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Maternal and Neonatal Effects of Remifentanil in Women Undergoing Cesarean Section in Relation to *ABCB1* and *OPRM1* Polymorphisms

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Summary

The aim of our study was to evaluate possible effect of ABCB1, and OPRM1 polymorphisms on the efficacy and safety of remifentanil in women undergoing elective cesarean section under general anesthesia. Women received remifentanil (1 μg/kg i.v.) 30 s prior to the induction to standardized general anesthesia. The ABCB1 (rs2032582, rs1045642) and OPRM1 (rs1799971) polymorphisms were analyzed from maternal peripheral blood. The basal hemodynamic and demographic parameters in the study population (n=54) were similar in all the subgroups. The median ± SD increase of systolic blood pressure at 5 min from the baseline was practically completely abolished in homozygous carriers of ABCB1 variants in comparison with wild-type subjects -2.67±25.0 vs. 16.57±15.7 mm Hg, $p<0.05$ for rs2032582, and 2.00±23.9 vs. 22.13±16.8 mm Hg, $p<0.05$, for rs1045642, respectively. While no neonate belonging to ABCB1 wild-type homozygous or OPRM1 variant carrying mothers needed any resuscitative measure, 10.5 % of the neonates belonging to OPRM1 wild-type homozygous mothers received resuscitative support similarly as 11.1 %, and 12.5 % of neonates of mothers carrying variants of rs2032582, and rs1045642, respectively. Decreased stabilizing effects of remifentanil on maternal hemodynamics has been observed in ABCB1 wild type mothers, while the adaptation of the neonates was clinically worse in OPRM1 wild type, and ABCB1 variant allele carriers.

Key words

Pharmacogenetics • Remifentanil • Opioids • Polymorphism

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Introduction

Suboptimal analgesia during surgery may lead to sympathetic stress response resulting in increased risk of cardiovascular complications. Opioids are considered as a gold standard for achieving good analgesic action. However, opioids are usually avoided during the general anesthesia for cesarean delivery until the delivery of newborn because of possible risk of placental transfer and neonatal respiratory depression that is well described side effect of the opioid class (Chestnut 2008, Bouattour *et al.* 2007). The avoidance of opioids can on the other hand lead to insufficient level of analgesia (Amin *et al.* 2011). Since approximately 15-26 % of patients undergoing surgery under insufficient analgesia react to painful stimuli by an exaggerated sympathetic response with pronounced release of endogenous catecholamines into the circulation resulting in increased blood pressure, heart rate, intracranial pressure and decreased uteroplacental blood flow (Yeo *et al.* 2002). The stress response to pain may be particularly risky for pregnant women with chronic or gestational hypertension, including preeclampsia or HELLP syndrome in whose marked

increase of blood pressure in the initial phase of CS may lead to increased intracranial pressure with a high risk of cerebrovascular accident. Moreover, other severe complications as malignant arrhythmia, pulmonary edema and hypoxia of the newborn are also recognized (Lanska *et al.* 2000, Langesaeter *et al.* 2011). Pre-eclampsia complicates about 3 % of pregnancies and all hypertensive disorders affect about 5 to 10 % of pregnancies (Hutcheon *et al.* 2011). The reported rate of inadequate anesthesia during CS is approximately 2 %.

One of the best options among opioids for providing labor analgesia could be remifentanil (Hill 2008). Remifentanil is a 4-anilido-piperidine with a small volume of distribution of 0.39 l/kg with a rapid redistribution phase of 0.94 min, and a short elimination half-life of 9.5 min. Remifentanil quickly transfers across the placenta with a mean umbilical vein to maternal artery concentration ratio of 0.88, but it is metabolized rapidly by nonspecific plasma and tissue esterases in the fetus. The mean umbilical artery to umbilical vein concentration ratio is 0.29. The rapid onset of action is approximately 30-60 s, within one minute following intravenous injection. This unique pharmacokinetic profile of the compound should substantially reduce the risk of neonatal side effects and minimize the effects on early neonatal adaptation (Hinova and Fernadez 2009, Kan *et al*. 1998). However, in a recent double-blind, randomized study enrolling 151 parturients undergoing cesarean delivery under general anesthesia remifentanil prior to induction of general anesthesia significantly increased the risk of neonatal respiratory depression during first minutes after cesarean delivery, although the negative effects on neonatal adaptation were transient when appropriate resuscitative measures have been applied (Noskova *et al*. 2015).

