Comparison of parturient – controlled remifentanil with epidural bupivacain and sufentanil for labour analgesia: Randomised controlled trial

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Introduction. Epidural analgesia (EA) has significant contraindications including coagulation disorders and parturient refusal. One alternative is intravenous self-administered analgesia using the ultra short-acting opioid remifentanil (rPCA). We compared the efficiency and safety of standard epidural analgesia with parturient-controlled intravenous analgesia using remifentanil as well as personal satisfaction.

Materials and Methods. We enrolled twelve ASA I classified women with singleton pregnancy who delivered vaginally in the period 3/2010-5/2010 and who received rPCA (n=12) in standard analgesic protocol: 20 μg boluses using PCA pump with a lockout interval of 3 min. The control group consisted of 12 pregnant women who received EA (n=12): 0.125% bupivacaine with sufentanil 0.5 μg/mL in top-up boluses every hour until delivery. Data were acquired from standard Acute Pain Service (APS) form and patient medical records (demographic, labour course parameters), Visual Analogue Scale (VAS), Bromage Scale (BS) and adverse effects of analgesia.

Results. There were no demographic or labour course parameter differences between groups ($P>0.05$). The differences in VAS decrease ($P=0.056$) and parturient satisfaction ($P=0.24$) during the whole analgesia administration were statistically insignificant. The main limitation of the study was small sample and enrolment of healthy singleton pregnant women only.

Conclusion. Remifentanil use in obstetric analgesia is a viable alternative to EA, especially in cases of EA contraindications and parturient disapproval.

Key words: obstetric analgesia, epidural analgesia, parturient-controlled intravenous analgesia, remifentanil

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INTRODUCTION

Pain perception during labour is very individual. Many women, despite being well- prepared, are shocked by the intensity of the acute pain. Labour pain management decreases the excessive stress which could lead to undesired pathological somatic and psychological reactions[1-4].

Lumbar epidural analgesia offers a safe and effective method for pain relief during labour. While there are a large number of relative contraindications, there are a few absolute contraindications to neuroaxial analgesia. These include patient refusal, overt maternal coagulopathy, infection at the needle site, and maternal hemodynamic instability[5].

Therefore, there is a need find an effective alternative to epidural analgesia, which would have an easier and lower-risk administration procedure, fast effect onset and minimal side effects on the parturient and foetus. One alternative is intravenous parturient-controlled analgesia using remifentanil (rPCA) (ref.[6]).

Remifentanil is a relatively new, ultra-short acting synthetic opioid with fast onset and which is rapidly metabolised by non-specific plasma and tissue esterases[7]. Its estimated half-life is 1.3 min, and prolonged administration does not appear to cause accumulation of this drug[8,9].

The aim of the present study was to compare the analgesic efficacy of parturient controlled intravenous remifentanil administration with epidural analgesia during first stage of labour with regard to maternal and early neonatal side-effects. We also aimed to confirm this clinically very simple method (rigid dosage regimen of remifentanil) of patient-controlled administration of remifentanil.

MATERIAL AND METHODS

We obtained the consent of the local ethics committee to this prospective, randomised trial, at the outset. The study lasted from March 2010 to May 2010. Inclusion criteria (N=81) were : no comorbidities (ASA I), singleton

head-down full term pregnancy, spontaneous or induced labour. The informed consent of the women was obtained before administration of analgesia. In the case of refusal to sign informed consent (N=53), the data were excluded from statistical evaluation. Women who had asked for obstetric analgesia and met the inclusion criteria were offered the PCA using remifentanil (randomisation by the parturient). The data of the parturients whose pregnancies were terminated by Caesarean Section were excluded from statistical evaluation.

