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Original Research

Association between *ABCB1* Gene Polymorphisms and Labor Analgesia in Primiparas

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Abstract

Background: The present study aimed to explore the association of ATP-binding cassette B1 (*ABCB1*)/multiple drug resistance 1 (*MDR1*) gene polymorphisms (rs1128503 and rs1045642) with labor analgesia in primiparas. **Methods**: The cohort comprised 239 primiparas who received epidural analgesia (0.5 µg/L sufentanil + 0.1% ropivacaine). Visual analog scale (VAS) scores were recorded at 0, 1, and 2 h, respectively, after epidural analgesia. The outcomes (VAS score and adverse reactions) of labor analgesia among patients carrying different genotypes of *ABCB1* gene polymorphisms were compared using a one-way analysis of variance (ANOVA) or chi-square test. *ABCB1* polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The correlation between *ABCB1* gene polymorphisms and labor analgesia outcomes (including VAS score and adverse reactions) was evaluated using logistic regression analysis. **Results**: Genotype distributions of rs1128503 and rs1045642 polymorphisms were detected using Hardy-Weinberg equilibrium (HWE) test. Age, body mass index, and gestational age did not differ significantly between genotypes of rs1128503 and rs1045642 polymorphisms. A higher 2 h-VAS score was observed in the rs1045642 TT genotype than in the rs1045642 CC and CT genotypes, while abnormal fetal heart rate (FHR) monitoring and 1 min Apgar scores were frequently discovered in patients with the rs1128503 TT genotype ($p < 0.05$). Logistic regression analysis suggested that 2 h-VAS score ($p = 0.025$, odds ratio (OR) = 0.497, 95% confidence interval (95% CI) = 0.270–0.915), nausea ($p = 0.042$, OR = 0.188, 95% CI = 0.038–0.940) and Apgar score at 1 min ($p = 0.026$, OR = 1.774, 95% CI = 1.069–2.942) were distinctly correlated with the rs1128503 TC + CC genotypes. VAS 2 h score ($p = 0.000$, OR = 3.673, 95% CI = 1.900–7.101) was positively related to the rs1045642 CT + TT genotypes. **Conclusions**: *ABCB1* gene rs1128503 and rs1045642 polymorphisms were significantly correlated with the analgesic effect and adverse reactions of labor analgesia in primiparas.

Keywords: labor analgesia; primiparas; *ABCB1*; polymorphisms

1. Introduction

Labor pain is a common physiological phenomenon during pregnancy and occurs due to uterine contractions. However, it causes tension, anxiety, and weak contractions of puerpera that result in prolonged labor, fetal hypoxemia, acidosis, or fetal distress [1,2]. Labor analgesia has been widely accepted in recent years, with lifestyle improvement. Currently, labor analgesia mainly includes non-drug and drug analgesics [3,4]. Non-drug labor analgesia has no adverse effects on the labor process and fetus, however, the analgesic effect is poor or inaccurate and is adequate only for mild or moderate labor pain. Thus, drug labor analgesics are widely used for labor analgesia [5,6]; especially opioid-based drugs are preferred for peri-and postoperative pain management [7,8]. Sufentanil, a derivative of fentanyl, has a strong analgesic effect and a long analgesic duration. Thus, it is a commonly used drug for drug labor analgesia [9,10].

ATP-binding cassette B1 (*ABCB1*), also known as the *multiple drug resistance 1* (*MDR1*) gene encodes a transporter of the blood-brain barrier (BBB) that participates in opioid tolerance [11,12]. Polymorphisms rs1128503 (1236C>T, p.G412G, exon 12) and rs1045642 (3435C>T, p.I1145I, exon 26) are the most continually studied mutations in different populations [13,14]. The TT genotypes of these two polymorphisms are related to decreased expression of ABCB1 protein, which restricts opioid distribution [12]. The rs1128503 genotype is associated with the analgesic effect and sufentanil dose in lung cancer patients [15]. However, the correlation between *ABCB1* gene polymorphisms and analgesic effect and adverse reactions of labor analgesia in primiparas has not yet been reported.

