Tohoku J. Exp. Med., 2025, **266**, 257-264

Effects of Neurotrophic Tyrosine Kinase Receptor Type I NTRK1 Polymorphism on Epidural Analgesia with Hydromorphone during Labor

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Epidural labor analgesia is a widely employed method of analgesia in current clinical practice. This study aimed to investigate the relationship between *NTRK1* gene polymorphism and epidural labor analgesia, offering a novel perspective for labor analgesia related research. Epidural labor analgesia was administered with hydromorphone in 208 eligible pregnant women. Genomic DNA was extracted from EDTA anticoagulant blood samples. The *NTRK1* single nucleotide polymorphisms (SNPs) rs1800880 (T > C) and rs6334 (G > A) were genotyped utilizing PCR-RFLP. Parameters such as the 24 h visual analogue score (VAS), modified Bromage score, 48 h patient controlled intravenous analgesia (PCIA) compression counts, dosage of anesthetic, adverse reactions were meticulously recorded. The immune functions were assessed by flow cytometry, and oxidative stress levels were measured by radioimmunoassay. The findings indicated that *NTRK1* rs1800880 T > C and rs6334 G > A were similar, 24 h VAS score and anesthetic dosage were decreased. rs1800880 C allele was no significant difference in adverse reactions, but the level of oxidative stress was significantly reduced. The nausea and emesis response of rs6334 mutant AA was significantly reduced. Both rs1800880 TC + CC vs. TT and rs6334 GA + AA vs. GG showed significant effects on 24 h VAS score. Mutations in rs1800880 and rs6334 reduce postoperative pain, adverse reactions, and oxidative stress responses. The *NTRK1* SNP may play an important role in labor analgesia and may be an effective predictor of individual pain perception, thereby providing patients with a more personalized approach to labor analgesia.

Keywords: epidural analgesia; *NTRK1*; SNP
Tohoku J. Exp. Med., 2025 July, **266** (3), 257-264.
doi: 10.1620/tjem.2024.J135

Introduction

Delivery is a normal physiological process in the last stage of a woman's pregnancy. The pain during labor is severe and long-lasting, especially for first-time mothers (Whitburn et al. 2017). This discomfort is mainly caused by increased contractions of the uterus, which causes the uterine muscles to be starved of oxygen and the opening of the cervix and the lower portion of the uterus to dilate (Kovavisarach 2004). Consequently, the clinical administration of labor analgesia is very necessary. Labor analgesia alleviates maternal pain and thus reduces the proportion of caesarean sections (Sitras et al. 2017). At present, epidural analgesia is a common method of labor analgesia in China and internationally (Braga et al. 2019). This technique has the advantages of good analgesic effect, light movement block, and no inhibition on the central nervous system (Halliday et al. 2022). Hydromorphone is a commonly used opioid analgesic drug, which has the characteristics of fast onset, high safety, and effective analgesic properties (Cao et al. 2024).

The *NTRK1* gene, also referred to as TRKA, located in the q21-22 region of chromosome 1, encodes a type I neurotrophic receptor tyrosine kinase (RTK) (Greco et al. 1993; Weier et al. 1995). Among the many pain-related genes, *NTRK1* stands out as one of the few genes that are tightly linked to nociceptors at the beginning of their differentiation. In the embryo, the tyrosine kinase receptor encoded by the *NTRK1* gene mediates neuronal survival, development, and differentiation by binding to nerve growth factor (NGF) (Mizumura and Murase 2015). A notable condition associated with the *NTRK1* gene is Congenital Insensitivity

Received August 1, 2024; revised and accepted November 6, 2024; J-STAGE Advance online publication November 21, 2024
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to Pain with Anhidrosis (CIPA), which stems from a biallelic mutation in this gene (Geng et al. 2018). The Gly571Arg mutation is associated with CIPA and results in the inactivation of the *NTRK1* nerve growth factor receptor (Greco et al. 2000). Single nucleotide polymorphisms (SNP) with *NTRK1* related to disease aspects have also been widely reported. One relevant SNP, H604Y, was significantly associated with postoperative motor pain, and the motor pain scores of patients with CT and TT genotypes were significantly higher than those of patients with CC genotypes (Mamie et al. 2013). In the study of *NTRK1* polymorphism and pain perception, four SNPS rs1800880, rs6334, rs2644604 and rs943552 were found to be associated with pain (Li et al. 2018). The thymine on the tyrosine kinase domain of SNP rs1800880 is replaced by cytosine. SNP rs6334 is located on exon 14 of *NTRK1* gene, resulting in the substitution of guanine for adenine on the structural domain of the tyrosine kinase (Lipska et al. 2009). At present, research on the implications of rs6334 in pain is limited, but some studies have shown that it has a certain effect on various diseases. For example, rs6334 is strongly associated with the development of asthma, with elevated plasma levels of NGF are significantly upregulated in asthmatic children, indicative of a promoting role in the condition (Szczepankiewicz et al. 2013). Notably, the role of *NTRK1* SNPs in labor analgesia remains an area yet to be thoroughly investigated.