Acute Pain Service Form

The data were recorded using the standard Acute Pain Service (APS) form used in our hospital for peripartal monitoring including the basic information about the parturient, coagulation parameters, gynaecological anamnesis, history of headache, timing (regular contractions initiation time, time of analgesia request and its administration and the respective results of vaginal examination), delivery details (pregnancy termination method, Apgar score and umbilical blood pH), medication including prostaglandins, oxytocine or spasmolytics, analgesia details (method of epidural space access, concentration and amount of the analgetics given, administration method and anaesthesiological complications). The APS form also contained a detailed labour analgesia monitoring table where blood pressure, heart rate, amount of analgetics given, administration of other systemic analgetics, VAS pain score and Bromage score were recorded regularly: immediately before the first administration of analgesia, every 30 min up to the delivery and 2 h and 24 h after the delivery. Visual Analogue Scale (VAS) objectifies the parturient's pain perception on a special scale from 0 (no pain) to 10 (the worst imaginable pain). Bromage score (BS) (ref.[10]) reflects the level of motor block of lower extremities after neuraxial analgesia administration (I – free movement of legs and feet, II – just able to flex knees with free movement of feet, III – unable to flex knees, but with free movement of feet, IV – unable to move legs or feet). After the delivery, the Apgar score was assessed by perinatologist and the umbilical cord blood sample was taken for pH analysis. Level of the parturient satisfaction and their comments on the analgesia provided analgesia evaluation, additional to the information obtained by VAS pain score analysis. The level of the parturient satisfaction was assessed by mean percentage score (100% – fully satisfied, 75% – somewhat satisfied, 25% – somewhat dissatisfied, 0% – fully dissatisfied) for both methods.

Epidural administration

The parturients undergoing EA had an epidural catheter inserted into the epidural space by an anaesthesiologist. The dosage regimen of bupivacaine and sufentanil in the EA group was rigidly set to induction dose of 12.5 mg of bupivacaine and 5 μg of sufentanil in 10 mL of normal saline; top-up boluses of half-size dose were repeated in 60-90 min intervals. The epidural catheter was extracted after the delivery, at least two hours before the parturient's transport to post-natal care ward.

Remifentanil administration

The parturients were closely informed by an anaesthesiologist of this method and its possible side effects and instructed in the PCA device operation. After the parturient's consent, her peripheral vein was cannulated and infusion of normal saline up to 2 mL/kg/h was started. The PCA device was connected to the same cannula. Remifentanil (Ultiva, Glaxo-Smith-Kline, Great Britain) was then administered via the PCA device (Technic 1, AMV Technics, Czech Republic) from a 50 mL syringe in a concentration of 20 μg/mL. On demand, the parturient received an intravenous bolus of 20 μg (1 mL) of remifentanil. Lock-out interval was set to 3 min. The significant analgesic effect was set to a minimal VAS score decrease of 2, based on existing evidence[6]. In case of inadequate analgesic VAS decrease (<2), it was possible for the anaesthesiologist to increase the dose in 10 μg steps.

Monitoring

The parturient was observed by a healthcare worker continously in the delivery room and her blood pressure, VAS pain score, amount of analgetic administered and sedation level were recorded every 30 min. If any signs of sedation (drowsiness), dizzines, muscle rigidity or bradypnoe (breaths under 10 per min) were observed, the lock-out interval could be extended by 1 minute.

Side effects

Side effects of remifentanil, such as respiratory depression (breaths under 10 per minute), bradycardia (<50 bpm), hypotension, muscle rigidity, nausea and vomiting were recorded thoroughly. Hypotension criteria were set as a systolic blood pressure decrease of 25% or more from the baseline blood pressure (i.e. the blood pressure recorded before initiation of analgesia).

Statistical methods

According to average number of labours per month in the local Obstetrics Department we aimed to enroll in both groups 30 parturients with the power set at >80%. *P* values less then 0.05 were considered significant.

The data were analysed using the software Statistica 7.0 (StatSoft, Czech Republic). The data were summarised as means, median, standard deviation and confidence interval). The Wilcoxon Matched Pairs Test was used for VAS pain score decrease analysis. The Mann-Whitney U-Test was used for comparison of differencies between both groups. The level of the parturients' satisfaction was assessed by mean percentage score for both methods used.

RESULTS

During the study period, 28 parturients met the requirements to take part in this prospective randomised trial. This low count was caused by high parturient refusal to participate in the study (N=53) despite agreement with labour analgesia. We are aware of the decreased power

with the lower sample size; nevertheless the 95% confidence interval for endpoint estimate in the groups showed clinically non-significant results within its whole range which supports our findings from the statistical testing. Therefore we decide to terminate the enrolment. Four pregnancies were terminated by Caesarean Section (2 of them due to labour progress stagnancy, 2 because of a pathological cardiotocography (CTG) record (1 in each branch)).

Parturient study flow is shown in Fig. 1.

