SIDE EFFECTS OF INTRAVENOUS PATIENT-CONTROLLED ANALGESIA WITH REMIFENTANIL COMPARED WITH INTERMITTENT EPIDURAL BOLUS FOR LABOUR ANALGESIA – A RANDOMIZED CONTROLLED TRIAL

Dafina Karadjova¹, Mirjana Shosholcheva², Emilija Ivanov¹, Atanas Sivevski¹, Ivo Kjaev¹,
Adrijan Kartalov³, Biljana Kuzmanovska³, Rosa Spasova¹, Goran Kocovski¹, Irena Aleksiovska-Papestiev¹

¹ University Clinic for Gynaecology and Obstetrics, Skopje, North Macedonia

² University Clinic for surgical diseases “St. Naum Ohridski“, Skopje, North Macedonia

³ University Clinic for TOARILUC, Skopje, North Macedonia

Corresponding author: Dafina Karadjova, University Clinic for Gynaecology and Obstetrics, Skopje, North Macedonia, e-mail: dafinakaradzova@yahoo.com

ABSTRACT

Introduction: Epidural analgesia is considered a gold standard in obstetric anaesthesia and analgesia. However, in situation when it is contraindicated, unwanted by the patient or simply unavailable, remifentanyl can be an excellent alternative. The goal of our study is to analyse the side effects of intravenous patient-controlled analgesia (IV PCA) with remifentanyl compared with epidural analgesia during delivery.

Material and methods: This study included 155 pregnant women in term for birth, divided into 2 groups: a remifentanyl group (RG), and an epidural group (EG). Patients in the RG received intravenous PCA with remifentanyl, while patients in the EG received epidural analgesia with programmed intermittent bolus dosing. Our primary outcome was maternal safety; the secondary outcome was neonatal safety.

Results: The results present a significantly lower SaO₂ value of the parturients in the RG (96.95 ± 1.4 vs 98.22 ± 0.6), and a significantly higher respiratory rate per minute in the EG at all time points after the onset of analgesia (20.85 ± 1.4 vs 18.67 ± 0.9). There was more frequent sedation, nausea and vomiting in the RG, while in the EG there was a more elevated temperature, itching and irregularities in the CTG record. Regarding the newborn, there was no significant difference between the two groups in the Apgar scores, pH, pCO₂, pO₂, and bicarbonate, while there was a significantly lower value of the base excess in the RG group.

Conclusion: PCA with remifentanyl is safe for the mother, foetus and the newborn, with minimal side effects. Continuous respiratory monitoring, oxygen supply and following of all consensus recommendations are mandatory.

Keywords: remifentanyl, epidural analgesia, side effects

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.

Neuroaxial analgesia is the most effective method for pain relief in labour, while epidural analgesia is considered a gold standard in obstetric anaesthesia. [1] But there are conditions that limit

the use of epidural analgesia: [2] when it is contraindicated, when there are some technical difficulties, or simply when it is not wanted from the parturient, because it is an invasive procedure and the side effects, although rare, can be very serious. An effective and safe alternative should be established.

Remifentanyl with its pharmacokinetic capacities can be ideal medicine for labour analgesia. It is an ultra-short acting, μ -1 opioid receptor agonist, metabolized to an inactive metabolite by plasma and tissue esterases. It is characterized with a fast onset of analgesia, an analgesic half-life of 3.5-6 minutes and without an accumulation effect after its long-term use. [3] Plasma concentrations of remifentanyl 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 foetus. [4]

In the last few years many studies have been discussing and debating the respiratory side effects associated with remifentanyl analgesia. The goal of our study is to analyse the side effects of intravenous patient-controlled analgesia (IV PCA) with remifentanyl compared with epidural analgesia.

