Review Article
The effects of prophylactic ondansetron on fentanyl-induced pruritus: a meta-analysis

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Abstract: Objective: The aim of this meta-analysis is to evaluate the effect of ondansetron in the prevention of pruritus after use of intrathecal fentanyl. Methods: The main outcomes were the relative risks (RR) and the 95% confidence intervals (CI) regarding the incidence of pruritus and other side effects. Results: Ten trials totaling 1,084 patients were analyzed. Subgroups results suggested that there was a significant reduction in the incidence of fentanyl-induced pruritus compared with control [RR=0.72, 95% CI (0.56, 0.93)], while no reduction was detected in the incidence of fentanyl-morphine-induced pruritus [RR=1.05, 95% CI (0.94, 1.16)] or ondansetron 8 mg reduced fentanyl-induced pruritus [RR=0.63, 95% CI (0.53, 0.74)]. Conclusions: Prophylactic ondansetron 8 mg may be an effective strategy for preventing fentanyl-induced pruritus, however it may be ineffective in reducing the incidence of fentanyl-morphine-induced pruritus.

Keywords: Ondansetron, fentanyl, pruritus, meta-analysis

Introduction
The administration of opioids is commonly used in the treatment of pain during surgical procedures and in labor and delivery [1-4]. However, opioids are always accompanied by various side effects such as pruritus, which is thought to occur most frequently after intrathecal fentanyl administration [5]. Transdermal opioids such as fentanyl, are popular and provide rapid pain relief [6]. The reported incidence of pruritus varies between 60% and 100% [7, 8]. Pruritus can be persistent and troublesome, and this has significant effects on quality of life as well as increased morbidity [9-11]. Pruritus can be difficult to treat [12], and the mechanism of opioid-related pruritus is not fully understood, which may limit the application of intrathecal opioids [12].

Many drugs with different potential mechanisms of action have been used to prevent pruritus. Their relative effects as well as their optimal doses for side effects are not well understood [13]. The opioid antagonist naloxone has been shown to be beneficial, and is commonly used for the treatment of opioid-induced pruritus. However, it also reverses the analgesic effect of the opioid, which limits the use of naloxone during surgery.

Ondansetron is one of the 5-HT3 receptors which is used commonly in the administration of intrathecal fentanyl. Clinical evidence has demonstrated the significant antipruritic effect of ondansetron in patients with renal failure and cholestatic jaundice [14-16]. Results from single-institution experiences have also suggested that prophylactic ondansetron reduces the incidence of intrathecal morphine-induced pruritus in patients undergoing surgery or cesarean delivery [17, 18]. However, there are conflicting results regarding the efficacy of prophylactic ondansetron in the treatment of fentanyl-induced pruritus. Gurkan et al. [19] showed that prophylactic ondansetron reduces the incidence of intrathecal fentanyl-induced pruritus in a prospective, randomized and double-blind trial. However, several investigators have examined the effectiveness of ondansetron for the prevention of pruritus with contradictory results [20-22].
In addition, despite several review articles [23-27] being published on pharmacological prevention of spinal and epidural opioid induced pruritus, thus far none have systematically evaluated the role of ondansetron in the treatment of fentanyl-induced pruritus. Furthermore, trials with respect to the approach in these reviews have been limited. Consequently, a systematic review and meta-analysis was conducted, intended to update the clinical information on ondansetron for the prevention of intrathecal fentanyl-induced pruritus.

Materials and methods

Search strategy

We identified studies by searching the following databases: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Web of Knowledge, and Google Scholar. The text word terms and MESH headings for search were: ondansetron, fentanyl, and pruritus. Other studies were identified by manually reviewing the reference lists and review articles on the subject, and by contacting experts in the respective fields. There were no language restrictions for either the search strategies or the trial inclusion.

Study selection and data extraction

Trials were included in the analysis if they met the following criteria: 1) RCTs on treating fentanyl-induced pruritus in both ondansetron group and placebo group should have a minimum of 10 participants; 2) There were no restrictions on dose, dosing regimen, or the administration of ondansetron; 3) Interventions were administered with spinal anesthesia or a combined spinal-epidural (CSE) technique; 4) Sufficient data for evaluation of pruritus existed.