The following analysis is based only on the data from the observation of 24 women who delivered vaginally. Parturient characteristics, labour course and neonatal parameters are shown in Table1. Both groups characteristic, labour and VAS course and neonatal parameters differencies were found statistically insignificant (Table 2). The only statistically significant difference between the two studied groups was the cervical dilatation at the time of the analgesia initiation (P=0.013) without clinical significance.

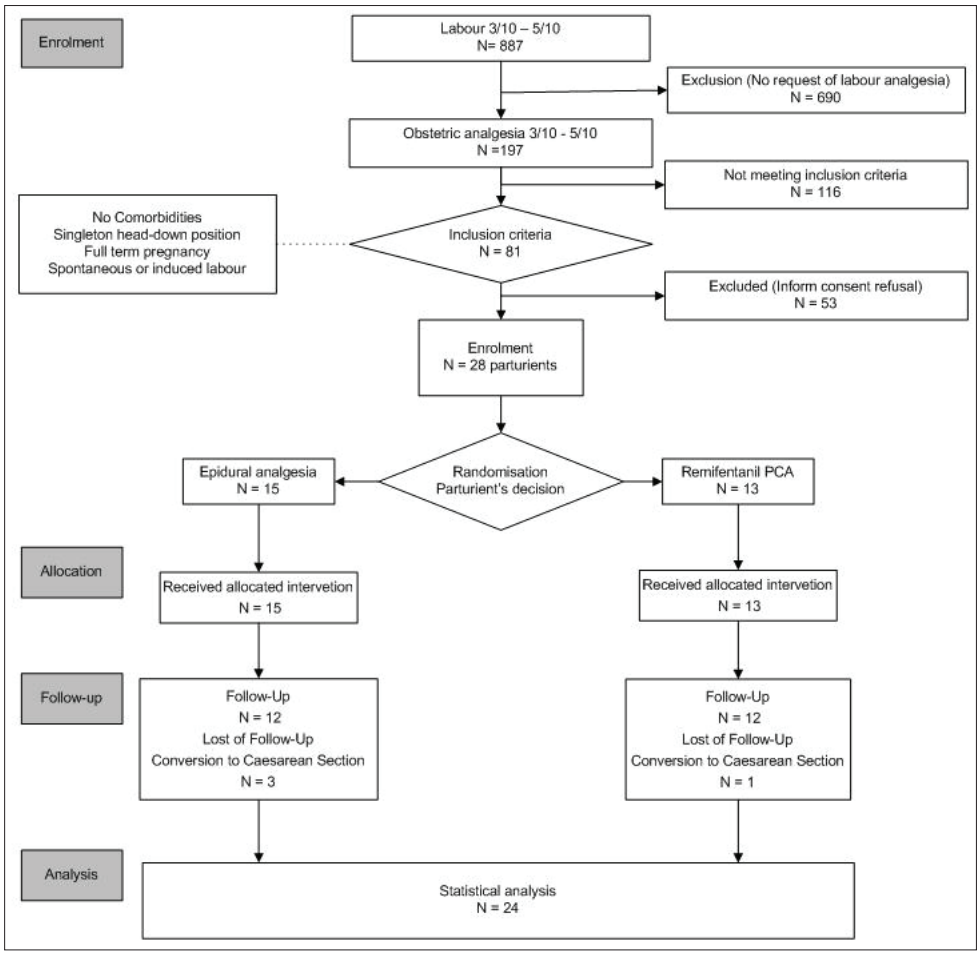

Fig. 1. Study patient flow.

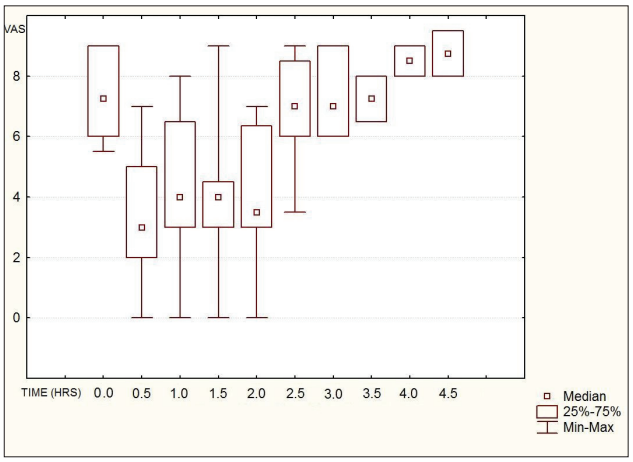

Fig. 2. Visual Analogue Scale (VAS) Pain Score during Application of Epidural Analgesia.