ATP-binding cassette sub-family B member 1 (ABCB1), an important efflux transport protein is highly expressed in many tissues. Its activity contributes to functions of placental barrier, blood-brain barrier, reduces bioavailability of drugs from the intestine and increases drug excretion into urine, bile, and the intestinal lumen. ABCB1 in the maternal-facing apical membrane of the syncytiotrophoblast was shown to play an important role in efflux transfer across the placental barrier for opioids (Kosarac *et al.* 2009). Variability in ABCB1 expression in human tissues has been reported while genetic polymorphisms are believed to significantly contribute to the inter-individual variation. More than 50 single nucleotide polymorphisms (SNPs) have been reported in the *ABCB1* gene (Ni *et al.* 2011), but only a few of them with potential clinical relevance, namely rs2032582, rs1045642 and rs1128503 (Ni *et al.* 2011, Pechandova *et al.* 2006, Sadhasivam *et al.* 2012). SNP rs1045642 was associated with pain relief in patients treated with morphine (Campa *et al.* 2008). Fujita *et al.* (2010) described association between significantly lower fatigue and frequency of vomiting and T/T genotype at rs1128503 or TT/TT diplotype at rs2032582 and rs1045642 (Fujita *et al*. 2010). Polymorphisms within OPRM1 gene coding for μ1-opioid receptor represent another candidate source of interindividual variability in the reaction to opioids including remifentanil. A common polymorphism of OPRM1, rs1799971 has been shown to result in the substitution of amino acid Asparagine with Aspartate at position 40 (Camorcia *et al.* 2011), which is subsequently associated with higher pain scores, higher morphine usage, and lower nausea score in some clinical trials (Klepstad *et al.* 2004). The clinical impact of OPRM1 (rs1799971*)* variant was recently evaluated in a meta-analysis involving 18 studies and more than 4.600 subjects (Hwang *et al.* 2014). Patients, carriers of the variant allele needed higher doses of opioids to achieve sufficient analgesia. These genetic variations were clinically most important in Asian patients, morphine users, and those undergoing visceral organ surgery. In addition, polymorphisms in other genes coding for drug metabolizing enzymes can influence the response of opioids in a population-specific manner through the changes of blood levels. Other pathophysiological studies have further described that carriers of rs1799971 G allele were more sensitive to electrical stimuli, chemically induced pain, and also pressure pain (Fillingim *et al.* 2005).

The aim of our study was to evaluate, if the genetic polymorphisms in the *ABCB1* and *OPRM1* genes influence the therapeutic efficacy and safety of remifentanil in women undergoing elective cesarean section under general anesthesia.

Materials and Methods

After obtaining written informed consent, women undergoing elective CS were enrolled in a prospective study (ACTRN12612001165875) conducted in accordance with the Declaration of Helsinki. The study was conducted at the Department of Anesthesiology and Intensive Care, General Teaching Hospital in Prague and the responsible Ethics Committee approval was obtained before the study start up. Patients

received a bolus of remifentanil (1 μg kg^{-1}) 30 s before the introduction into the general anesthesia. Induction of anesthesia was performed with thiopental 5 mg kg^{-1}. Trachea was intubated after muscle paralysis with suxamethonium 75-125 mg, and atracurium 0.35 mg kg^{-1} was administered to achieve further muscle relaxation. Anesthesia was maintained with sevoflurane 0.7 vol % in combination with 50 % nitrous oxide in oxygen, until the time of delivery. After delivery and umbilical cord ligation sufentanil 0.3-0.5 mg kg^{-1}, as required, nitrous oxide in oxygen (50/50 %, v/v) and sevoflurane (0.7-1 %) were administered to achieve adequate sedation and analgesia till the end of surgery. Standard monitoring included non-invasive blood pressure measurement, pulse oximetry (SpO_2), capnography, inspired oxygen fraction, electrocardiography (heart rate, ST segment trending), inspired and expired gas fraction. The bispectral index (BIS) values were also monitored. All clinical parameters were recorded at 0, 2.5, 5, 7.5, 10, 12.5, and 15 min. Time note was taken of the following events: transfer to delivery room, administration of remifentanil, laryngoscopy and endotracheal intubation, skin incision, uterine incision, delivery, the end of the operation and extubation. Primary time points for clinical evaluation were set at 5 and 12.5 min. Neonates were assessed using Apgar scores and clinical examination was done by an experienced neonatologist. Umbillical blood gases were checked at the delivery room using ABL90 FLEX blood gas analyzer (Radiometer, Brønshøj, Denmark). Exclusion criterias were multiparity, gestational age < 35 weeks, estimated fetal weight < 2500 g, hypoxia or signs of fetal stress and mother´s hypotension.