NTRK1 is an indispensable research object for pain research. The relationship between polymorphisms in the *NTRK1* gene and labor analgesia remains unexplored. In this study, *NTRK1* rs1800880 (T > C) and rs6334 (G > A) genotypes on influence of postoperative indicators and clinical risk assessment were studied. The purpose of this study was to conduct a comprehensive analysis of the association between SNPs in the *NTRK1* gene and epidural analgesia during labor, thereby offering a novel perspective for future research on labor analgesia.

Materials and Methods

Study population

A total of 208 parturient admitted to Central People's Hospital of Zhanjiang from October 2022 to July 2023 were retrospectively enrolled in the study. The inclusion criteria consisted of individuals classified as American Society of Anesthesiologists physical status II-III, within the gestational period of 37-42 weeks gestation, aged between 22 and 45 years, and possessing no contraindications to epidural anesthesia. Conversely, the exclusion criteria encompassed a history of opioid intolerance or adverse reactions, contraindications to spinal anesthesia, coagulation dysfunction, history of painkillers, alcohol, and other addictive substances, mental or nervous disorders in the first two weeks, as well as any skin infection at the site to be punctured.

This study was approved by the Ethics Committee of Central People's Hospital of Zhanjiang and adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Analgesia methods

The woman is lying on her left side, and the anesthesiologist performed epidural puncture at the L2-L3 interspace. After confirming successful puncture, a 4-5 cm of catheter was introduced at the head end. 3 ml of 1.5% lidocaine (SFDA approval no. H33021639, Zhejiang Taikang Pharmaceutical Group Co. Ltd., China) was injected through an epidural catheter as a test dose. Observation for 5 min without subarachnoid block and signs of local anesthetic toxicity confirms that the catheter is in the epidural space. Hydromorphone hydrochloride injection (SFDA approval no. H20217021; Yichang Renfu Pharmaceuticals Co., Ltd., China) 20 μg/ml + 0.1% ropivacaine hydrochloride injection (SFDA approval no. H20020248; AstraZeneca AB, Britain) mixture 8 ml was given as the initial dose. The total amount of drug in the analgesic pump was 100 mL in all cases, with no background dose. Patient controlled intravenous analgesia (PCIA) is initiated, allowing for 10 mL per administration, with a locking time of 30 minutes, and analgesia continued until 1 h after delivery.

Genotyping

SNPs of *NTRK1* were selected based on the phase 3 data of the HapMap CHB reference population database. The labels SNPs were then selected from them using Haploview 4.2 software (Broad Institute, Cambridge, MA, USA). Only SNPs with minor allele frequencies > 5% were obtained and the limit of paired r^2 was set to ≥ 0.8. Finally, 2 reliable SNPs were selected for analysis. Genomic DNA was extracted from EDTA anticoagulated blood samples. Two SNPs were genotyped using PCR-RFLP.

Observe and detect indicators

Postoperative analgesia was evaluated using a 24 h visual analogue scale (VAS). Maternal motor nerve block was assessed using a modified Bromage score (0 = no motor nerve block; 1 = unable to lift leg but knee-ankle mobile; 2 = unable to bend knee but ankle mobile; 3 = unable to bend ankle). 48 h PCIA was monitored through compression counts to evaluate the total analgesic drug dosage administered over this period. Dizziness, nausea and emesis, urinary retention, constipation, pruritus, shiver, abnormal fetal heart rate (FHR) monitoring, and Apgar (appearance, pulse, grimace, activity and respiration) scores at 1 min after birth were recorded. Moreover, immune function, including CD3+, CD4+, CD8+, and CD4+ / CD8+ were measured by flow cytometry. The oxidative stress levels including pulse oxygen saturation (SpO2), reactive oxygen species (ROS), reactive nitrogen species (RNS), catalase (CAT), and glutathione peroxidase (GSH-Px) were assessed by radioimmunoassay.