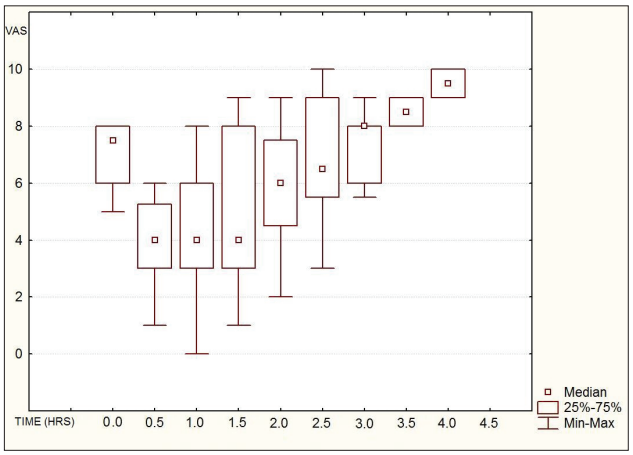

Fig. 3. Visual Analogue Scale (VAS) Pain Score during Application of Remifentanil Parturient-Controlled Analgesia.

Table 1. Characteristics of the Parturients Completing the Study.

No.	Analgesia	Age (years)	Gravidity duration (weeks + days)	Parity	Labour induction	Height (cm)	Weight (kg)	BMI (m^2/kg)	Duration of labour stages (min)			Analgesia Duration (min)	Apgar score			pH
									1st	2nd	3rd		1st min	5th min	10th min	
1	EA	32	40+0	II	W/O	171	101	34.54	260	10	45	122	9	10	10	-
2	EA	28	37+3	I	W/O	165	96	35.26	340	0	2	325	9	10	10	7.32
3	EA	29	41+0	I	YES	168	87	30.82	150	50	25	150	9	10	10	7.31
4	EA	30	41+2	I	YES	167	78	27.97	260	5	10	190	9	9	9	-
5	EA	31	39+4	II	YES	170	93	32.18	160	10	10	60	7	8	9	7.21
6	EA	28	39+0	I	YES	158	54	21.63	135	5	10	100	10	10	10	7.4
7	EA	30	40+4	I	YES	168	73	25.86	265	10	35	220	3	6	8	6.99
8	EA	24	39+4	I	W/O	173	82	27.4	335	10	10	185	9	10	10	7.18
9	EA	32	40+2	I	YES	171	76	25.99	220	15	15	225	9	9	10	-
10	EA	29	39+3	I	YES	163	83	31.24	270	30	10	150	9	10	10	7.33
11	EA	30	40+3	I	W/O	170	124	42.91	365	10	10	300	9	10	10	-
12	EA	30	41+1	I	YES	175	83	27.1	200	10	10	105	10	10	10	7.4
	Mean	29.4	40+0			168.3	85.83	30.24	246.7	13.75	16	177.67	8.5	9.3	9.67	7.27
	SD	2.05	1+0			4.42	16.75	5.35	76.3	13.51	12.54	80.17	1.88	1.23	0.65	0.137
	Median	30	40+1			169	83	29.395	260	10	10	167.5	9	10	10	7.315
13	rPCA	24	41+5	I	YES	165	80	29.38	340	15	45	273	7	8	8	-
14	rPCA	23	37+6	I	YES	165	74	27.18	165	10	10	65	8	10	10	7.14
15	rPCA	31	39+2	I	W/O	172	70	23.66	260	10	25	160	9	10	10	-
16	rPCA	29	38+4	III	YES	162	69	26.29	335	5	5	205	9	10	10	7.31
17	rPCA	32	40+2	II	YES	168	75	26.57	150	15	25	50	8	9	9	7.32
18	rPCA	29	38+1	II	YES	168	89	31.53	355	5	5	170	10	10	10	7.06
19	rPCA	32	39+2	II	YES	170	77	26.64	235	5	5	90	9	9	10	7.4
20	rPCA	29	40+2	I	W/O	165	86	31.59	240	10	15	195	9	10	10	-
21	rPCA	27	41+4	I	YES	165	133	48.85	250	10	15	200	9	9	10	7.2
22	rPCA	25	39+1	I	YES	164	81	30.12	315	40	10	290	9	10	10	-
23	rPCA	29	40+3	I	YES	176	98	31.64	230	10	10	90	9	9	9	7.31
24	rPCA	25	36+6	I	YES	164	76	28.26	255	0	15	165	9	10	10	7.33
	Mean	27.9	39+3			167	84	30.14	260.8	11.25	15.42	162.75	8.75	9.5	9.67	7.26
	SD	2.95	1+3			3.83	16.75	6.13	65.5	10.01	11.57	77.15	0.75	0.67	0.65	0.107
	Median	29	39+1.5			165	78.5	28.82	252.5	10	12.5	167.5	9	9	10	7.31