Genotyping

Samples of peripheral venous blood for DNA isolation were collected in tubes containing citric acid during delivery and immediately frozen and stored at –20 °C until further processing (Selinger *et al.* 1994, Bender *et al.* 1999). DNA was subsequently isolated using QIAamp DNA Blood Mini Kit (Quiagen Ltd.). The genotypes of MDR1 (rs1045642 and rs2032582 SNPs) were determined as described previously (Pechandova *et al.* 2006).

Polymorphisms OPRM rs1799971 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis by using a modification of a published method (Ginosar *et al.* 2009). The primer sequences were 5'-AAC ACATACATGACCAGGAAGT and 5'-GGTCAACTT GTCCCACTTAGATC. The amplification of the DNA was be made in the termocycler My-Cycler (Bio-Rad, USA). The PCR amplification were conducted in 27 μl reaction volume, containing 60 ng of genomic DNA, 3 μl of $MgCl_2$ 25 mM (Fermentas, Lithuania), 0.5 μl of 10 mM primer solutions, 2.5 μl of dNTP 2 mM (Fermentas, Lithuania), 2.5 μl of 10 × Biotherm Puffer (Fermentas, Lithuania), 0.15 μl of Tag DNA polymerase (Fermentas, Lithuania) and 15.85 μl of sterile PCR water. The amplification started with an initial denaturation at 94 °C for 2 min followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 61 °C for 1 min and extension at 72 °C for 1 min, followed by 7-min terminal extension at 72 °C. The amplification product was subsequently digested by Bsh1236 I (New England Biolabs, USA) overnight at 37 °C. The fragments were analyzed in a 3.5 % agarose gel dyed by 0.5 μg/ml of ethidium bromide for 5 to 10 min. The DNA fragments were identified using GelDocum 2000 imaging system (Bio-Rad, USA).

Statistical analysis

Descriptive statistics was used for demographic and medical history records. One-way ANOVA, Kruskal-Wallis and Multiple range tests were used for statistical evaluation of differences between the genotype groups. A Pearson´s χ^2 test was used for categorical data. Differences were considered statistically significant for $p<0.05$.

Results

Totally 54 patients have been enrolled into the study. There were no significant differences between subgroups of patients according to weight and comorbidities (Table 1). Polymorphism rs1045642 could not be analyzed in one patient. The allelic frequencies for SNPs ABCB1 rs1045642, rs2032582, and OPRM1 rs1799971 were 79.4, 71.9, and 27.7 %, respectively. The distribution of the variant alleles in our study population did not substantially differ from normal distribution. There was an initial increase in SBP, MAP, and heart rate followed by subsequent decline in all these hemodynamic parameters in the whole study population as well as in all genotype subgroups. Figure 1 shows the blood pressure, mean arterial pressure and heart rate variability during the time in relation to ABCB1 polymorphisms rs1045642 and rs2032582. Homozygous carriers of ABCB1 variant alleles in both polymorphisms studied displayed trend

towards lower increase/larger decline in SBP, MAP, and heart rate as compared with wild type homozygotes. However, this difference has been statistically significant only at 5 min for change of SBP and MAP from the baseline, and at 7.5 min or later for change of heart rate from the baseline value.

Table 1. Demographic data of patients in MDR1 and OPRM genotype subgroups.