The present study explored the association of *ABCB1* gene polymorphisms (rs1128503 and rs1045642) with the analgesic effect and adverse reactions of labor analgesia in primiparas.

Table 1. Distributions of primiparas features among *ABCB1* gene rs1128503 genotypes.

Features	Total (n = 239)	TT (n = 121)	TC (n = 93)	CC (n = 25)	*p*
Age (years)	28.36 ± 5.62	28.19 ± 5.41	28.56 ± 5.71	28.44 ± 6.40	0.891
BMI (kg/m^2)	23.25 ± 2.59	23.49 ± 2.56	22.98 ± 2.73	23.08 ± 2.14	0.343
Gestational age (weeks)	39.27 ± 0.64	39.28 ± 0.65	39.28 ± 0.61	39.16 ± 0.75	0.678
VAS score					
0 h	8.80 ± 0.43	8.79 ± 0.42	8.81 ± 0.45	8.80 ± 0.44	0.969
1 h	5.28 ± 0.52	5.31 ± 0.52	5.30 ± 0.51	5.02 ± 0.50	0.035
2 h	4.06 ± 0.47	4.13 ± 0.47	4.08 ± 0.44	3.67 ± 0.38	0.000
Adverse reactions					
Dizziness	13	8	3	2	0.466
Nausea	11	9	1	1	0.088
Urinary retention	10	5	3	2	0.571
Constipation	14	8	4	2	0.690
Pruritus	12	6	3	3	0.204
Abnormal FHR monitoring	7	2	2	3	0.017
Apgar scores at 1 minute	9.38 ± 0.54	9.31 ± 0.52	9.37 ± 0.57	9.76 ± 0.44	0.001

Notes: Continuous variables were described as mean ± standard deviation (SD); BMI, body mass index; VAS, visual analog scale; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity, and respiration score.

2. Materials and Methods

2.1 Information on Patients

A total of 239 primiparas who had a vaginal delivery in The Second Affiliated Hospital of Chengdu Medical College (China National Nuclear Corporation 416 Hospital) from January 2022 to December 2023 were enrolled in this study. Adequate study information was provided to the patients and families before they signed the written informed consent. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Chengdu Medical College (China National Nuclear Corporation 416 Hospital).

2.2 Inclusion and Exclusion Criteria

Patients who fulfilled the following criteria were included in this study: (1) Primiparas who had a vaginal delivery were evaluated by two obstetricians; (2) patients who accepted epidural analgesia by their own volition; (3) the age range was 18–40 years, and body mass index (BMI) was within the normal range (1 ± 20%); (4) full-term singleton pregnancy ≥38 weeks; (5) patients who had normal antenatal examination; (6) patients had no obstetric comorbidities (gestational diabetes mellitus, gestational hypertension, placental abruption and fetal dysplasia).

On the other hand, patients who had any of the following conditions were excluded from this study: (1) American Society of Anesthesiologists (ASA) stage ≥3; (2) age, weight, and gestational age of patients were out of the range mentioned above; (3) prenatal examination revealed heart, lung, liver, kidney, inflammatory diseases and obstetric complications; (4) patients had severe surgical diseases, fetal development problems and fetal distress, head basin misalignment, amniotic fluid contamination, and intrauterine infection; (5) patients had some contraindications associated with intraspinal anesthesia block.

2.3 Management of Labor Analgesia

All the primiparas lay on the left side, and epidural analgesia was administered in the L3–4 lumbar vertebra space. After gentle extraction with a sterile syringe to confirm that there was no blood and cerebrospinal fluid outflow, a test dose of 1% lidocaine was injected in 3 mL volume through an epidural catheter. If there were no complications after 5 min, a 6 mL saline solution (containing 0.5 µg/L sufentanil + 0.1% ropivacaine) was injected. This was marked as the 0-time point. The maintenance phase was sustained using a 100 mL analgesia pump (containing 0.5 µg/L sufentanil + 0.1% ropivacaine) at 4 mL/h via a patient-controlled analgesia mode with the supplemental dose of 6 mL, and 10 min locking time. All patients were administered the same regimen. Visual analog scale (VAS) was recorded at 0, 1, and 2 h, respectively, after sufentanil injection. In addition, adverse reactions after epidural analgesia were recorded by professional nurses.