Statistical analysis

SPSS 27.0 statistical software was used for data analysis. The Hardy-Weinberg equilibrium law tests the group representation of a sample. Normally distributed measurements are expressed as mean ± standard deviation, and comparisons between the two groups were made using one-way ANOVA. The association between SNP and labor analgesia was assessed using calculated odd ratios (OR) and 95% confidence intervals (95% CI). Differences were considered statistically significant at $P < 0.05$.

Results

Relationship between characteristics of primipara and rs1800880 genotype of NTRK1 gene

The genotypes of *NTRK1* rs1800880 were performed on 208 maternal, who were divided into TT, TC, and CC genotypes (54, 103, and 51, respectively). All genotypes were in accordance with Hardy-Weinberg equilibrium ($P > 0.05$). Comparisons of basic maternal age, MBI, and weeks of gestation among the three genotypes showed no statistically significant differences ($P > 0.05$). 24 h VAS score of pure sum mutant CC and heterozygous TC were signifi-

Table 1. Distributions of primiparas features among *NTRK1* gene rs1800880 genotypes.

Features	Total (208)	TT (n=54)	TC (n=103)	CC (n=51)	*P*
Age (years)	31.889 ± 4.245	31.370 ± 4.217	32.146 ± 3.917	31.922 ± 4.902	0.555
BMI (kg/m^2)	26.546 ± 2.729	26.195 ± 2.428	26.636 ± 2.951	26.737 ± 2.577	0.537
Gestational age (weeks)	39.293 ± 1.043	39.352 ± 1.049	39.320 ± 1.050	39.177 ± 1.034	0.646
24h VAS score	4.053 ± 0.494	4.259 ± 0.556	4.049 ± 0.405	3.843 ± 0.505	0.000
24h Modified Bromage scale					0.395
0	202	51	101	50	
1	6	3	2	1	
48h PCIA count	6.053 ± 1.240	6.185 ± 1.415	6.049 ± 1.224	5.922 ± 1.074	0.555
Dosage of hydromorphone (mg)	1.035 ± 0.574	1.314 ± 0.630	1.025 ± 0.534	0.761 ± 0.448	0.000
Dosage of ropivacaine (mg)	60.009 ± 17.118	65.813 ± 16.932	59.860 ± 17.105	54.166 ± 15.529	0.002
Delivery mode					0.198
Natural labor	198	50	100	48	
Cesarean delivery	10	4	3	3	
Adverse reactions					
Dizziness	9	5	3	1	0.113
Nausea and emesis	38	15	13	10	0.063
Urinary retention	11	6	3	2	0.082
Constipation	9	4	3	2	0.416
Pruritus	6	3	2	1	0.395
Shiver	10	5	3	2	0.198
Abnormal FHR monitoring	10	5	3	2	0.198
Apgar scores at 1 minute	9.688 ± 0.532	9.648 ± 0.677	9.699 ± 0.482	9.706 ± 0.460	0.819
Immune function					
CD3+	60.780 ± 5.211	60.113 ± 5.069	60.644 ± 5.302	61.762 ± 5.133	0.252
CD4+	36.706 ± 3.663	35.832 ± 3.358	36.696 ± 3.675	37.650 ± 3.782	0.039
CD8+	29.470 ± 3.603	30.099 ± 3.458	29.395 ± 3.712	28.955 ± 3.498	0.256
CD4+/CD8+	1.228 ± 0.304	1.187 ± 0.260	1.233 ± 0.312	1.260 ± 0.332	0.456
Oxidative stress					
SpO_2 (U/L)	98.582 ± 0.903	98.167 ± 0.795	98.563 ± 0.825	99.059 ± 0.947	0.000
ROS (U/L)	8.317 ± 1.074	8.648 ± 1.164	8.199 ± 1.036	8.204 ± 0.994	0.030
RNS (U/L)	1.254 ± 0.214	1.300 ± 0.219	1.263 ± 0.201	1.185 ± 0.223	0.018
CAT (U/L)	23.649 ± 3.291	23.797 ± 3.543	23.768 ± 3.199	23.253 ± 3.232	0.614
GSH-Px (U/L)	42.073 ± 4.172	42.688 ± 4.515	42.016 ± 4.044	41.535 ± 4.048	0.362

BMI, body mass index; VAS, visual analogue scale; PCIA, patient controlled intravenous analgesia; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity and respiration score; SpO2, transcutaneous oxygen saturation; ROS, reactive oxygen species; RNS, reactive nitrogen species; CAT, catalase; GSH-Px, glutathione peroxidase.