SNP	Genotype	Age (years)	Height (cm)	Initial weight (kg)	Active weight (kg)
MDR1 rs1045642	wt/wt (n=8)	32.5 ± 6.0	164.5 ± 9.2	67.5 ± 10.1	79.0 ± 11.6
	wt/v (n=28)	35.0 ± 4.4	168.0 ± 7.1	64.0 ± 13.9	79.0 ± 13.7
	v/v (n=17)	34.0 ± 5.9	170.0 ± 5.2	73.0 ± 13.4	82.0 ± 15.2
MDR1 Rs2032582	wt/wt (n=14)	31.0 ± 5.0	169.0 ± 9.1	66.5 ± 10.3	79.0 ± 12.6
	wt/v (n=27)	36.0 ± 4.2	168.0 ± 6.8	67.0 ± 14.3	80.0 ± 13.9
	v/v (n=13)	35.0 ± 6.3	168.0 ± 5.0	69.0 ± 14.3	81.0 ± 15.9
OPRM rs1799971	wt/wt (n=38)	35.5 ± 5.3	168.0 ± 6.4	67.5 ± 14.0	80.0 ± 15.8

Data are mean ± SD; number of subjects.

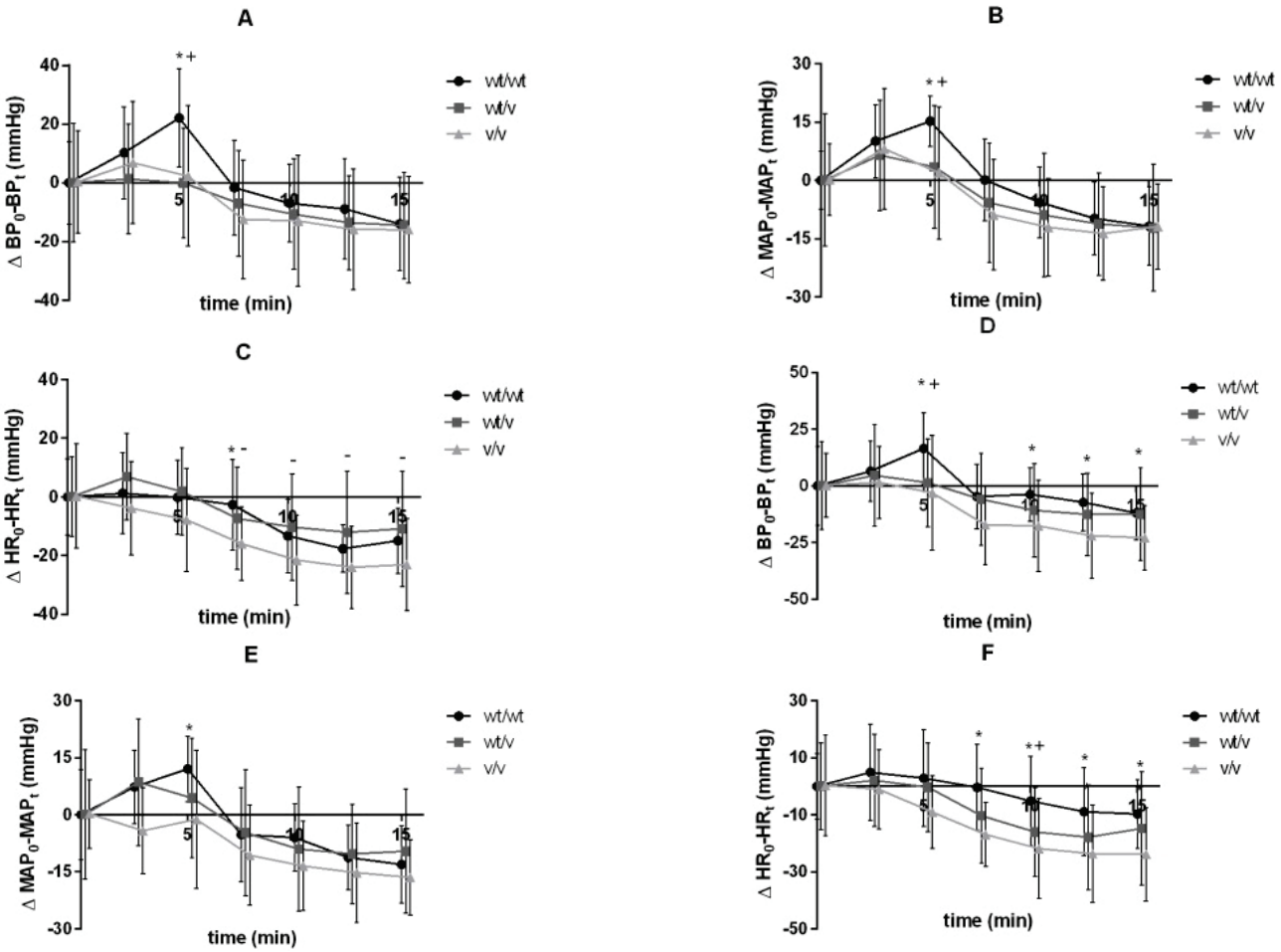

Fig. 1. Serial changes in: **A**) systolic arterial pressure (BP) in MDR1 rs1045642 subgroups; **B**) mean arterial pressure (MAP) in MDR1 rs1045642 subgroups; **C**) heart rate (HR) in MDR1 rs1045642 subgroups; **D**) systolic arterial pressure (BP) in MDR1 rs2032582 subgroups; **E**) mean arterial pressure (MAP) in MDR1 rs2032582 subgroups; **F**) heart rate (HR) in MDR1 rs2032582 subgroups. * $p<0.05$ for v/v vs. wt/wt, + $p<0.05$ for wt/v vs. wt/wt, – $p<0.05$ for v/v vs. wt/v.

Table 2. Systolic blood pressure changes at primary time points according to genotype subgroups.

SNP	Genotype	Δ systolic blood pressure t_0-t_t at 5 min	Δ systolic blood pressure t_0-t_t at 12.5 min
MDR1 rs1045642	wt/wt (n=8)	22.13 ± 16.8	-8.88 ± 17.1
	wt/v (n=28)	-0.14 ± 18.7*	-13.64 ± 16.1
	v/v (n=17)	2.00 ± 23.9*	-16.18 ± 20.6
MDR1 rs2032582	wt/wt (n=14)	16.57 ± 15.7	-7.21 ± 12.5
	wt/v (n=27)	1.36 ± 19.26*	-12.67 ± 18.1
	v/v (n=13)	-2.67 ± 25.0*	-23.92 ± 17.0