MATERIAL 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. Inclusion criteria for the study were: primiparous, patients older than 18 years of age, healthy or with a mild systemic disease (ASA 1 or 2), singleton pregnancy, vertex presentation and at term for birth (gestational age > 36 weeks). Exclusion criteria were: complicated pregnancy, body weight >120 kg, contraindication for epidural analgesia and medical indication for epidural analgesia. All patients signed an informed consent before entering the study. The randomization took place after the patients were admitted in the hospital; there was not blindness and patients knew exactly in which group they were randomized. Patients were randomized into two groups: remifentanyl intravenous analgesia group, and epidural analgesia group. Parturients in both groups, before the start of the analgesia, were 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 attending obstetrician.

Patients in the remifentanyl group (RG) received intravenous remifentanyl in bolus doses on a pump for patient-controlled analgesia (PCA) with 2 minutes locked interval. We started the remifentanyl analgesia with smaller doses and increased them gradually. We started with 0,2 μ g/kg remifentanyl

(solution 20 μ g/ml), gradually increased for 0.1 μ g/kg up to the maximum bolus dose of 1 μ g/kg. All patients were explained how to operate the pump and when to give the bolus dose. We advised all the patients to apply the bolus when they felt that there was pain coming. A few labour pains were enough and the patients knew when to give the bolus. Analgesia was stopped ten minutes before the expected expulsion of the newborn. The whole time during the analgesia with remifentanyl, the anaesthesiologist or experienced nurse remained in the delivery box with the labouring parturient.

Patients distributed in the epidural group (EG) received epidural analgesia with programmed intermittent bolus dosing. After the placement of the epidural catheter on level L2 – L3 or level L3 – L4 and a negative test dose (3 ml 0.25% Bupivacain), all patients received a bolus dose of 10 ml 0.1% Bupivacain with Fentanyl 0.05 mg. Further on, all patients received an epidural bolus of 10 ml 0.0625% Bupivacain with Fentanyl 2 μ g/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. Patients received the last bolus dose at least 30 minutes before the expected completion of the birth.

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

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 or RSS was 4 or greater than 4, then we temporarily stopped with analgesia. After the normalization of the physiological parameters, the analgesia was started again with one step lower doses.

For neonatal safety, the foetal heart rate (FHR) was monitored with continuous cardiotocograph recording. If the FHR recordings became pathological (fetal bradycardia, late decelerations), we temporarily stopped with remifentanyl analgesia. After the delivery, Apgar scores at the 1st, 5th and 10th minute were determined by the neonatologist. Any neonatal interventions in the immediate postnatal period were recorded. Blood

from the umbilical artery (UA) was taken immediately after delivery and the acid-base status (ph, pCO₂, pO₂, bicarbonate and base excess) was measured.

During labour, both of the groups of patients were asked to answer two separate questions, to determine the level of pain and to determine the patient satisfaction with analgesia on specially designed scales for pain and satisfaction (visual analogue scale - VAS) from 0 (no pain/extremely dissatisfied) to 100 (highest possible pain/very satisfied).

For the statistical processing of the data obtained during the research, a database was created in the statistical program SPSS 17.0. For comparison of the analysed variables between the two groups independent tests (t-test for independent samples, Mann-Whitney U test, Chi-square Pearson test, Fisher exact test) were used, while to compare maternal and neonatal parameters in the remifentanil group, depending on the distribution of data, tests for dependent samples (McNemar tests, t-test for dependent samples, Friedman ANOVA test) were used.

RESULTS

155 patients were randomized to receive either PCA with remifentanil (80 patients) or intermittent epidural analgesia (75 patients) for painless delivery. Patient characteristics are given in Table 1.

Table 2 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 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.

In the RG, we analysed the relationship between the dose of remifentanil and oxygen saturation using Pearson's correlation coefficient, and we found that these two parameters correlated negatively with each other, which means that the increase in the dose of remifentanil reduces oxygen

saturation. But statistically this correlation was not significant, $R = -0.0575$, $P = 0.61$.

The mean values of systolic blood pressure, diastolic blood pressure and heart rate in different time points during analgesia are shown in Table 3.

Mild hypotension appeared in 2 patients from the EG, but only 1 needed vasopressors.