BMI – body mass index; EA – epidural analgesia; rPCA – remifentanil parturient controlled analgesia;

The rPCA rigid administration scheme (20 μg bolus with lock-out interval 3 min) was used for all parturients. Three parturients required a further dose increase to 30 μg and 40 μg due to insufficient analgesic effect.

Comparison of VAS decrease during labour is given in Table 2. There is no significant difference between the groups. A pain score of ≤3 (bearable pain) was recorded by 67% parturients in the EA group and by 42% parturients in the rPCA group. Statistically significant difference (P=0.002) between the baseline pain scores and the lowest recorded pain scores was found for both analgesic groups. Progression of VAS in the EA group during labour is shown in Fig. 2. Progression of VAS score in the rPCA group is shown in the Fig. 3. The differences between the pain scores recorded during EA and those recorded during rPCA administration were not statistically significant (P>0.05) throughout the entire administration period.

Satisfaction

Level of the parturients' satisfaction with analgesia was 88% (0-100%) in the EA group and 85% (75-100%) in the rPCA group (P=0.24). Complete dissatisfaction was expressed by one woman in EA group, the most of

Table 2. Comparison of Parturients Characteristics, Neonatal, Labour and VAS Course Parameters.

	EA Mean	rPCA Mean	P
Age (years)	29.42	27.92	NS
Gestures (days)	279.83	276.16	NS
Labor induction	0.66	0.83	NS
Height (cm)	168.25	167.00	NS
Weight (kg)	85.83	84.00	NS
BMI (m2/kg)	30.24	30.14	NS
1st stage (min)	246.67	260.83	NS
2nd stage (min)	13.75	11.25	NS
3rd stage (min)	16.00	15.42	NS
pH	7.27	7.26	NS
VAS 0 h (N=24)	7.33	7.04	NS
VAS 0.5 h (N=24)	3.29	4.13	NS
VAS 1.0 h (N=22)	4.14	4.64	NS
VAS 1.5 h (N=19)	4.05	5.33	NS
VAS 2.0 h (N=16)	4.09	5.88	NS
Satisfaction (%)	88	85	NS

NS (Not Significant$P$>0.05); BMI (Body Mass Index); VAS (Visual Analogue Score)

parturients were fully satisfied (9 women in EA group, 5 women in rPCA group).

Complications

Hypotension occurred in one parturient from the rPCA group two hours after delivery (i.e. over two hours after the last dose of remifentanil was administered), and it was more likely associated with a greater blood loss during the delivery than the analgesia itself. Bradycardia did not occur in any of the parturients.

All the parturients with rPCA experienced a certain level of drowsiness and dizziness (100%). Advantageously, all the parturients with rPCA also experienced at least a temporary anxiolysis. Muscle rigidity was not observed in any of the parturients. Nausea and vomiting occurred in two (17%) parturients before the rPCA was initiated, and persisted during the analgesia.

The most common complications of EA were repetitive puncture in 33% of cases, and tingling without paresthesia in 17% of cases. In one case (8%), blood appeared in the inserted epidural catheter. Bromage score did not exceed its grade I in any of the parturients with EA.

DISCUSSION

The difference in the analgetic efficiency of EA and rPCA in the used dosage regimen [bupivacaine 12.5 mg and sufentanil 5 μg in 10 mL for EA and 20 μg of remifentanil for rPCA] during the whole analgesia administration period was statistically insignificant. However, EA is temporarily able to cause a greater pain score decrement, which was not found for the rPCA group [the maximum pain score decrement from the baseline during the analgesia administration was 5.25 (3-6) in the EA group and only 3.75 (1-5) in the rPCA group]. Pain may increase with the progression of labour as a result of sensitization[11]. For this reason, the baseline pain score comparison with the pain scores recorded during the analgesia administration (i.e. later) has only limited significance. Another fact is that VAS pain score assessment always carries a significant subjective factor of pain perception, hence the recorded pain scores always have more or less limited significance.