OPRM rs1799971	wt/wt (n=38)	3.21 ± 22.9	-13.25 ± 21.5
	wt/v (n=16)	6.50 ± 17.4	-18.25 ± 14.8
OPRM rs1799971+ MDR1 rs1045642	wt/wt + wt/wt (n=46)	6.5 ± 23.06	-11.11 ± 18.40
OPRM rs1799971 + MDR1 rs1045642	wt/wt + v/v (n=55)	2.84 ± 23.20	-13.00 ± 19.38
OPRM rs1799971 + MDR1 rs1045642	wt/v + wt/wt (n=24)	11.71 ± 19.06	-15.13 ± 16.24
OPRM rs1799971 + MDR1 rs1045642	wt/v + v/v (n=33)	4.18 ± 21.37	-17.18 ± 18.08

Data are mean ± SD; number of subjects; $p<0.05$ vs. wt/wt.

The OPRM1 polymorphism did not affect the hemodynamic parameters significantly. Table 2 shows the declines of systolic blood pressure in genotypes subgroups and ABCB1, OPRM1, and ABCB1-OPRM1 haplotype groups. The SBP increase at 5 min was twice as high in OPRM1 rs1799971 heterozygous group as compared with wild-type homozygotes when analyzed in ABCB1 homogenous subgroups. The mean heart rate increase at 5 min ranged between 3.5±15.5 to 9.0±13.6 beats per minute in all haplotype groups without reaching statistically significance of the differences.

Although there were no statistically significant differences between infant outcome variables (Table 3), a numerical difference in the need for resuscitative measures was noted. While no neonate belonging to ABCB1 wild-type homozygous or OPRM1 variant allele carrying mothers needed any resuscitative measure, 10.5 % of the neonates belonging to OPRM1 wild-type homozygous mothers received early resuscitative support similarly as 11.1 %, and 12.5 % of neonates belonging to mothers carrying variants of rs2032582, and rs1045642, respectively.

