Effects of OPRM1 A118G Polymorphism on Epidural Analgesia with Fentanyl During Labor: A Meta-Analysis

Zheming Song,1,* Boxiang Du,1,* Kai Wang,2 and Xueyin Shi1

Background: Emerging evidence has shown that the most common polymorphism (A118G; rs1799971 A > G) in the \( \mu \)-opioid receptor (OPRM1) gene may influence the response to labor analgesia, but individually published studies showed inconclusive results. Objective: This meta-analysis aimed to derive a more precise estimation of the effects of the OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor. Methods: A literature search was conducted on PubMed, Embase, Web of Science, and China BioMedicine databases before April 1st, 2013. The crude standardized mean difference (SMD) or odds ratio (OR) with 95% confidence interval (CI) was calculated. Results: Six clinical studies were included with a total 838 women who received epidural analgesia with fentanyl during labor. The meta-analysis results indicated that women carrying the G allele (AG + GG) of the OPRM1 A118G polymorphism required less fentanyl doses to achieve adequate pain relief compared with those with the AA homozygote (SMD = -0.24, 95% CI [-0.44, -0.03], \( p = 0.022 \)). The 118G variant was associated with a decreased ED50 of fentanyl for labor analgesia (SMD = -1.56, 95% CI [-1.97, -1.15], \( p < 0.001 \)). The analgesia satisfaction in women carrying the G allele (AG + GG) was higher than those with the AA homozygote (SMD = 0.22, 95% CI [0.05, 0.39], \( p = 0.012 \)). However, there were no statistically significant differences between an AA homozygote and a G carrier (AG + GG) in the incidence of nausea and vomiting (OR = 1.99, 95% CI [0.88, 4.52], \( p = 0.101 \)). Conclusion: In conclusion, the current meta-analysis indicates that women carrying the G allele (AG + GG) of OPRM1 A118G polymorphism may have a good response to epidural analgesia with fentanyl during labor. The OPRM1 A118G polymorphism may help predict individuals’ response to epidural labor analgesia and so optimize postoperative pain control.

Introduction

Labor pain has been described as one of the most intense pains that a woman can experience in her lifetime (Lowe, 2002). Pain intensity and analgesic requests during labor and delivery are variable and unpredictable (Gambling et al., 2013), however, multiple factors have an impact on labor pain sensitivity, such as age, ethnicity, anxiety, type of labor and delivery, and preoperative pain (Orejuela et al., 2012). Although some women want to undergo labor without pain medications, most women receive epidural analgesia, which provides relatively consistent pain relief for labor analgesia (Agaram et al., 2009). Nowadays, epidural opioids, including morphine, meperidine, sufentanil, and fentanyl, have become increasingly popular as an option for labor analgesia (Hawkins, 2010). However, a large interindividual variability has been observed in analgesic efficacy, incidence and severity of side effects, and tolerance profiles (Bauchat et al., 2012). Recent advances in genetic research have indicated that genetic polymorphisms may contribute to individuals’ variability in response to opioid treatment. Emerging evidence indicates that genetic variations in opioid receptor genes may influence the response to epidural opioid analgesia during labor (Oertel et al., 2006; Wong et al., 2010; Pettersson et al., 2012).

The \( \mu \)-opioid receptor (OPRM1), which is encoded by the OPRM1 gene, is the primary receptor mediating the analgesic and euphoric effects of opioid drugs (Deb et al., 2010). The human OPRM1 gene is located on chromosome 6q24-q25, spanning ~1.9 kb, and it contains two exons (Kleinjan et al., 2012). More than 100 single-nucleotide polymorphisms (SNPs) in the OPRM1 gene have been identified (Pettersson et al., 2012). The most widely studied one is A118G (rs1799971 A > G), which encodes an Asn40Asp amino substitution and may increase the binding affinity and potency of \( \beta \)-endorphin (Rhodin et al., 2013). In recent years, the influence of the most common polymorphism OPRM1 A118G on the analgesic
response to various opioids in different routes of administration and clinical settings has been evaluated (Chou et al., 2006a, 2006b; Hayashida et al., 2008; Sia et al., 2008; Liao et al., 2013). Hypothetically, individuals carrying the OPRM1 gene variant may show differences in OPRM1 functions, resulting in interindividual differences in the clinical response to opioid analgesics (Deb et al., 2010). Several recent studies have indicated that the OPRM1 A118G polymorphism might play a critical role in the response to epidural analgesia with fentanyl during labor (Landau et al., 2008; Zhang et al., 2010; De Capraris et al., 2011; Zhang et al., 2011; Camorcia et al., 2012; Zhang et al., 2013). However, some other studies exist, which suggest that OPRM1 A118G polymorphism has no influence on the efficacy and safety of epidural fentanyl for labor analgesia (Wong et al., 2010; Landau et al., 2013). In view of the conflicting results from previous studies, we performed a meta-analysis of all available data to evaluate the effects of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor.