Extraction criteria: 1) Data was only available for the evaluation of sufentanil and sufentanil-morphine-induced pruritus; 2) The outcomes of interest were not reported; 3) Case report; 4) The research objects were patients with pre-existing pruritus, or were at risk of pruritus before receiving ondansetron.

Data extraction

Two review authors (Yu-Ting Yang and Cheng-Mao Zhou) independently scanned the titles and abstracts identified by electronic search and manual retrieval. Potentially relevant studies were retrieved in full-text version and were evaluated for inclusion. Data from the selected studies were extracted independently by at least two review authors (Yu-Ting Yang and Cheng-Mao Zhou) using a standard data extraction form. Disagreements were settled by discussion with a third review author (Lin Ruan). When necessary, we contacted the original authors for further information.

We extracted information pertaining to the name of the first author, published year, sample size, type of surgery, pharmacological interventions, placebo, anesthetic technique and study methodology (for example, method of randomization, allocation concealment, and blinding). The data was entered independently, and was checked by Yu-Ting Yang and Cheng-Mao Zhou. The two reviewers’ decisions were recorded, and any disagreements were resolved based on the evaluation of a third reviewer (Lin Ruan).

Outcome measures

The following outcomes were used to evaluate the efficacies of ondansetron in the prevention of pruritus induced by fentanyl in patients undergoing surgery or during labor. The primary outcomes included the incidence of pruritus and the rescue treatment for pruritus.

Quality assessment

The risk of selected randomized-controlled studies was assessed according to the 4 item Oxford scale [28], which including the reporting and adequacy of randomization (0 to 2 points), allocation concealment (0 to 1 points), double blinding (0 to 2 points), and description of drop-outs (0 to 2 points). The items are summed, with summary scores varying from 0 to 7. Two reviewers (Yu-Ting Yang and Cheng-Mao Zhou) independently assessed the quality of each study. Any disagreements were resolved by consensus, with the aid of a third author (Lin Ruan).

Statistical analysis

The Cochrane Collaboration’s statistical software (RevMan 5.0) was used for data input, statistical analysis, and creation of graphs. If
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Results

Included studies

A total of 255 studies were relevant to the key terms after searching. Of these, 20 duplicate records and 211 irrelevant records were removed. Another 13 articles were excluded for the following reasons: 1) One trial studied the efficacy of ondansetron on sufentanil-morphine-induced pruritus [29]; 2) Two studies evaluated the effect of ondansetron on the prevention of intrathecal sufentanil-mediated pruritus [30, 31]; 3) Eight studies only estimated the efficacy of ondansetron on fentanyl-induced nausea and vomiting [32-39]; 4) One trial did not report available data [40]; 5) One trial was a case report [41]; 5) One trial studied the efficacy of ondansetron on morphine-induced pruritus [52]. In the end, 11 articles [42-52] met eligibility criteria. Eight trials [42, 43, 45-50] contained results regarding prophylaxis against fentanyl-induced pruritus, and three trials [44, 51, 52] contained results regarding prophylaxis against fentanyl-morphine-induced pruritus. The flow chart for the process is shown in Figure 1.

Study characteristics

In total, ten trials covering 1,084 patients were included in our meta-analysis. Of the 10 analysed trials, nine were published in English, two were in Chinese; six trials were in obstetrics (labour or Caesarean section), and the others included knee arthroscopy (one study), arthroscopic knee and urologic surgery (one study), hysterectomy and hernioplasty (one study), pelvic and lower extremity surgery (one study). Analgesia was with fentanyl in 8 trials, and with intrathecal morphine-fentanyl in two others. Ondansetron 4 mg was tested in four studies, and ondansetron 8 mg in ten studies. Results are described in Table 1.