Table 4 shows the different RS scores in patients from both groups, analysed at different time points after the onset of analgesia. Sedation was significantly higher in the RG at all times during birth, $p < 0.0001$. 2 patients from the RG reached the sedation score 4 according to RSS. Remifentanil was stopped temporarily and after 3 minutes the analgesia proceeded with one step lower doses.

The side effects of both types of analgesia are presented in Table 5. The incidence of nausea was higher in the RG, vomiting was almost the same in both groups, while itching and hyperthermia were more common in the EG.

In this study, the main cause of CTG irregularities was the reduction of variability and early decelerations, however, 4 patients from the RG and 5 patients in the EG experienced serious disorders or pathological CTG records, and in those patients, babies were rapidly delivered. All babies in this study, born with a Caesarean section under a foetal distress, had good Apgar scores and good acid-base status.

Neonatal outcomes are shown in Table 6. Apgar scores of the neonates are almost the same in both groups, there was not a need for use of naloxone or neonatal resuscitation. The median values of all parameters of the umbilical arterial acid-base status of neonates in the current study were within the normal limits. All the parameters we examined were similar in both groups, except the values of base excess, which was significantly lower in the RG.

The mean total consumption of remifentanil during a PCA with remifentanil was 1950 µg (450-6400 µg) over a median period of 165 minutes. The average effective bolus during remifentanil analgesia was 0.33 µg / kgTT (0.1-1 µg / kgTT).

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. [5-8] The

Table 1. Patient characteristics, duration of analgesia, average VAS pain scores and average VAS satisfaction scores

	PCA remifentanil group (N=80)	Epidural group (N=75)	P value
Age (years)	29.85±5.2	31.3±3.8	0.0497*
Weight (kg)	80.34±8.6	81.55±8.6	0.38 ns
Level of education			
High	37 (46.25%)	51 (68%)	0.01*
Medium	34 (42.5%)	22 (29.33%)	
Basic	9 (11.25%)	2 (2.67%)	
ASA classification			
ASA 1	61 (76.25%)	61 (81.33%)	0.44 ns
ASA 2	19 (23.75%)	14 (18.67%)	0.0078**
Duration of analgesia (minutes)	165.22±63.1	194.75±60.1	
Delivery ended with	13 (16.25%)	14 (18.67%)	0.6 ns
Cesarean section			
Average VAS pain scores	46.44±8.5 (10-100)	28.33±11.8 (0-100)	<0.0001**
Average VAS satisfaction scores	93.41±9.1 (65-100)	94.01±9.5 (65-100)	0.688 ns
VAS satisfaction scores 8-16 hours after delivery	9.73±0.5	9.75±0.5	0.8 ns

group 1 – PCA with remifentanil group

group 2 – epidural analgesia group

*sig<0.05,

**sig<0.01

p(Chi-square test)

p(Student t-test)

Table 2. 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

SaO ₂		Remifentanil group			Epidural group			p value
		N	mean ± SD	min – max	N	mean ± SD	min – max	
Before start	SaO ₂	80	98.35±0.9	96-100	75	98.55±0.8	96-100	0.646ns
	RR		22.22±0.7	21-24		22.36±1.5	14-26	0.5 ns
15min	SaO ₂	80	96.86±1.5	89-100	75	98.08±0.9	96-100	<0.0001**
	RR		19.62±2.1	7-22		20.91±1.6	12-23	0.00006**
30 min	SaO ₂	79	96.78±1.2	93-100	75	98.12±0.8	96-100	<0.0001**
	RR		18.51±1.6	9-21		20.71±1.8	12-24	<0.0001**
60 min	SaO ₂	70	96.88±1.4	92-100	70	98.09±0.8	95-99	<0.0001**
	RR		18.29±1.6	10-21		20.61±1.8	12-24	<0.0001**
120 min	SaO ₂	50	96.54±1.2	95-99	61	98.03±0.8	97-98	<0.0001**
	RR		17.59±1.6	11-20		20.56±1.9	11-24	<0.0001**
240 min	SaO ₂	9	96.57±0.9	95-98	12	98.3±0.8	97-99	0.0013**
	RR		17.1±2.0	12-19		21.07±0.8	20-23	<0.00001**
Average	SaO ₂	80	96.95 ± 1.4	89-100	75	98.22 ± 0.6	95-100	<0.0001**
	RR		18.67 ± 0.9	7-24		20.85 ± 1.4	11-26	<0.0001**