Materials and Methods

Literature search strategy

Relevant articles published before April 1st, 2013 were identified through a search on PubMed, Embase, Web of Science, and China BioMedicine databases using the following terms: (“genetic polymorphism” or “polymorphism” or “SNP” or “single nucleotide polymorphism” or “gene mutation” or “genetic variants”) and (“Receptors, Opioid, mu” or “mu Opioid Receptors” or “Morphine Receptor” or “mu

Table 1. Characteristics of Included Studies in This Meta-Analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Case number</th>
<th>Genotype</th>
<th>Genotype method</th>
<th>SNP ID</th>
<th>Evaluating indicators</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landau et al.</td>
<td>2013</td>
<td>USA</td>
<td>Caucasian</td>
<td>98</td>
<td>AA 59 AG 34 GG 5 AG+GG 39</td>
<td>PCR-SSP/Pyrosequencing</td>
<td>rs1799971</td>
<td>2</td>
<td>14/16</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>96</td>
<td>AA 35 AG 45 GG 16 AG+GG 61</td>
<td>Direct sequencing</td>
<td>rs1799971</td>
<td>1①</td>
<td>11/16</td>
</tr>
<tr>
<td>Camorcia et al.</td>
<td>2012</td>
<td>Italy</td>
<td>Caucasian</td>
<td>57</td>
<td>AA 33 AG 23 GG 1 AG+GG 24</td>
<td>PCR-SSP/Pyrosequencing</td>
<td>rs1799971</td>
<td>2②</td>
<td>12/16</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>2011</td>
<td>China</td>
<td>Asian</td>
<td>174</td>
<td>AA 80 AG 63 GG 22 AG+GG 85</td>
<td>Direct sequencing</td>
<td>rs1799971</td>
<td>①④</td>
<td>10/16</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>2010</td>
<td>USA</td>
<td>Caucasian</td>
<td>190</td>
<td>AA 144 AG 34 GG 12 AG+GG 46</td>
<td>Direct sequencing</td>
<td>rs1799971</td>
<td>①④</td>
<td>13/16</td>
</tr>
<tr>
<td>Landau et al.</td>
<td>2008</td>
<td>Switzerland</td>
<td>Caucasian</td>
<td>223</td>
<td>AA 150 AG 62 GG 11 AG+GG 73</td>
<td>PCR-SSP/Pyrosequencing</td>
<td>rs1799971</td>
<td>①④</td>
<td>10/16</td>
</tr>
</tbody>
</table>

①: Fentanyl consumption; ②: analgesia satisfaction; ③: ED50; ④: postoperative nausea and vomiting.
PCR-SSP, polymerase chain reaction with sequence-specific primer; SNP, single-nucleotide polymorphism; NOS, Newcastle–Ottawa score.
Receptors’ or “OPRM1”) and (“Fentanyl” or “Fentora” or “Phentanyl” or “Fentanest” or “Sublimaze” or “R-4263” or “Duragesic”). The references from the eligible articles or textbooks were also reviewed to find other potential sources. Disagreements were resolved through discussions among the authors.

Inclusion and exclusion criteria

Studies included in our meta-analysis had to meet the following criteria: (1) clinical studies focused on the effects of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor; (2) all women received epidural analgesia with fentanyl for labor pain relief; (3) published data about the efficacy and safety of epidural analgesia with fentanyl were sufficient. Studies were excluded when they were (1) not a clinical study on OPRM1 A118G polymorphism and labor analgesia; (2) duplicates of previous publications; (3) publications with incomplete data; (4) meta-analyses, letters, reviews, or editorial articles. If more than one study by the same author using the same case series was published, either the study with the largest sample size or the most recently published study was included.

Data extraction

Data from the published studies were extracted independently by two authors into a standardized form. For each study, the following characteristics and numbers were collected: the first author, year of publication, country, language, study design, ethnicity of subjects, numbers of subjects, mean age, analgesia type, genotype method, genotype frequencies, and clinical indicators († fentanyl consumption; ¨ analgesia satisfaction; § median effective dose [ED50]; ¶ postoperative nausea and vomiting). In case of conflicting evaluations, an agreement was reached following a discussion with a third reviewer.

Quality assessment of included studies

Two authors independently assessed the quality of included articles according to the modified Newcastle–Ottawa quality assessment scale (Stang, 2010; Oremus et al., 2012). The scale uses a score system based on three criteria: selection of participants, comparability of study groups, and assessment of exposure. Eight assessment items related to the quality appraisal were used in this meta-analysis with scores ranging from 0 to 16. Scores of 0–8, 9–12, and 13–16 were defined as low, moderate, and high quality, respectively. Disagreement between the two reviewing authors was resolved by consensus. If consensus could not be reached, a third author was deferred to arbitration and consensus.