2.4 Genotyping Method

Before delivery, 2 mL blood samples were collected in the tubes containing ethylene diamine tetraacetic acid (EDTA). Total DNA was extracted from samples using PureLink™ Genomic DNA Extraction Kits (K182002, Invitrogen, Carlsbad, CA, USA).

ABCB1 gene rs1128503 and rs1045642 polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), as described previously, using restriction endonucleases BsuRI (HZ-F681, HZbscience, Shanghai, China) and MboI (hz0811, HZbscience, Shanghai, China) for rs1128503 and

Table 2. Regression analysis of *ABCB1* gene rs1128503 polymorphism with labor analgesia.

Features	Correlation with rs1128503 TC + CC genotypes				
	B	SE	Wald	*p*	OR (95% CI)
Age (years)	0.013	0.025	0.296	0.587	1.013 (0.966–1.063)
BMI (kg/m^2)	–0.051	0.053	0.924	0.336	0.950 (0.856–1.055)
Gestational age (weeks)	–0.158	0.220	0.517	0.472	0.854 (0.555–1.313)
VAS score					
0 h	0.228	0.327	0.487	0.485	1.256 (0.662–2.384)
1 h	–0.191	0.270	0.503	0.478	0.826 (0.487–1.401)
2 h	–0.699	0.311	5.051	0.025	0.497 (0.270–0.915)
Adverse reactions					
Dizziness	–0.287	0.621	0.213	0.644	0.751 (0.222–2.536)
Nausea	–1.671	0.821	4.144	0.042	0.188 (0.038–0.940)
Urinary retention	–0.078	0.698	0.013	0.911	0.925 (0.235–3.634)
Constipation	–0.055	0.613	0.008	0.929	0.947 (0.284–3.150)
Pruritus	–0.276	0.629	0.193	0.661	0.759 (0.221–2.602)
Abnormal FHR monitoring	1.076	0.907	1.406	0.236	2.932 (0.495–17.360)
Apgar scores at 1 minute	0.573	0.258	4.926	0.026	1.774 (1.069–2.942)

Notes: SE, standard error; VAS, visual analog scale; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity, and respiration score; OR, odds ratio; 95% CI, 95% confidence interval.

rs1045642 respectively [16]. PCR and restriction cleavage products were examined using agarose gel electrophoresis.

2.5 Statistical Analysis

The data were analyzed using SPSS 22.0 (IBM Corp., Chicago, IL, USA). The differences in characteristics were analyzed using a one-way analysis of variance (ANOVA) or chi-squared test among patients carrying different genotypes. The correlation between *ABCB1* gene polymorphisms and labor analgesia outcomes (including VAS score and adverse reactions) was evaluated by logistic regression analysis. Gpower 3.1 (http://www.gpower.hhu.de/) was used to calculate the statistical power, with an alpha error of 0.05, with a medium effect size of 0.30; and found the statistic power was 99.80%.

3. Results

3.1 Characteristics of Primiparas

The cohort comprised 239 primiparas. Their mean age was 28.36 $\pm$ 5.62 years, BMI was 23.25 $\pm$ 2.59 kg/m^2, and gestational age was 39.27 $\pm$ 0.64 weeks. The VAS score at 0, 1, and 2 h was 8.80 $\pm$ 0.43, 5.28 $\pm$ 0.52, and 4.06 $\pm$ 0.47, respectively. The adverse events after labor analgesia included dizziness (13/239), nausea (11/239), urinary retention (10/239), constipation (14/239), and pruritus (12/239). Abnormal fetal heart rate (FHR) was discovered in seven primiparas. The Apgar score of newborns at 1 min was 9.38 $\pm$ 0.54 (Table 1). The genotype distributions of rs1128503 and rs1045642 polymorphisms were assessed using the Hardy-Weinberg equilibrium (HWE) test.