Table 2. Regression analysis of *NTRK1* gene rs1800880 polymorphism with labor analgesia under TC+CC vs. TT model.

Features	B	*P*	OR (95%CI)
Age (years)	−0.339	0.394	0.713 (0.327-1.553)
BMI (kg/m^2)	0.103	0.793	1.108 (0.514-2.391)
Gestational age (weeks)	−0.074	0.860	0.929 (0.409-2.110)
24h VAS score	−2.367	0.000	0.094 (0.028-0.315)
24h Modified Bromage scale	−1.085	0.192	0.338 (0.066-1.726)
48h PCIA count	0.153	0.722	1.165 (0.502-2.701)
Dosage of hydromorphone (mg)	−0.592	0.154	0.553 (0.245-1.249)
Dosage of ropivacaine (mg)	−0.694	0.089	0.500 (0.225-1.111)
Delivery mode	−0.532	0.457	0.588 (0.145-2.386)
Dizziness	−0.462	0.579	0.630 (0.124-3.213)
Nausea and emesis	−0.464	0.276	0.629 (0.273-1.449)
Urinary retention	−0.908	0.222	0.403 (0.094-1.733)
Constipation	−0.475	0.542	0.622 (0.135-2.870)
Pruritus	−0.769	0.400	0.464 (0.078-2.773)
Shiver	−0.305	0.708	0.737 (0.150-3.629)
Abnormal FHR monitoring	−0.532	0.457	0.588 (0.145-2.386)
Apgar scores at 1 minute	−1.080	0.041	0.339 (0.120-0.957)
CD3+	0.190	0.641	1.209 (0.544-2.689)
CD4+	0.586	0.208	1.797 (0.722-4.477)
CD8+	−1.131	0.073	0.323 (0.094-1.109)
CD4+/CD8+	−0.559	0.410	0.572 (0.151-2.165)
SpO_2 (U/L)	1.255	0.005	3.506 (1.455-8.451)
ROS (U/L)	−0.370	0.387	0.691 (0.299-1.598)
RNS (U/L)	−0.124	0.748	0.883 (0.414-1.886)
CAT (U/L)	0.073	0.859	1.076 (0.480-2.414)
GSH-Px (U/L)	0.379	0.354	1.461 (0.655-3.259)

B, regression coefficient; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; VAS, visual analogue scale; PCIA, patient controlled intravenous analgesia; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity and respiration score; SpO2, transcutaneous oxygen saturation; ROS, reactive oxygen species; RNS, reactive nitrogen species; CAT, catalase; GSH-Px, glutathione peroxidase.

cantly lower than those of wild-type TT ($P < 0.001$). Genotype CC had the fewest number of primiparas with modified Bromage scale of 1, but there was no significant difference ($P > 0.05$). The dosage of self-administration in pregnant women with C allele was significantly lower than that of wild-type TT (dosage of hydromorphone $P < 0.001$, dosage of ropivacaine $P = 0.002$). Compared with parturients with wild-type TT, parturients with genotypes CC and TC produced fewer postoperative adverse reactions, but did not show a statistical difference ($P > 0.05$). Immune function and oxidative stress levels were measured 24 h after surgery. As shown in Table 1, CD4+ level of the C allele was significantly higher than genotype TT ($P = 0.039$). The SpO_2 level of genotype CC (99.059 ± 0.947 U/L) was significantly higher than that of TT (98.167 ± 0.795 U/L), and the levels of ROS and RNS in C allele were significantly lower than those of wild-type TT, with a difference was statistically significant ($P < 0.05$, Table 1).