Statistical analysis

The crude standardized mean difference (SMD) or odds ratio (OR) with 95% confidence interval (CI) were calculated. The statistical significance of the pooled estimate was
examined using the Z test. Between-study variations and heterogeneities were estimated using Cochran's Q statistic with a p-value < 0.05 as statistically significant heterogeneity (Jackson et al., 2012). We also quantified the effects of heterogeneity by using the I^2 test (ranges from 0% to 100%), which represents the proportion of interstudy variability that can be contributed to heterogeneity rather than to chance (Peters et al., 2006). When a significant Q-test with p < 0.05 or I^2 > 50% indicated that heterogeneity among studies existed, the random effects model (DerSimonian Laird method) was conducted for the meta-analysis; otherwise, the fixed effects model (Mantel-Haenszel method) was used. Sensitivity analysis was performed by omitting each study in turn to assess the quality and consistency of the results. Begger’s funnel plots and Egger’s linear regression tests were also used to evaluate the publication biases (Zintzaras and Ioannidis, 2005). All the p values were two-sided. All analyses were calculated using the STATA Version 12.0 software (Stata Corp., College Station, TX).

**Results**

**Characteristics of included studies**

In accordance with the inclusion criteria, six clinical studies were included in this meta-analysis and 153 were excluded (Landau et al., 2008; Wong et al., 2010; Zhang et al., 2011; Camorcia et al., 2012; Landau et al., 2013; Zhang et al., 2013). The flow chart of the study selection process is shown in Figure 1. The publication years of the involved studies ranged from 2008 to 2013. Four studies were conducted among Caucasian populations, while the other two studies were conducted among Asian populations. A combination of sequence-specific primer polymerase chain reaction (PCR) and automatic DNA pyrosequencing (PCR sequence-specific primer/Pyrosequencing) methods was performed in three studies, and the other study used direct sequencing. All quality scores of included studies were higher than 8 (moderate high quality). The characteristics and methodological quality of the included studies are summarized in Table 1.

**Quantitative data synthesis**

The effect of OPRM1 A118G polymorphism on the fentanyl consumption for labor analgesia is discussed in three studies. Since obvious heterogeneity existed, the random effects model was used. The meta-analysis results showed that women carrying the G allele (AG + GG) of OPRM1 A118G polymorphism required less fentanyl to achieve adequate pain relief compared with those who were AA homozygous (SMD = −0.24, 95% CI [−0.44, −0.03], p = 0.022) (Fig. 2).

Analgesia satisfaction of epidural analgesia with fentanyl during labor was investigated in five studies. No heterogeneity was observed, so the fixed effects model was used. The results showed that women carrying the G allele carrier (AG + GG) and the AA homozygote on analgesia satisfaction (SMD = 0.22, 95% CI [0.05, 0.39], p = 0.012) (Fig. 3).

Only two studies referred to the effect of OPRM1 A118G polymorphism on the ED50 of epidural analgesia with fentanyl during labor. The meta-analysis results showed that women carrying the G allele (AG + GG) of OPRM1 A118G polymorphism required less fentanyl to achieve adequate pain relief compared with those who were AA homozygous (SMD = −0.71, 95% CI [−1.25, −0.17], p = 0.043) (Fig. 4).

**Incidence of postoperative nausea and vomiting**

The effect of OPRM1 A118G polymorphism on the incidence of postoperative nausea and vomiting was discussed in three studies. Since obvious heterogeneity existed, the random effects model was used. The meta-analysis showed that women carrying the G allele (AG + GG) and the AA homozygote on the incidence of postoperative nausea and vomiting (SMD = 1.99, 95% CI [1.63, 2.35], p = 0.002) (Fig. 5).
fentanyl during labor. Since no heterogeneity existed, the fixed effects model was used. Meta-analysis of these studies indicated that the 118G variant was associated with decreased IV fentanyl ED50 for labor analgesia (SMD = -1.56, 95% CI [-1.97, -1.15], p < 0.001) (Fig. 4).

There were also only two studies that reported results on the effect of OPRM1 A118G polymorphism on the incidence of postoperative nausea and vomiting. Heterogeneity was not obvious; so, the fixed effects model was used. No significant difference was found in the incidence of postoperative nausea and vomiting between the G allele carrier (AG + GG) and the AA homozygote for labor analgesia (OR = 1.99, 95% CI [0.88, 4.52], p = 0.101) (Fig. 5).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled SMD of analgesia satisfaction by omission of individual studies. The analysis results suggested that no individual studies significantly affected the pooled SMD of the effect of OPRM1 A118G polymorphism on the analgesia satisfaction for labor analgesia, indicating a statistically robust result (Fig. 6). The Begger’s funnel plot and Egger’s linear regression test were performed to assess publication biases in the included studies. The shapes of the funnel plots of the effect of OPRM1 A118G polymorphism on analgesia satisfaction for labor analgesia did not reveal any evidence of obvious asymmetry (Fig. 7). The Egger’s test also did not indicate any strong statistical evidence of publication bias (t = -0.84, p = 0.488).