3.2 Association of rs1128503 Polymorphism with Labor Analgesia

Age, BMI, gestational age, and 0 h-VAS score did not differ significantly among the rs1128503 genotypes. Conversely, 1 h- and 2 h-VAS scores were significantly lower in primiparas carrying rs1128503 CC genotype than in those with TT and TC genotypes (Table 1, $p < 0.05$). Dizziness, nausea, urinary retention, constipation, pruritus, and abnormal FHR were discovered more frequently in the rs1128503 TT genotype than the other genotype carriers, although the difference was not significant. Apgar score at 1 min was obviously higher in primiparas carrying rs1128503 CC genotype than in those with TC and TT genotypes, as indicated by ANOVA (Table 1, $p < 0.05$).

In order to analyze the association of rs1128503 polymorphism with labor analgesia, primiparas were divided into the rs1128503 TT and rs1128503 TC + CC genotype groups. Logistic regression analysis indicated that 2 h-VAS score ($p = 0.025$, odds ratio (OR) = 0.497, 95% confidence interval (CI) = 0.270–0.915), nausea ($p = 0.042$, OR = 0.188, 95% CI = 0.038–0.940) and Apgar score at 1 min ($p = 0.026$, OR = 1.774, 95% CI = 1.069–2.942) were distinctly correlated with rs1128503 TC + CC genotypes (Table 2). Conversely, rs1128503 TC + CC genotypes had no significant association with other outcomes of labor analgesia.

3.3 Association of rs1045642 Genotype with Labor Analgesia

The 2 h-VAS score was distinctly higher in rs1045642 TT genotype carriers than primiparas with CC genotype and CT genotypes respectively (Table 3, $p < 0.05$). On

Table 3. Distributions of primiparas features among *ABCB1* gene rs1045642 genotypes.

Features	Total (n = 239)	CC (n = 101)	CT (n = 98)	TT (n = 40)	*p*
Age (years)	28.36 ± 5.62	28.46 ± 5.86	28.35 ± 5.74	28.15 ± 6.40	0.958
BMI (kg/m^2)	23.25 ± 2.59	23.30 ± 2.48	23.11 ± 2.82	23.47 ± 2.29	0.741
Gestational age (weeks)	39.27 ± 0.64	39.21 ± 0.64	39.31 ± 0.68	39.33 ± 0.57	0.466
VAS score					
0 h	8.80 ± 0.43	8.79 ± 0.46	8.78 ± 0.44	8.86 ± 0.35	0.633
1 h	5.28 ± 0.52	5.24 ± 0.55	5.26 ± 0.44	5.40 ± 0.60	0.271
2 h	4.06 ± 0.47	3.93 ± 0.38	4.09 ± 0.43	4.32 ± 0.63	0.000
Adverse reactions					
Dizziness	13	5	6	2	0.927
Nausea	11	6	4	1	0.646
Urinary retention	10	3	4	3	0.479
Constipation	14	9	4	1	0.214
Pruritus	12	5	6	1	0.676
Abnormal FHR monitoring	7	3	2	2	0.645
Apgar score at 1 min	9.38 ± 0.54	9.42 ± 0.57	9.37 ± 0.48	9.33 ± 0.62	0.639

Notes: Continuous variables were described as mean ± standard deviation (SD); VAS, visual analog scale; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity, and respiration score.

Table 4. Regression analysis of *ABCB1* gene rs1045642 polymorphism with labor analgesia.