Discussion

In agreement with previously published studies, remifentanil administration lead in our study to an attenuation of the hemodynamic stress response of the patients at the beginning of the anesthesia (Twersky *et al.* 2001, Penido *et al.* 2010), when compared with a historical control group formed from literature data (Heesen *et al.* 2013). Since the aim of this study was not to evaluate the effects of remifentanil *per se*, but to compare between genotype subpopulations, no placebo group was used for comparison in this study. The protocol of this study specified 5 min interval for clinical parameters as primary as this was the expected mean time of fetus expulsion representing the last time point before sufentanil administration. The 12.5 min interval was considered to reflect more effect of sufentanil on the stabilization of hemodynamic parameters.

Mean systolic blood pressure increase that was observed until delivery was almost completely diminished in groups of patients homozygous or heterozygous for variant alleles in MDR1 polymorphisms rs1045642 and rs2032582. This finding compares well

Table 3. Neonatal characteristics and outcome in MDR1 and OPRM genotype subgroups.

Gene	Genotype	Fetal weight (g)	Time from induction to delivery (min)	Oxygen saturation (arterial, %)	Apgar scores at 1 min n (%)			Apgar scores at 5 min n (%)	Apgar scores at 10 min n (%)	Resuscitative measures			
					8-10	4-7	0-3	8-10	8-10	BVM n (%)	Tactile stimulation	Oxygen tubing	All methods
MDR1 rs2032582	wt/wt (n=8)	3150 ± 200.9	4 ± 1.4	41.5 ± 10.1	6 (75.0)	2 (25.0)	0 (0.0)	8 (100.0)	8 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	wt/v (n=28)	3160 ± 492.2	5 ± 1.3	38.3 ± 15.2	22 (78.6)	6 (21.4)	0 (0.0)	27 (96.4)	28 (100.0)	2 (7.1)	0 (0.0)	1 (3.6)	3 (10.7)
	v/v (n=17)	3260 ± 414.1	5 ± 1.1	39.4 ± 8.6	13 (76.5)	3 (17.6)	2 (11.8)	15 (88.2)	17 (100.0)	1 (5.9)	1 (5.9)	0 (0.0)	2 (11.8)
MDR1 rs2032582	wt/wt (n=14)	3160 ± 290.9	4 ± 1.6	41.5 ± 10.6	10 (71.4)	4 (28.6)	0 (0.0)	14 (100.0)	14 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	wt/v (n=27)	3170 ± 513.0	5 ± 1.3	37.8 ± 15.5	20 (74.1)	6 (22.2)	1 (4.0)	26 (96.3)	27 (100.0)	2 (8.0)	0 (0.0)	1(4.0)	3 (12.0)
	v/v (n=13)	3140 ± 309.9	5 ± 1.1	43.6 ± 9.8	10 (76.7)	2 (15.4)	1 (6.7)	10 (76.7)	13 (100.0)	1 (6.7)	1 (6.7)	0 (0.0)	2 (13.3)
OPRM rs1799971	wt/wt (n=38)	3145 ± 390.6	5 ± 1.2	33.7 ± 14.5	27 (71.1)	9 (23.7)	2 (5.3)	36 (94.7)	38 (100.0)	3 (7.9)	1 (2.6)	1 (2.6)	4 (10.5)
	v/v (n=16)	3180 ± 515.3	4.5 ± 1.7	41.5 ± 13.3	13 (81.3)	3 (18.9)	0 (0.0)	15 (93.8)	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are mean ± SD; number of subjects.

with previous *in vitro*, and non-clinical data. The variant rs1045642 genotype has been previously reported to lead to the lowest P-glycoprotein expression in target tissues (Song *et al.* 2006). Further, *in vivo* models with P-gp knockout mice indicated that functional impairment of P-gp transport results in increased brain concentrations of its substrates (King *et al.* 2001). Finally, haplotype consisting of variant alleles at three positions in the ABCB1 gene (rs1128503(T), rs2032582(T), and rs1045642(T) was found to be associated with increased susceptibility to clinical effects of fentanyl (Park *et al.* 2007). Although the ABCB1 polymorphisms are not recognized as an important predictive factor for the efficacy of opioids in pain treatment, it needs to be emphasized that the clinical situation of cesarean section delivery is incomparable with any of the commonly used acute pain model situations either on clinical or pre-clinical level. The principal difference is caused by the very short timeframe of approximately 5 min, over which the drug efficacy and safety needs to be maintained only, but the safety for the newborn may be critical for the clinical usefulness of the drug.