Three parturients required a further dose increase due to an insufficient analgesic effect, but only one of these women experienced further pain relief. Two other women experienced more drowsiness than any significant pain score decrement.

Both types of analgesia appear to be equally safe for the neonates. An Apgar score below 8 for the 1st minute or umbilical blood pH below 7.1 was recorded in two cases in the EA group. In one of these cases forceps was used due to the labour stagnation and CTG decelerations in the second stage of labour (Apgar score was 7, 8, 9 and the umbilical blood pH was 7.21), the second labour terminated spontaneously with CTG decelerations (Apgar score was 3, 6, 8 and umbilical blood pH was 6.99). In the rPCA group, these parameters were also recorded in two neonates. Both of these labours terminated spontaneously, with second stage stagnation and CTG decelerations (Apgar score was 7, 8, 8 and umbilical blood pH was 7.14, resp. 8, 9, 9 and 7.06). CTG decelerations observed in the rest were the same in both analgesia groups and corresponded to normal CTG records of parturients with no analgesia. The CTG records of the three parturients requiring higher doses of remifentanil showed no changes related to the dose increase.

The level of satisfaction with both of the analgesia methods was approximately the same: 88% (0-100%) in the EA group and 85% (75-100%) in the rPCA group. The most common complaint was insufficient analgetic effect, especially in the second stage of the labour. Main positive comments on the rPCA were epidural catheter insertion avoidance and the possibility of remifentanil self-administration according to the individual needs. This led to absence of dissatisfied parturients given rPCA despite the smaller pain reduction.

When we were designing the study, there were no published comparative studies on remifentanil and epidural labour analgesia. Nevertheless, the maternal and neonatal effects of remifentanil were described. The feasibility and safety were proven and the regimen of accurate dosage was found. As the study progressed, three similar studies emerged. Volmanen et al.[12] used higher doses of remifentanil and shorter lock-out interval. The PCA dose of remifentanil was given over 1 min with a lockout time of 1 min. The dose was increased starting from a bolus of 0.1 μg/kg and following a dose escalation scheme up until the individual-effective dose was reached. Sedation and low haemoglobin oxygen saturation were found more often during remifentanil analgesia. Foetal heart rate tracing abnormalities were as common in both groups. However, there was no difference in the pain relief scores between the treatments. The observation period was limited to the first hour of treatment. El-Kerdawy et al.[13] demonstrated a significant decrease in VAS score in the first hour after administration of analgesia to 30 preeclamptic patients (randomly assigned to two equal groups- EA and rPCA) using different regimen with background infusion. PCA remifentanil infusion administered until the time of delivery produced no observable maternal, foetal or neonatal side effects. VAS pain scores were reported at only three points: a baseline scores before starting analgesia, 1h after starting treatment, and after delivery. The investigation of Douma et al.[14] on a group of 20 patients (EA=10, rPCA=10) showed a distinct outcome: pain relief in labour with epidural ropivacaine/sufentanil was more effective than intravenous remifentanil patient-controlled analgesia.

The main limitation of the study was the small parturient sample although the 95% CI of endpoint estimate in the groups showed clinically non-significant results within their whole range which supports our findings from the statistical testing.

The other fact is that size of our study group is similar to the studies mentioned above, especially when our inclusion criteria are applied. For example, the newest study of Tveit et al. (EA=20, rPCA=17) represents comparable results on a slightly wider group of parturients. However,

the number of patients matching our inclusion criteria is almost the same (EA=13, rPCA=12). Therefore we suggest that a too tight inclusion criteria might be another limitation of our study.

CONCLUSION

Remifentanil parturient-controlled intravenous analgesia and epidural analgesia provided effective analgesia with high parturient's satisfaction scores and clinically good neonatal outcomes. The data support the clinical use of rPCA as an alternative to standard epidural analgesia.

CONFLICT OF INTEREST STATEMENT

The authors state that there are no conflicts of interest regarding the publication of this article.

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