Features	Correlation with rs1045642 CT + TT genotypes				
	B	SE	Wald	*p*	OR (95% CI)
Age (years)	–0.007	0.025	0.076	0.783	0.993 (0.945–1.043)
BMI (kg/m^2)	–0.060	0.055	1.207	0.272	0.941 (0.845–1.048)
Gestational age (weeks)	0.410	0.227	3.249	0.071	1.506 (0.965–2.352)
VAS score					
0 h	–0.040	0.330	0.015	0.904	0.961 (0.503–1.835)
1 h	0.218	0.273	0.633	0.426	1.243 (0.727–2.125)
2 h	1.301	0.336	14.960	0.000	3.673 (1.900–7.101)
Adverse reactions					
Dizziness	0.261	0.623	0.175	0.675	1.298 (0.383–4.401)
Nausea	–0.322	0.668	0.233	0.630	0.724 (0.196–2.684)
Urinary retention	0.581	0.777	0.558	0.455	1.787 (0.389–8.203)
Constipation	–1.144	0.631	3.290	0.070	0.319 (0.093–1.097)
Pruritus	0.240	0.645	0.138	0.710	1.271 (0.359–4.503)
Abnormal FHR monitoring	–0.102	0.863	0.014	0.906	0.903 (0.166–4.907)
Apgar scores at 1 min	–0.273	0.261	1.099	0.295	0.761 (0.457–1.268)

Notes: VAS, visual analog scale; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity, and respiration score; OR, odds ratio; 95% CI, 95% confidence interval.

the other hand, baseline features (age, BMI, and gestational age) and labor analgesia outcomes (0 h-VAS score, 1 h-VAS score, and adverse reactions) showed no diversity among rs1045642 genotypes.

Furthermore, to analyze the association of rs1045642 polymorphism with labor analgesia, primiparas were divided into rs1045642 CC and rs1045642 CT + TT genotype groups. Then, logistic regression analysis suggested that the 2 h-VAS score (p = 0.000, OR = 3.673, 95% CI = 1.900–7.101) was positively correlated with rs1045642 CT + TT genotypes (Table 4).

4. Discussion

All opioid drugs can cause side effects in a puerperant [17,18]. A previous study demonstrated that *ABCB1* is involved in the pharmacokinetics and resistance of different drugs, including opioids [14,19,20]. Opioid exposure results in overexpressed *ABCB1* in the brain [12]. Elevated expression and activity of *ABCB1* at BBB may lead to side effects of the central nervous system drugs [21]. Wang and Sadee [22] demonstrated that rs1128503 and rs1045642 alter the stability and expression level of *ABCB1* mRNA. Polymorphisms in the *ABCB1* gene are correlated with the efficacy, consumption, and toxicity of opioids, such as

methadone [23]. *ABCB1* gene polymorphisms may be associated with the outcomes of sufentanil in labor analgesia via altering the stability and expression level of *ABCB1* mRNA.

The current cohort study recruited 239 primiparas to analyze the association of *ABCB1* gene polymorphisms (rs1128503 and rs1045642) with the analgesic effect and adverse reactions of labor analgesia. All primiparas received the same dose of sufentanil. Consequently, rs1128503 CC genotype carriers had significantly lower 1 h- and 2 h-VAS scores compared to the rs1128503 TT genotype, and adverse reactions were discovered more frequently in the rs1128503 TT genotype carriers, while the Apgar score at 1 min was significantly higher in rs1128503 CC genotype carriers. These results demonstrated that rs1128503 CC genotype carriers had better labor analgesic effects and fewer adverse reactions than rs1128503 TT genotype. However, logistic regression analysis indicated that rs1128503 TC + CC genotypes were negatively related to the 2 h-VAS score and nausea, and positively correlated with Apgar score at 1 min. The present results were following the previous findings conducted in a study with post-caesarean analgesia. Zhang *et al*. [24] showed that Chinese women who adopted post-caesarean fentanyl analgesia with the rs1128503 TT genotype had significantly higher fentanyl dosage than those with CC and CT genotypes. The current results also conformed with other studies focused on cancer patients. Zhao *et al*. [25] found that Chinese patients with lung cancer (who underwent curative resection) carrying the rs1128503 TT genotype had a significantly higher dose of sufentanil than the CC genotype. On the other hand, cancer patients carrying the rs1128503 TT genotype showed decreased fentanyl consumption than the rs1128503 C allele carriers. However, pharmacokinetics and adverse effects of fentanyl did not differ markedly between rs1128503 genotypes [26]. Based on these findings, we speculated that the rs1128503 TT genotype needed a high drug dosage to achieve the same analgesic effects or exhibited worse analgesic effects when obtaining the same drug dosage. Additionally, the association of rs1128503 polymorphism with analgesic effects and adverse reactions was affected by disease type and opioid drugs.