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Data were available and sufficient, we evaluated the overall effects by meta-analysis. Relative risks (RRs) and their 95% confidence intervals (CI) in regard to the incidence of pruritus for each trial were calculated. All analyses were performed in accordance with the intention-to-treat principle. Heterogeneity was tested by the Q-test and I-squared ($I^2$) test. Statistical significance was set at 0.10 for the Cochrane Q-tests, and $I^2$ was used to quantify the amount of heterogeneity. Heterogeneity was predefined as low, moderate and high with $I^2$ values of more than 25%, 50% and 75%, respectively. Data were pooled using a random effects model when $I^2$>50%, or a fixed effects model when $I^2$<50%. The significance of the pooled RR was determined by the Z-test, along with 95% confidence intervals. A p-value less than 0.05 was considered statistically significant. Publication bias was assessed with a funnel plot with the fixed or random effect RR on the x-axis and the standard error of the log RR on the y-axis. The incidence of pruritus was used as an endpoint to evaluate the publication bias.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study design</th>
<th>Language</th>
<th>Sample sizes</th>
<th>Treatment (Control)</th>
<th>Type of surgery</th>
<th>Anaesthesia techniques</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2003 [49]</td>
<td>China</td>
<td>Fentanyl (25ug)</td>
<td>Chinese</td>
<td>120</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Labour</td>
<td>SA</td>
<td>0/0/2/2</td>
</tr>
<tr>
<td>Gulhas 2007 [43]</td>
<td>Turkey</td>
<td>Fentanyl (25 µg)</td>
<td>English</td>
<td>72</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Cesarean section</td>
<td>CSE</td>
<td>2/1/1/2</td>
</tr>
<tr>
<td>Sarvela 2006 [44]</td>
<td>Finland</td>
<td>Fentanyl (15 mg) morphine (160 mg)</td>
<td>English</td>
<td>64</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Cesarean section</td>
<td>CSE</td>
<td>2/0/2/2</td>
</tr>
<tr>
<td>Wells 2004 [45]</td>
<td>Australia</td>
<td>Fentanyl (25 ug)</td>
<td>English</td>
<td>73</td>
<td>Ondansetron 4 mg/8 mg (saline)</td>
<td>Labour</td>
<td>CSE</td>
<td>2/0/0/2</td>
</tr>
<tr>
<td>Korhonen 2003 [46]</td>
<td>Finland</td>
<td>Fentanyl (10 mg)</td>
<td>English</td>
<td>90</td>
<td>Ondansetron 4 mg/8 mg (saline)</td>
<td>Knee arthroscopy</td>
<td>SA</td>
<td>2/1/0/2</td>
</tr>
<tr>
<td>Gürkan 2002 [43]</td>
<td>Turkey</td>
<td>Fentanyl (25 ug)</td>
<td>English</td>
<td>150</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Arthroscopic knee or urologic surgery</td>
<td>SA</td>
<td>0/0/2/2</td>
</tr>
<tr>
<td>Ji Gen-Lin 2001 [48]</td>
<td>China</td>
<td>Fentanyl (0.4 mg)</td>
<td>Chinese</td>
<td>100</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Hysterectomy and hernioplasty</td>
<td>CSE</td>
<td>0/1/0/2</td>
</tr>
<tr>
<td>Jahanbakhsh 2013 [42]</td>
<td>Iran</td>
<td>Fentanyl (25 ug)</td>
<td>English</td>
<td>207</td>
<td>Ondansetron 8 mg (saline)</td>
<td>Pelvic or lower extremity surgery</td>
<td>SA</td>
<td>2/0/0/2</td>
</tr>
<tr>
<td>Ortiz-Gomez 2014 [50]</td>
<td>Spain</td>
<td>Fentanyl (20 ug)</td>
<td>English</td>
<td>128</td>
<td>Ondansetron 2 mg/4 mg/8 mg (saline)</td>
<td>Elective caesarean delivery</td>
<td>SA</td>
<td>1/1/0/2</td>
</tr>
<tr>
<td>Tan 2010 [51]</td>
<td>Ireland</td>
<td>Fentanyl (25 ug), morphine (150 ug)</td>
<td>English</td>
<td>80</td>
<td>Ondansetron 8 mg (granisetron 3 mg)</td>
<td>Elective caesarean section</td>
<td>SA</td>
<td>2/1/0/2</td>
</tr>
</tbody>
</table>

CSE: combined spinal-epidural; SA: spinal anesthesia. RCT: randomized controlled trials.
Methodological quality of the included studies

For the ten studies included [42-51], six correctly described the random sequence generation method and five correctly described the allocation concealment method. Only three studies correctly described the blinding and only one was unclear in the description of drop-outs (Table 1).