The genotype-specific differences in BP and MAP among MDR1 genotype groups were diminished at 7.5 min or later, which indicates that MDR1 polymorphisms rs1045642 and rs2032582 did not affect hemodynamic stabilization achieved with sufentanil administered after delivery. This finding, however, goes in line with previous observations. Contrary to some other opioids, sufentanil did not behave as P-glycoprotein substrate in an *in vitro* study (Wandel *et al.* 2002) and thus substantial importance of MDR1 polymorphisms on sufentanil efficacy were not anticipated.

Although statistically non-significant, the subgroup analysis for OPRM1 polymorphism and the BP suggests better attenuation of BP increase at 5 min in the rs1799971(A) homozygotes as compared with heterozygotes. The pre-clinical findings indicate that the variant rs1799971(G) allele is associated with decreased activity of post-receptor signal transduction pathways (Oertel *et al.* 2009), while the affinity of the receptor towards both endogenous and exogenous opioids is not affected by this polymorphism (Bond *et al.* 1998). These pre-clinical data should result in decreased analgesic action of opioids in subjects carrying variant rs1799971(G) allele, which is indeed indicated in clinical studies. Although there was a small study in labor pain suggesting that women carrying the rs1799971(G) allele were more sensitive to analgesic effects of intrathecal fentanyl (Landau *et al.* 2008), majority of clinical data, similarly to our findings, indicate for this polymorphism in acute pain the opposite effect. Previous studies have shown that rs1799971(G) carriers require higher amount of morphine to manage cancer pain (Klepstad *et al.* 2004), total hysterectomy (Chou *et al.* 2006a, Kolesnikov *et al.* 2011), total knee arthroplasty (Chou *et al.* 2006b) and major abdominal surgery (Hayashida *et al.* 2008). Another study on cancer patients also found that those carrying at least one copy of rs1799971(G) were poorer responders to morphine and fentanyl (Reyes-Gibby *et al.* 2007, Campa *et al.* 2008). In agreement, a meta-analysis involving 18 studies and more than 4.600 subjects patients showed that patients carrying the variant allele needed higher doses of opioids to achieve sufficient analgesia (Hwang *et al.* 2014).

The safety for a newborn is a critical property for any medicine to be used during the cesarean section delivery. The non-significant tendency towards unequal risk for worsened early neonatal adaptation, which was reflected by worsened Apgar scores (1st and 5th minute) and trend to unequal distribution of resuscitation measures used in the different genotype subgroups, is thus of potential clinical relevance.

We are aware of limitations of our study that need to be taken into account while interpreting the results. Firstly, the study population is rather limited for genotype subgroup comparisons. Secondly, the tendency towards unequal neonatal adaptation could be related to the time to delivery. Indeed the mean times in the patients groups, in which some newborns required resuscitative measures, were insignificantly longer as compared with the no-need for resuscitative measures groups. However, the mean difference is very small (5 vs. 4 min). The individual time to delivery in newborns requiring resuscitative procedures was between 4-5 min for all the newborns except one whose time to delivery was approximately 6 min. Thus the worsened neonatal adaptation shall not be due to longer surgery duration in these genotype subgroups.

Significantly decreased stabilizing effects of remifentanil on maternal hemodynamics have been observed in ABCB1 wild type mothers, while the adaptation of the neonates was clinically worse in ABCB1 variant allele carriers.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

BIS, bispectral index; BP, arterial blood pressure; BVM, bag-mask ventilation; CPAP, continual positive airway pressure; CS, cesarean section; HET, heterozygous; HOM, homozygous; HR, heart rate; MAP, mean arterial pressure; P-gp, P-glycoprotein; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNPs, single nucleotide polymorphisms.

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