Discussion

The OPRM1, a member of the G-protein coupled receptor superfamily, mediates the analgesic and euphoric effects of opioid drugs (Fredriksson et al., 2003). A number of SNPs have been identified in the OPRM1 gene, which have been largely limited to the DNA sequence and short intron 2 so far.
(Deb et al., 2010). The most widely studied is A118G (rs1799971 A>G) polymorphism, which leads to a substitution of Asn/Asp within exon 1 and may increase the binding affinity and potency of β-endorphin, which mediates analgesia and pain threshold (Rhodin et al., 2013). Therefore, it is biologically plausible that genetic variations of OPRM1 A118G polymorphism may modulate an individual’s response to epidural analgesia with fentanyl during labor (Camorcia et al., 2012). Several studies have investigated the functional effects of OPRM1 A118G polymorphism, but their findings have been inconclusive. This meta-analysis aimed to derive more precise estimates of the effects of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor.

In this meta-analysis, six clinical studies were included with a total of 838 women who received epidural analgesia with fentanyl during labor. When all the eligible studies were pooled into the meta-analysis, we demonstrated that women carrying the G allele (AG + GG) of OPRM1 A118G polymorphism had a dramatically decreased fentanyl dose for labor analgesia, suggesting that the 118G variant might be associated with an increased sensitivity to epidural opioid analgesia. One explanation for a significant increase in pain tolerance and decreased fentanyl consumption in 118G carriers could be the change of quantity and binding affinity of OPRM1 due to genetic variability at the OPRM1. These results provide support for the potential use of genetic data in predicting the fentanyl dosage for postoperative labor pain control. The present results also suggested that the analgesia satisfaction in women carrying the G allele (AG + GG) was higher than those who are AA, which is consistent with previous studies. A major goal of labor analgesia is minimal motor impairment, emphasizing the need to minimize local anesthetic use. Similarly, there is a need to reduce opioid doses to minimize opioid-related side effects such as pruritus and fetal bradycardia. Our findings indicated that women carrying the 118G variant had a lower ED50 with a 1.15- to 1.97-fold decrease in fentanyl dose for labor analgesia. One explanation for decreased ED50 of fentanyl analgesia in 118G carriers would be that the 118G variant might enhance β-endorphins binding and thereby increase the response to fentanyl. Postoperative nausea and vomiting are common side effects of labor analgesia. Theoretically, with a decrease in fentanyl dosage, side effects may correspondingly decrease during labor analgesia. However, no statistically significant differences were found between the AA homozygote and the G carrier (AG + GG) in the incidence of nausea and vomiting, suggesting that OPRM1 A118G polymorphism does not explain the nausea and vomiting caused by fentanyl.

Similar to other meta-analyses, our study also bears some limitations and shortages. First, the sample size is relatively small and may not provide sufficient power to estimate the effects of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor. Therefore, more research with a larger sample size is needed to accurately provide a more representative statistical analysis. Second, as a retrospective study, a meta-analysis may encounter recall or selection bias, possibly influencing the reliability of our study results (Camorcia et al., 2012). Third, our lack of access to the original data from the studies limited further evaluation of potential effects of epidural analgesia with fentanyl on analgesia success, VAS score, VPS score, and other side effects (van Melle et al., 2004). In spite of these limitations, however, this is the first meta-analysis on the influences of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor. It is also worthwhile to mention that we established an efficient searching strategy based on computer-assisted programs, as well as manual searches, which allowed us to include as many as possible. According to our selection criteria, the quality of studies included in this meta-analysis is sufficient. Nonetheless, explicit methods for study selection, data extraction, and data analysis were well designed before initiating. Finally, there was no evidence of publication bias in this meta-analysis and the sensitivity analysis indicated that our results are statistically robust.

In conclusion, our meta-analysis suggests that women carrying the G allele (AG + GG) of OPRM1 A118G polymorphism may have a good response to epidural analgesia with fentanyl during labor. The OPRM1 A118G polymorphism may help predict individuals’ response to epidural labor analgesia, and thus optimize postoperative pain control. Based on the limitations mentioned earlier, detailed studies are needed to confirm our findings. Further studies are still needed to warrant and validate the effects of OPRM1 A118G polymorphism on epidural labor analgesia.

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Author Disclosure Statement

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