Pruritus

Incidence of pruritus: The incidence of pruritus was reported respectively by ten RCTs. When all studies reporting pruritus were combined, the result suggested no significant difference in the incidence of pruritus with ondansetron compared with placebo [RR=0.80, 95% CI (0.62, 1.03), P=0.008]. This was because significant heterogeneity was detected (I²=84%), and the combined result was not reliable enough. Therefore, subgroups were made according to the anaesthesia method, and results suggested that there was significant reduction in the incidence of fentanyl-induced pruritus with ondansetron [RR=0.72, 95% CI (0.56, 0.93), P=0.01, I²=66%]. However, no reduction was detected in the incidence of fentanyl-morphine-induced pruritus [RR=1.05, 95% CI (0.94, 1.16), P=0.39, I²=0%] (Figure 2).

To test for dose-responsiveness, subgroups were made according to the different doses of ondansetron. Results suggested that ondansetron 8 mg was effective in preventing fentanyl-induced pruritus, compared with the control [RR=0.63, 95% CI (0.53, 0.74), P<0.00001, I²=20%]; however ondansetron 8 mg was not effective in the prevention of fentanyl-morphine-induced pruritus [RR=1.07, 95% CI (0.95, 1.21), P=0.38, I²=0%] (Figure 3). For the ondansetron 4 mg, there was no significant difference in the incidence of fentanyl-induced pruritus compared with the placebo [RR=1.02, 95% CI (0.79, 1.32), P=0.87, I²=23%] (Table 2).

Need for treatment: Eight trials reported data regarding the need for treatment of pruritus, with drugs for rescue treatment consisting of hydroxyzine hydrochloride, naloxone, propofol, and chlorphenarimine. There was a reduction in the need for treatment of fentanyl-induced pruritus [RR=0.54, 95% CI (0.35, 0.83), P=0.006, I²=0%], however no reduction in the need for
Ondansetron on fentanyl-induced pruritus

1.1 fentanyl

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ondansetron</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M.H. Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M.H. Fixed</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortiz-Gómez 2014</td>
<td>1</td>
<td>32</td>
<td>0.4%</td>
<td>1.00 [0.07, 15.30]</td>
</tr>
<tr>
<td>Krommenen 2003</td>
<td>10</td>
<td>27</td>
<td>3.0%</td>
<td>1.39 [0.64, 3.00]</td>
</tr>
<tr>
<td>Ji Gen-Lin 2001</td>
<td>7</td>
<td>50</td>
<td>3.2%</td>
<td>0.68 [0.34, 2.23]</td>
</tr>
<tr>
<td>Veils 2004</td>
<td>10</td>
<td>20</td>
<td>5.6%</td>
<td>0.73 [0.43, 1.24]</td>
</tr>
<tr>
<td>Guhae 2007</td>
<td>18</td>
<td>36</td>
<td>9.5%</td>
<td>0.75 [0.50, 1.12]</td>
</tr>
<tr>
<td>Wang Xiu-Huan 2003</td>
<td>17</td>
<td>80</td>
<td>10.5%</td>
<td>0.42 [0.25, 0.72]</td>
</tr>
<tr>
<td>Gurkan 2002</td>
<td>29</td>
<td>75</td>
<td>20.1%</td>
<td>0.57 [0.41, 0.79]</td>
</tr>
<tr>
<td>Jahanbakhsh 2013</td>
<td>36</td>
<td>107</td>
<td>24.4%</td>
<td>0.56 [0.41, 0.76]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>427</td>
<td>385</td>
<td>76.6%</td>
<td>0.63 [0.53, 0.74]</td>
</tr>
<tr>
<td>Total events</td>
<td>128</td>
<td>187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 8.77, df = 7 (P = 0.27); I² = 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.47 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.1.2 fentanyl plus morphine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ondansetron</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M.H. Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M.H. Fixed</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarela 2008</td>
<td>26</td>
<td>30</td>
<td>8.8%</td>
<td>1.14 [0.89, 1.46]</td>
</tr>
<tr>
<td>Tan 2010</td>
<td>38</td>
<td>40</td>
<td>14.6%</td>
<td>1.03 [0.92, 1.15]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>70</td>
<td>69</td>
<td>23.1%</td>
<td>1.07 [0.95, 1.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>64</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.12 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI)            | 497         | 454     | 100.0%         | 0.73 [0.65, 0.83] |
| Total events             | 192         | 246     |                 |                |
| Heterogeneity: Chi² = 59.00, df = 9 (P < 0.00001); I² = 85% |
| Test for overall effect: Z = 4.99 (P = 0.00001) |
| Test for subgroup differences: Chi² = 26.10. df = 1 (P < 0.00001). I² = 96.2% |