The 2 h-VAS score was distinctly lower in rs1045642 TT and CT genotype carriers compared to primiparas carrying the CC genotype, respectively, whereas the 0 h- and 1 h- VAS scores, adverse reactions, and Apgar score at 1 min among rs1045642 genotypes did not differ significantly. Logistic regression analysis revealed that the 2 h-VAS score was positively correlated with rs1045642 CT + TT genotypes compared to the rs1045642 CC genotype. Zhao *et al*. [25] showed that there was no marked diversity in adverse reactions between rs1045642 genotypes in lung cancer patients who underwent radical resection. In addition, rs1045642 genotypes had no obvious impact on sufentanil doses and VAS scores of lung cancer patients. Also, plasma concentration and adverse effects of fentanyl did not differ markedly between rs1045642 genotypes. Fentanyl consumption was slightly lower in Japanese cancer patients who carried the rs1045642 CC genotype; however, the difference was not significant [26]. Gong *et al*. [27] demonstrated that cancer patients with rs1045642 TT genotype received lower opioid dosage than those with C allele carriers, although the difference was not significant. Together, these results demonstrated that the rs1045642 genotype had no obvious effects on adverse reactions to sufentanil in different diseases. Recent evidence shows increased rates of intrapartum compromise in fetuses of mothers undergoing epidural, particularly when the fetal weight is reduced (i.e., below the 10 centiles) as a proxy of placental dysfunction [28,29]. These findings suggested that the analgesia effect regulated genetically is interested in the mechanism of intrapartum compromise.

Nevertheless, the current study has some limitations. First, *ABCB1* gene rs1128503 and rs1045642 polymorphisms did not alter the amino acids, and the mechanism of these polymorphisms underlying labor analgesia was not explored. Second, this study was conducted on only one population, which might limit the generalizability of the results to other populations. Third, the current study did not explore the effects of rs1128503 and rs1045642 polymorphisms for the dosage of sufentanil during labor analgesia and their association with other drugs. Fourth, other polymorphisms in the *ABCB1* gene or other genes involved in drug metabolism were not explored concerning the association of analgesic effects and adverse reactions of sufentanil. Finally, the relationship between *ABCB1* gene polymorphisms and other drugs for labor analgesia was not explored. Moreover, although the statistical power was 99.80%, larger sample sizes could enhance the reliability of the findings. Therefore, additional studies across multiple centers, using large sample sizes, and several analgesic drugs should be performed to substantiate the association of *ABCB1* gene polymorphisms with labor analgesia.

5. Conclusions

In conclusion, *ABCB1* gene rs1128503 and rs1045642 polymorphisms are significantly correlated with the analgesic effect and adverse reactions of labor analgesia in primiparas. Taken together, the current results open a novel direction to explore the individual dosages of sufentanil during labor analgesia.

Abbreviations

ABCB1, ATP-binding cassette B1; *MDR1*, multiple drug resistance 1; VAS, visual analog scale; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HWE, hardy-weinberg equilibrium; BMI, body mass index; BBB, blood-brain barrier; VAS, visual analog scale; AGE, agarose gel electrophoresis; ANOVA, analysis of variance; FHR, fetal heart rate.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Author Contributions

WL, TKX, and JYW designed the research study. XHW, XYW, RX, and HFL performed the research and analyzed the data. WL and TKX wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Study information was noticed by the patients and families. They signed the written informed consent. Ethic committee of The Second Affiliated Hospital of Chengdu Medical College (China National Nuclear Corporation 416 Hospital) (No.20210006) approved this study.

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Conflict of Interest

The authors declare no conflict of interest.

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