**sig<0.01

p(Student t-test)

Table 3. The mean values of blood pressure (systolic and diastolic) and heart rate in different time points during labor analgesia

BP and HR	Remifentanil group			Epidural group			p value
	N	Mean $\pm$ SD SBP (mmHg) DBP (mmHg) HR beats/min	min – max	N	mean $\pm$ SD DBP (mmHg) SBP (mmHg) HR beats/min	min– max	
Before beginning	80	131.9 $\pm$ 10.9 82.97 $\pm$ 6.7 85.88 $\pm$ 8.1	110-160 70-102 68-102	75	133.45 $\pm$ 10.6 83.43 $\pm$ 6.6 88.06 $\pm$ 7.6	110-154 65-99 66-110	0.37 ns 0.67 ns 0.1 ns
30 min	80	130.62 $\pm$ 9.8 82.23 $\pm$ 6.6 82.56 $\pm$ 8.8	112-160 64-101 60-102	75	127.43 $\pm$ 10.8 76.55 $\pm$ 6.5 85.75 $\pm$ 7.5	107-150 60-94 65-112	0.057 ns <0.0001** 0.02*
60 min	79	129.74 $\pm$ 9.6 80.86 $\pm$ 6.6 80.67 $\pm$ 8.5	109-155 68-109 62-102	75	125.16 $\pm$ 9.4 74.32 $\pm$ 6.6 83.97 $\pm$ 6.9	104-144 58-87 66-108	0.003** <0.0001** 0.012*
90 min	70	130.23 $\pm$ 9.6 79.38 $\pm$ 7.2 79.88 $\pm$ 7.5	105-157 51-94 60-97	70	126.53 $\pm$ 8.6 76.03 $\pm$ 6.1 84.56 $\pm$ 7.6	110-152 62-90 62-106	0.016* 0.003** 0.0004**
120 min	50	131.47 $\pm$ 10.4 80.83 $\pm$ 5.4 79.65 $\pm$ 7.34	108-169 69-92 58-94	61	127.68 $\pm$ 8.3 77.47 $\pm$ 4.9 85.32 $\pm$ 8.1	110-148 69-89 58-94	0.031* 0.0007** 0.00013**
240 min	9	129.67 $\pm$ 7.9 78.89 $\pm$ 4.2 79.55 $\pm$ 8.3	119-142 70-84 65-89	12	132.19 $\pm$ 9.3 81.28 $\pm$ 7.6 84.38 $\pm$ 8.0	112-142 65-95 72-102	0.5 ns 0.4 ns 0.0004**

SBP – systolic blood pressure

*sig<0.05

DBP – diastolic blood pressure

**sig<0.01

HR – heart rate

p(Student t-test)

Table 4. Ramsey sedation score in different time points after the start of analgesia

RSS	Remifentanil group				Epidural group			
	1 n(%)	2 n(%)	3 n(%)	4 n(%)	1 n(%)	2 n(%)	3n(%)	4n(%)
15 min	75(93.75)	5(6.25)	0	0	75(100)	0	0	0
30 min	25(31.25)	54(67.5)	1(1.25)	0	75(100)	0	0	0
60 min	10(12.66)	51(64.56)	18(22.78)	0	69(92)	6(8)	0	0
90 min	8(11.73)	38(54.29)	24(34.28)	0	49(70)	21(30)	0	0
120 min	2(3.77)	30(56.60)	20(37.73)	1(1.88)	31(50.82)	30(49.18)	0	0
240 min	0	4(40)	5(50)	1(10)	10(66.67)	5(33.33)	0	0
300 min	0	0	2(100)	0	3(50)	3(50)	0	0