Discussion

Methodological quality summary

Eleven randomized controlled trials (published between 2001 and 2014) were included in our study. The incidence of pruritus with ondansetron (8 mg) compared with placebo was detected [RR=0.97, 95% CI (0.71, 1.34), P=0.87, I²=30%] (Table 2).

Publication bias

A funnel plot was performed to evaluate publication bias regarding the incidence of pruritus. It was symmetrically distributed, and did not show a significant publication bias (Figure 4).

Figure 3. The incidence of pruritus with ondansetron (8 mg) compared with placebo.

Table 2. The Effect of prophylactic ondansetron on the incidence of pruritus, PONV and headache and the need for treatment of pruritus

<table>
<thead>
<tr>
<th>Anaesthesia technique</th>
<th>Risk of treatment group (%)</th>
<th>Risk of control group (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of pruritus</td>
<td>Fentanyl</td>
<td>182/545 (33.4)</td>
<td>200/385 (52.0)</td>
<td>0.72 [0.56, 0.93]</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Fentanyl-morphine</td>
<td>64/70 (91.4)</td>
<td>59/69 (85.5)</td>
<td>1.05 [0.94, 1.16]</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>All studies combined</td>
<td>246/615 (40.0)</td>
<td>259/454 (57.0)</td>
<td>0.80 [0.62, 1.03]</td>
<td>0.008</td>
</tr>
<tr>
<td>Ondansetron 8 mg</td>
<td>Fentanyl</td>
<td>128/427 (30.0)</td>
<td>187/385 (48.6)</td>
<td>0.63 [0.53, 0.74]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>Fentanyl-morphine</td>
<td>64/70 (91.4)</td>
<td>59/69 (85.5)</td>
<td>1.07 [0.95, 1.21]</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Studies combined</td>
<td>192/497 (38.6)</td>
<td>246/454 (54.2)</td>
<td>0.73 [0.65, 0.83]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ondansetron 4 mg</td>
<td>Fentanyl</td>
<td>37/83 (44.6)</td>
<td>37/84 (44.0)</td>
<td>1.02 [0.79, 1.32]</td>
<td>0.87</td>
</tr>
<tr>
<td>Need for treatment of pruritus</td>
<td>Fentanyl</td>
<td>23/363 (6.3)</td>
<td>43/319 (13.5)</td>
<td>0.54 [0.35, 0.83]</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Fentanyl-morphine</td>
<td>47/149 (31.5)</td>
<td>49/150 (32.7)</td>
<td>0.97 [0.71, 1.34]</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Studies combined</td>
<td>70/512 (13.7)</td>
<td>92/469 (19.6)</td>
<td>0.77 [0.59, 0.99]</td>
<td>0.04</td>
</tr>
<tr>
<td>PONV</td>
<td>Fentanyl</td>
<td>12/194 (6.2)</td>
<td>14/197 (7.1)</td>
<td>0.90 [0.45, 1.82]</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Fentanyl-morphine</td>
<td>79/149 (53.0)</td>
<td>88/151 (58.3)</td>
<td>1.06 [0.58, 1.93]</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Studies combined</td>
<td>91/343 (26.5)</td>
<td>102/348 (29.3)</td>
<td>0.98 [0.66, 1.44]</td>
<td>0.74</td>
</tr>
<tr>
<td>Headache</td>
<td>Fentanyl</td>
<td>18/195 (9.2)</td>
<td>28/197 (14.2)</td>
<td>0.64 [0.37, 1.11]</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Ondansetron on fentanyl-induced pruritus

Figure 4. A funnel plot to evaluate publication Bias.

