respirations per minute and is a common side effect of remifentanil analgesia. [2] [3] In newer studies special attention is paid to respiratory frequency as an early warning sign for apnea, along with capnography at times when monitoring of SpO2 can overlook the apnea. [9] In our study, which noted the respiratory rate every 15 minutes, a significantly lower number of respirations was observed in the RG compared to the EG at all time points during labor. A large systematic review of Cochrane of 2017, comparing all available papers with regard to respiratory depression, did not find a difference between remifentanil and epidural analgesia, with a graded 'low' quality of evidence. [11]

There are several case reports of very serious complications in obstetric patients, started as remifentanil labor analgesia, 2 patients with respiratory arrest and 1 patient with cardiac arrest. [12] [13] [14] What is to be noted is that all of the cases were with the simultaneous use of multiple methods of analgesia and without a continuous presence of an anesthesiologist or nurse during analgesia. Everything ended well, but these cases suggest further required caution, continuous respiratory monitoring, preparation at all times and respect for specific recommendations and protocols for obstetric patients during remifentanil labor analgesia. All recommendations and protocols were respected in the study.

Conclusion: Patient-controlled intravenous analgesia with remifentanil can be a great alternative to epidural analgesia, but continuous respiratory monitoring and use of all consensus recommendations for maternal and fetal safety are mandatory.

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