Table 5. Side effects during labor analgesia

	Remifentanil group (80)	Epidural group (75)	P value
Nausea	23 (28.75%)	14 (18.67%)	0.14 ns
Vomiting	3 (3.75%)	2 (2.67%)	^a 0.86 ns
Itching	5 (6.25%)	11 (14.67%)	^a 0.08 ns
Hyperthermia (T > 37°)	2 (2.5%)	9 (12%)	0.028*
FHR abnormalities	12 (15%)	13 (17.33%)	0.69 ns

p(Chi-square test)

^ap(Fisher exact two-tailed test)

*sig<0.05

FHR- fetal heart rate

Table 6. Neonatal outcomes (Apgar scores in 1st, 5th and 10th minute, fetal acid base status-UA, use of naloxane and neonatal resuscitation)

	Remifentanil group			Epidural group		
	N	mean ± SD	min-max	N	mean ± SD	min-max
Apgar score(VD)	67			61		
1 st minute		8.07 ± 0.8	3 - 9		8.08 ± 0.5	7 - 9
5 th minute		9.07 ± 0.7	5 - 10		9.06 ± 0.4	6 - 10
10 th min		9.8 ± 0.4	8 - 10		9.9 ± 0.3	8 - 10
Apgar score(SC)	13			14		
1 st minute		7.85 ± 0.5	7 - 9		7.92 ± 0.5	7 - 9
5 th minute		8.85 ± 0.6	8 - 10		8.92 ± 0.5	8 - 10
10 th min		9.77 ± 0.4	8 - 10		9.61 ± 0.6	8 - 10
Fetal acid-base status (UA)	67			61		
pH		7.28±0.15	7.03-7.32		7.27±0.09	6.98-7.38
pCO ₂ (mmHg)		52.38±11.27	26.4-79		52.35±12.49	32.8-87.5
pO ₂ (mmHg)		18.61±5.77	10.5-34.4		17.65±4.2	10.3-26.3
HCO ₃ act (mmol/l)		22.33±2.13	16.5-26.9		22.14±2.48	14.9-27.0
HCO ₃ std (mmol/l)		19.07±1.97	15.1-22.9		19.12±2.02	16.5-24.2
BE (mmol/l)		-5.28±2.85	-12.2 - -1.0		-3.74±2.58	-11.4 - -0.9
Use of naloxane	80	0		75	0	
Neonatal resuscitation	80	0		75	0	

p(Student t-test)

**p<0.01

^ap(Mann-Whitney test)

VD – vaginal delivery

SC – Cesarean section

UA – umbilical artery

incidence of maternal desaturation under 95% in remifentanil analgesia was published in 25-75% of cases. [6–9] The largest number of studies that investigate remifentanil as labour 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. [7, 9, 10] 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. [11] 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. [5, 8, 10] It is known that episodes of desaturation occur during normal delivery. Some studies have shown a decrease in sat-

uration and below 90% during childbirth, and this is getting worse with receiving opioids. [12, 13]

In recent years many studies have discussed the respiratory side effects associated with remifentanil analgesia. Stocki et al analysing ETCO₂, report 27 cases of apnoea in 9 patients during PCA with remifentanil. [6] What is interesting in these cases is that in only 6 cases of apnoea, 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 apnoea. [14] Using RR and ETCO₂ they counted 62 apnoeas in 10 of 19 patients using remifentanil for labour 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.