Analysis of the association between rs1800880 polymorphism in NTRK1 gene and labor analgesia

Logistic regression analysis was conducted to explore the relationship between rs1800880 polymorphism of *NTRK1* gene and labor analgesia, specifically comparing the TC + CC genotype to the TT genotype. It was found that TC + CC vs. TT had a great effect with hydromorphone epidural labor analgesia in 24 h VAS score ($P < 0.001$), Apgar scores at 1 minute after birth ($P = 0.041$), and the oxidative stress index SpO_2 ($P = 0.005$). These findings indicate significant differences, while other indicators had little effect ($P > 0.05$, Table 2).

Relationship between characteristics of primipara and rs6334 genotype of NTRK1 gene

The genotypes of *NTRK1* rs6334 locus among of 208 primiparas were analyzed and divided into GG, GA, and AA genotypes (85, 102, and 21, respectively). Genotypes were in accordance with Hardy-Weinberg equilibrium ($P > 0.05$). There were no significant differences in age, MBI,

Table 3. Distributions of primiparas features among *NTRK1* gene rs6334 genotypes.

Features	Total (n=208)	GG (n=85)	GA (n=102)	AA (n=21)	*P*
Age (years)	31.889 ± 4.245	31.965 ± 4.327	31.745 ± 4.214	32.286 ± 4.233	0.850
BMI (kg/m^2)	26.546 ± 2.729	26.524 ± 2.513	26.646 ± 2.861	26.152 ± 3.000	0.750
Gestational age (weeks)	39.293 ± 1.043	39.365 ± 1.122	39.265 ± 0.984	39.143 ± 1.014	0.636
24h VAS score	4.053 ± 0.494	4.165 ± 0.553	4.069 ± 0.352	3.524 ± 0.512	0.000
24h Modified Bromage scale					0.269
0	202	81	101	20	
1	6	4	1	1	
48h PCIA count	6.053 ± 1.240	6.000 ± 1.380	6.128 ± 1.123	5.905 ± 1.221	0.665
Dosage of hydromorphone (mg)	1.035 ± 0.574	1.111 ± 0.617	1.050 ± 0.531	0.658 ± 0.457	0.004
Dosage of ropivacaine (mg)	60.009 ± 17.118	61.035 ± 16.864	60.337 ± 17.170	54.265 ± 17.603	0.259
Delivery mode					0.366
Natural labor	198	80	99	19	
Cesarean delivery	10	5	3	2	
Adverse reactions					
Dizziness	9	7	1	1	0.052
Nausea and emesis	38	23	11	4	0.016
Urinary retention	11	6	4	1	0.630
Constipation	9	5	3	1	0.613
Pruritus	6	4	1	1	0.274
Shiver	10	7	2	1	0.136
Abnormal FHR monitoring	10	6	3	1	0.424
Apgar scores at 1 minute	9.688 ± 0.532	9.600 ± 0.621	9.755 ± 0.455	9.714 ± 0.463	0.136
Immune function					
CD3+	60.780 ± 5.211	60.531 ± 5.250	60.784 ± 5.286	61.768 ± 4.786	0.625
CD4+	36.706 ± 3.663	36.859 ± 3.998	36.739 ± 3.315	35.921 ± 3.932	0.573
CD8+	29.470 ± 3.603	29.344 ± 3.531	29.535 ± 3.434	29.660 ± 4.719	0.908
CD4+/CD8+	1.228 ± 0.304	1.199 ± 0.372	1.264 ± 0.217	1.167 ± 0.354	0.216
Oxidative stress					
SpO_2	98.582 ± 0.903	98.553 ± 0.932	98.549 ± 0.863	98.857 ± 0.964	0.339
ROS	8.317 ± 1.074	8.383 ± 1.224	8.266 ± 0.950	8.294 ± 1.027	0.758
RNS	1.254 ± 0.214	1.225 ± 0.233	1.283 ± 0.193	1.225 ± 0.225	0.145
CAT	23.649 ± 3.291	23.936 ± 3.602	23.518 ± 2.853	23.123 ± 3.972	0.514
GSH-Px	42.073 ± 4.172	41.762 ± 4.168	42.180 ± 3.932	42.805 ± 5.301	0.555

BMI, body mass index; VAS, visual analogue scale; PCIA, patient controlled intravenous analgesia; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity and respiration score; SpO2, transcutaneous oxygen saturation; ROS, reactive oxygen species; RNS, reactive nitrogen species; CAT, catalase; GSH-Px, glutathione peroxidase.