Preventing the side effects of intrathecal fentanyl with the clinical efficiency of ondansetron

Intrathecal fentanyl can induce some side effects, with skin pruritus being one of the common complications. Our systematic review and meta-analysis showed that: ondansetron 8 mg reduced fentanyl-induced pruritus and the need for treatment of pruritus, and did not increase the incidence of postoperative nausea, vomiting, or headache. However, ondansetron 8 mg may not be effective in the prevention of fentanyl-morphine-induced pruritus. Large sample sizes are needed to provide reliable results. In addition, ondansetron 4 mg may not be effective in the prevention of fentanyl-induced pruritus, large sample sizes are needed as it just included 167 patients. When all studies were combined, data suggested that ondansetron reduced the incidence of pruritus with ondansetron compared to the placebo. However, the difference did not reach statistical significance, and significant heterogeneity (I²=84%) was detected. Therefore, the combined results may be unreliable. The reasons for high heterogeneity may lie in the different study designs. While other trials evaluated the effect of ondansetron in the prevention of intrathecal fentanyl-mediated pruritus, these two trials (Sarvela 2006, Tan 2010) explored the effect of ondansetron on fentanyl-morphine-mediated pruritus. In the trials, more incidence of pruritus occurred when fentanyl was administered with morphine than when fentanyl was administered alone. Therefore, we conducted subgroups where in Sarvela 2006 and Tan 2010 were removed from the overall analysis. As a result, heterogeneity was reduced significantly.

There were many 5-HT3 receptors in rat spinal dorsal horn regions [53], and it was hypothesized that the pruritus induced by opioid drugs was directly excited in the spinal cord dorsal horn [54]. The mechanism of ondansetron preventing fentanyl-induced pruritus may be associated with blocking 5-HT3 receptors in this area. Furthermore, meta-analysis [27] showed that ondansetron did not prevent the pruritus of opioid drugs from inducing birth in obstetric surgery. This hypothesis warrants deeper probing.

In the included studies, most had multiple comparison groups. We chose 8 mg or 4 mg ondansetron to compare with the control group, and the results show that different doses of ondansetron had different effects on preventing fentanyl-induced pruritus. There was also a study [55] which showed that the effect of different doses of naltrexone in preventing opioid-induced pruritus was not the same. In Bonnet’s meta-analysis, they put fentanyl, fentanyl-morphine, and sufentanil into the same group, and their result showed that ondansetron did not prevent the incidence of pruritus. Except for the impact of the dose factors, their results were also influenced by the different study design. In addition, one of the reasons the ondansetron did not prevent sufentanil-induced pruritus was that the fat-solubility of sufentanil was higher than it was in morphine and fentanyl [56].

Included studies had the flowing clinical problems in our meta-analysis: 1) The different epi-
Ondansetron on fentanyl-induced pruritus
dural local anesthesia drugs and their dosage
could cause different rates of pruritus [57]; 2) If
the other adverse reactions were severe, mis-
judgment of the pruritus feeling could occur in
patients [58]; 3) The research objects included
only the adults in our meta-analysis.

Statistical limitations of this meta-analysis

Limitations of this meta-analysis: 1) The num-
ber of included studies was not enough, and
the sample size was too small; 2) The included
studies all came from published articles.

Conclusion

Our meta-analysis shows that prophylactic
ondansetron was effective in reducing the inci-
dence of fentanyl-induced pruritus as well as
the need for treatment of pruritus, however it
may be ineffective in reducing the incidence
of fentanyl-morphine-induced pruritus. In the
future, multicenter, prospective, large-scale,
well-designed randomized controlled trials are
needed. In sum, evidence needs to be collect-
ed to draw a definite conclusion on the effects
of ondansetron in the prevention of fentanyl-
induced pruritus.

Disclosure of conflict of interest

None.

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