The existence of a link between the dose of remifentanil and the occurrence of desaturation is very often analysed in different studies. In their studies, Stocki and Messmer concluded that in parturients with an increase in the bolus doses

of remifentanyl there is no increase in the risk of desaturation. [6, 11] However, the risk of desaturation can be increased by the use of higher doses of remifentanyl over $0.75\mu\text{g/kg}$, somewhere above $1.05\mu\text{g/kg}$. [7, 15] Desaturation may occur at low doses of remifentanyl, even at doses of $0.2\mu\text{g/kg}$, possibly due to individual variations in opioid sensitivity. [7] [16] This demonstrates that it is impossible to determine an effective and safe dose that will be suitable for all parturients, so it is always the best to start with smaller doses $0.15\mu\text{g/kg}$ or $0.2\mu\text{g/kg}$, then gradually titrating and rising according to individual needs. [10, 15] Aspiring to a safer PCA with remifentanyl, Leong et al designed an interactive feedback system for continuous monitoring of side effects, for greater safety and better titration of doses. [17] 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. [18]

Respiratory depression is defined as a reduced respiratory rate, less than 8-9 respirations per minute and is a common side effect of remifentanyl analgesia. [5] [6] In newer studies special attention is paid to respiratory frequency as an early warning sign for apnoea, along with capnography at times when monitoring of SpO_2 can overlook the apnoea. [14] 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 labour. A large systematic review of Cochrane of 2017, comparing all available papers with regard to respiratory depression, did not find a difference between remifentanyl and epidural analgesia, with a graded 'low' quality of evidence. [19]

There are several case reports of very serious complications in obstetric patients, started as remifentanyl labour analgesia, 2 patients with respiratory arrest and 1 patient with cardiac arrest. [20–22] 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 anaesthesiologist 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 remifentanyl labour analgesia. All recommendations and protocols were respected in the study.

Sedation also appears as a frequent side effect of remifentanyl analgesia. Different levels of maternal sedation are common, while in some studies an incidence of sedation is observed of nearly 100%. [7, 9, 11, 15, 23] In our study there was a significantly higher level of sedation in RG than in EG, which was expected, with correlation to other studies. [6–8]

Several studies have shown that remifentanyl in doses used for labour analgesia is haemodynamically inert, but compared to epidural analgesia reduces the risk of hypotension. [5, 9, 15, 19, 23–25] On the other hand, a significantly lower pulse was measured in patients in the RG. In multiple studies that compare heart rate between remifentanyl and epidural analgesia, bradycardia associated with any type of analgesia has not been found. [9, 23] Although we do not have many cases of haemodynamic instability, the literature has described the case of a cardiac arrest in a patient during analgesia with remifentanyl. [22] Continuous measurement of the heart rate is obligatory in patients receiving remifentanyl for labour analgesia.

It is already known that nausea and vomiting occur during birth even when there is no analgesia and it is difficult to determine the incidence directly associated with opioids. The fact that in this study nausea is higher in the RG is probably the result of significantly higher pain scores in this group, which supports the view that pain has at least a partial role in the mechanisms of nausea and vomiting associated with labour. [26]

Loss of variability is a typical finding of opioid analgesia during labour, both in intravenous and epidural analgesia, and is due to the direct effect of the opioid on the central nervous system of the foetus. [27] Severe bradycardia in neonates and children has been reported in several cases of paediatric anaesthesia in the use of remifentanyl in intensive care or as part of general anaesthesia. [28] Many studies describe the changes in the CTG record during remifentanyl analgesia and all of them describe the changes as short-lived and without the need for obstetric intervention. [7, 9, 23] Compared to other methods of anaesthesia, in the large systemic review of Cochrane from 2017, analgesia with remifentanyl has a lower risk of CTG irregularities compared to another opioid, and quite the same compared to epidural analgesia. [19]

Several studies examined the acid-base status of the newborn after analgesia with remifentanyl, and most of them agree that remifentanyl analgesia is completely safe for the newborn, which is probably the result of a rapid metabolism or redistribution of remifentanyl. [6, 10] In terms of epidural analgesia, it is associated with the same or better pH and BE. [6, 7, 19] Although a major retrospective study of Lin and collaborators from 2014, showed a lower pH and a significantly lower BE in patients with analgesia with remifentanyl and suggests that despite the rapid and easy metabolism of remifentanyl in the newborn, it still has an effect on the newborn and the resuscitation kit should be at hand at all times. [29]

In our study, as well in all available studies, the Apgar scores of the neonates were in normal range after administration of remifentanyl. [5, 6] [7, 19]