and gestational weeks ($P > 0.05$). Wild-type GG had the highest 24 h VAS score compared with heterozygote GA and pure sum mutant AA, and the difference was statistically significant ($P < 0.001$). Furthermore, genotype AA also had the lowest 24-h modified Bromage scale, 48-h PCIA count, and anesthesia dose. Postoperative adverse reactions were reduced in primiparas with the A allele compared to those with the wild-type GG. There was a significant difference in nausea and emesis (GG = 23, GA = 11, AA = 4, $P = 0.016$). Genotypes AA and GA did not differ significantly in immune function and oxidative stress levels compared to genotype GG ($P > 0.05$, Table 3).

Analysis of the association between rs6334 polymorphism in NTRK1 gene and labor analgesia

Logistic regression analysis was conducted to explore the relationship between rs6334 polymorphism of *NTRK1* gene and labor analgesia in GA + AA and GG models. We found that parturients with GA + AA showed a significant difference in 24 h VAS score ($P < 0.001$) when compared to those with GG. However, no significant differences were observed in other indicators ($P > 0.05$, Table 4).

Discussion

The clinical research of labor analgesia holds significant importance. In this study, polymorphisms in the pain-related gene *NTRK1* were investigated. The effect of differ-

Table 4. Regression analysis of *NTRK1* gene rs6334 polymorphism with labor analgesia under GA+AA vs. GG model.

Features	B	*P*	OR (95%CI)
Age (years)	−0.173	0.591	0.841 (0.448-1.580)
BMI (kg/m^2)	0.145	0.652	1.156 (0.615-2.172)
Gestational age (weeks)	−0.520	0.124	0.594 (0.306-1.154)
24h VAS score	−1.025	0.035	0.359 (0.139-0.930)
24h Modified Bromage scale	−0.719	0.473	0.778 (0.201-3.009)
48h PCIA count	0.369	0.288	1.446 (0.732-2.856)
Dosage of hydromorphone (mg)	−0.335	0.311	0.715 (0.375-1.367)
Dosage of ropivacaine (mg)	−0.031	0.925	0.969 (0.505-1.860)
Delivery mode	−0.251	0.716	0.778 (0.201-3.009)
Dizziness	−1.129	0.208	0.323 (0.056-1.874)
Nausea and emesis	−0.689	0.085	0.502 (0.229-1.100)
Urinary retention	0.274	0.728	1.315 (0.282-6.136)
Constipation	0.207	0.801	1.230 (0.246-6.141)
Pruritus	−0.369	0.721	0.691 (0.091-5.231)
Shiver	−1.044	0.218	0.352 (0.067-1.850)
Abnormal FHR monitoring	−0.313	0.737	0.731 (0.118-4.546)
Apgar scores at 1 minute	0.072	0.848	1.074 (0.516-2.238)
CD3+	−0.135	0.682	0.874 (0.457-1.668)
CD4+	0.050	0.895	1.051 (0.501-2.204)
CD8+	−0.019	0.967	0.981 (0.401-2.405)
CD4+/CD8+	−0.190	0.704	0.827 (0.311-2.199)
SpO_2 (U/L)	0.159	0.635	1.172 (0.609-2.256)
ROS (U/L)	0.075	0.826	1.078 (0.552-2.104)
RNS (U/L)	0.199	0.529	1.221 (0.657-2.269)
CAT (U/L)	−0.076	0.819	0.926 (0.482-1.779)
GSH-Px (U/L)	0.448	0.175	1.565 (0.819-2.994)

B, regression coefficient; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; VAS, visual analogue scale; PCIA, patient controlled intravenous analgesia; FHR, fetal heart rate; Apgar score, appearance, pulse, grimace, activity and respiration score; SpO2, transcutaneous oxygen saturation; ROS, reactive oxygen species; RNS, reactive nitrogen species; CAT, catalase; GSH-Px, glutathione peroxidase.

ent mutant types of *NTRK1* polymorphisms rs1800880 and rs6334 on hydromorphone epidural labor analgesia were analyzed by experimental pain test and related indexes detection. This is the first study to investigate the possible association between labor analgesia and *NTRK1* gene polymorphism.