The difference in analgesic efficacy between PCA with remifentanyl and epidural analgesia at all times during labour was visible and statistically significant. On the other hand, the satisfaction scores of the patients in this study were almost the same in both groups at all times, with no statistically significant difference. Many studies investigated the satisfaction of the patients and in all of them, patients are satisfied with analgesia with remifentanyl, although compared with epidural analgesia, the results are different. A number of studies did not find a significant difference in maternal satisfaction, while some studies show us greater satisfaction in the epidural group compared to PCA with remifentanyl. [5, 6, 8, 10, 19, 23, 24, 30]

CONCLUSION

Patient-controlled intravenous analgesia with remifentanyl provides minimal side effects of the mother and the newborn with a satisfactory level of analgesia and high patient satisfaction. It can be a great alternative to epidural analgesia, but continuous respiratory monitoring and use of all consensus recommendations for maternal and foetal safety are mandatory.

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Резиме

НЕСАКАНИ ЕФЕКТИ ОД ИНТРАВЕНСКА АНАЛГЕЗИЈА СО РЕМИФЕНТАНИЛ КОНТРОЛИРАНА ОД ПАЦИЕНТ СПОРЕДЕНО СО ИНТЕРМИТЕНТНАТА ЕПИДУРАЛНА АНАЛГЕЗИЈА ПРИ ПОРОДУВАЊЕ –РАНДОМИЗИРАНО КОНТРОЛИРАНО ИСПИТУВАЊЕ

Дафина Карацова¹, Мирјана Шошолчева², Емилија Иванов¹, Атанас Сивевски¹, Иво Каев¹, Адријан Карталов³, Билјана Кузмановска³, Роза Спасова¹, Горан Кочовски¹, Ирена Алексиовска-Панестиев¹

¹ Универзитетска клиника за гинекологија и акушерство, Скопје, Северна Македонија

² Универзитетска клиника за хируршки болести „Св. Наум Охридски“, Скопје, Северна Македонија;

³ Универзитетска клиника за ТОАРИЛУЦ, Скопје, Северна Македонија

Вовед: Епидуралната аналгезија е златен стандард во акушерската анестезија и аналгезија. Но, во состојби кога е таа контраиндицирана, несакана од пациентот или, едноставно, достапна, ремифентанилот може да биде одлична алтернатива. Целта на оваа студија е да ги анализира несаканите ефекти на интравенозно даден ремифентанил на пумпа за пациент контролирана аналгезија (ПКА), споредени со епидуралната аналгезија при породување.

Материјал и методи: 155 бремени жени во термин беа вклучени во студијата и поделени во две групи: ремифентанил група (РГ) и епидурална група (ЕГ). Пациентките од РГ добија интравенски ремифентанил на пумпа за ПКА, додека пациентките од ЕГ добија епидурална аналгезија со програмирано интермитентно болус дозирање. Наша примарна цел беше мајчината безбедност, секундарна цел беше неонаталната безбедност.

Резултати: Резултатите ни покажуваат значително помали вредности на SaO₂ кај родилките од РГ ($96,95 \pm 1,4$ vs $98,22 \pm 0,6$) и значително повисока респираторна фреквенција во ЕГ во сите временски точки после почеток на аналгезијата ($20,85 \pm 1,4$ vs $18,67 \pm 0,9$). Седацијата, гадењето и повраќањето беше почесто кај РГ, додека во ЕГ почеста беше покачената температура, чешањето и неправилности во кардиотокографскиот запис. Во однос на новородените, не се најде значајна разлика меѓу двете групи во однос на Апгар-скоровите, рН, рСО₂, рО₂ и бикарбонатите, додека базниот ексцес беше значително понизок во РГ.

Заклучок: ПКА со ремифентанил е безбедна за мајката, фетусот и новороденчето, со минимални несакани ефекти. Континуиран респираторен мониторинг, достапност на кислород и следење на консензус препораки се задолжителни.

Клучни зборови: ремифентанил, епидурална аналгезија, несакани ефекти