Genetic polymorphisms have a large impact on the therapeutic efficacy of opioids for analgesia during surgery. A study examining the impact of the rs1799971 polymorphism in the *OPRM1* gene on the efficacy of opioid medication revealed that patients with mutant alleles A > G had a significantly increased need for sufentanil in patients receiving postoperative epidural analgesia (Zhao et al. 2019). Analysis of the *ABCB1* gene revealed a correlation between the SNP locus C3435T and the effect of fentanyl on postoperative intravenous analgesia, with a significant increase in the dosage of fentanyl at 24 h postoperatively in patients with genotype CC compared to those with genotypes CT and TT (Dzambazovska-Trajkovska et al. 2016). A synonymous G-A mutation in the exon 10 region of the *CYP3A4*1G* allele has been shown to cause alterations in CYP3A4 enzyme activity, leading to differences in drug metabolism and drug efficacy between patients (Yan et al. 2018). For our study population there were no individual differences in age, BMI, and gestational age. *NTRK1* rs1800880 T > C showed significant differences in 24 h VSA scores, with the T > C variant indicating that 24 h postoperative analgesia performed best for genotype CC. There were also significant differences in the dosages for hydromorphone and ropivacaine, with significantly lower dosages for the CC genotype. The same study found that the glutamine to histidine mutant rs6334 G > A showed a significant difference in 24 h VSA scores, with a decrease in G > A scores, suggesting that mutant A showed better analgesia. The mutation had a significant effect on hydromorphone dosage among the AA genotype. This is similar to the findings that rs6334 G > A had a significant effect on sharp pressure pain tolerance, increasing pain thresholds (Li et al. 2018).

While opioids are effective in reducing pain, they are

often accompanied by side effects such as itching, nausea, and respiratory depression (Valentino and Volkow 2018). One study showed that injectable morphine caused nausea in up to 52% of cases, with the incidence of nausea or vomiting escalating in correlation with increasing doses (Sharpe et al. 2020). Our study found that pregnant women with *NTRK1* rs1800880 the C allele had reduced postoperative adverse reactions than wild-type TT. Notably, rs6334 genotype AA had the fewest nausea and emesis. These findings indicate that rs1800880 T > C and rs6334 G > A may contribute to alleviating the pain of labor and reduce the dosage of anesthesia and postoperative adverse reactions.

CD3+, CD4+, CD8+, CD4+/CD8+ are important indexes reflecting the immune function, which can be suppressed to a certain extent after surgery-induced injury to the organism, and the stronger trauma stimulation, the more serious immunosuppression (Wu et al. 2022). In this study, only CD4+ of rs1800880 T > C showed significant difference, while other indicators, including rs6334's, were not statistically different in the analysis of immune function. This suggests that *NTRK1* polymorphisms may have little effect on immune function in labor analgesia. Oxidative stress is a negative effect produced in the body by free radicals, which is often considered a major contributor to disease (Forman and Zhang 2021). The levels of ROS and RNS were progressively and significantly lower in rs1800880 T > C, whereas there was no statistically significant difference in rs6334 G > A. These results revealed that rs1800880 T > C may reduce the level of oxidative stress during labor analgesia. The sample size of the above statistical results is small and needs to be expanded for further research verification.

Although rs1800880 is an intronic variant that is excised during transcription and is not directly involved in protein synthesis, it may affect subsequent mRNA transcription and expression, thereby impacting disease outcomes (Chorev and Carmel 2012; Bouyer et al. 2014). Analysis of genome-wide association studies of susceptibility loci associated with diseases or traits found that the vast majority of loci were located in non-coding regions, with only 7% located in coding regions (Hindorff et al. 2009; Pennisi 2011). This suggests that rs1800880 may play an important role in the effects on hydromorphone epidural labor analgesia. The study of *NTRK1* in labor analgesia is still in its infancy, and its specific molecular mechanism needs to be further studied. The validity of the application of *NTRK1* polymorphisms still needs to be verified by a large number of experiments.

This study demonstrates the effect of *NTRK1* polymorphisms on hydromorphone labor analgesia. Mutations in rs1800880 and rs6334 reduce postoperative pain, adverse reactions and oxidative stress responses. These findings indicate that *NTRK1* SNPs may play an important role in labor analgesia and may be an effective predictor of individual pain perception, thus providing patients with a more personalized approach to labor analgesia.

Conflict of Interest

The authors declare no conflict of interest.

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