Methylnaltrexone to prevent intrathecal morphine-induced pruritus after Caesarean delivery: a multicentre, randomized clinical trial

M. Paech\textsuperscript{1,2,*}, B. Sng\textsuperscript{3}, L. Ng\textsuperscript{2}, E. Nathan\textsuperscript{4}, A. Sia\textsuperscript{3} and B. Carvalho\textsuperscript{5}

\textsuperscript{1}Pharmacology, Pharmacy and Anaesthesiology Unit, School of Medicine and Pharmacology, The University of Western Australia, Crawley, WA 6009, Australia
\textsuperscript{2}Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, 374 Bagot Rd, Subiaco, WA 6008, Australia
\textsuperscript{3}Department of Women's Anaesthesia, KK Women's and Children's Hospital, Singapore
\textsuperscript{4}Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, 374 Bagot Rd, Subiaco, WA 6008, Australia
\textsuperscript{5}Women and Infants Research Foundation, Perth, WA, Australia

* Corresponding author. E-mail: michael.paech@health.wa.gov.au

Editor’s key points

- Pruritus due to intrathecal opioids can be distressing, with limited treatment options.
- Both peripheral and central mechanisms may contribute to opioid-induced pruritus.
- Methylnaltrexone (a peripherally acting opioid antagonist) was studied in women undergoing Caesarean section.
- More than 80% of patients reported pruritus, in both the active and control groups.
- Intrathecal (subarachnoid or spinal) morphine provides excellent postoperative analgesia after abdominal surgical procedures, including after Caesarean delivery.\textsuperscript{1} One of the major limitations to this highly effective method of analgesia is the high incidence of morphine-induced pruritus. This common (number needed to harm of two to three) side-effect is dose-dependent and is a frequent complaint and concern for parturients.\textsuperscript{1–6} In the post-partum setting, the incidence of pruritus after intrathecal morphine (with doses of 100–200 \(\mu g\)) is 70–90%. Intrathecal morphine-induced pruritus is described as moderate to severe in intensity by up to 50% of women, and up to 25% of patients request treatment.\textsuperscript{2,5–9} Although pruritus is believed to be predominantly of central origin, peripheral mechanisms also appear to be present.\textsuperscript{2,10}

Background. Intrathecal morphine-induced pruritus is a very common side-effect that is difficult to prevent or treat. Central and peripheral mechanisms are believed to be involved. The aim of this study was to determine if a peripherally acting, \(\mu\)-opioid antagonist would reduce morphine-induced pruritus.

Methods. We conducted a multicentre, randomized, blinded, placebo-controlled trial of women having elective Caesarean section under spinal anaesthesia with intrathecal morphine 100 \(\mu g\). After delivery, participants received either subcutaneous methylnaltrexone bromide 12 mg (MNTX group, \(n=69\)) or saline (placebo group, \(n=68\)). Pruritus, nausea, pain, analgesic use, and side-effects were assessed at 2, 4, 8, and 24 h. The primary outcome was the severity of pruritus (0–10 score).

Results. One hundred and thirty-seven women completed the study, with five major protocol violations. There was no statistically significant difference between the MNTX and placebo groups for the median (IQR) pruritus AUC scores \([24 (9–47) vs 36 (11–68)]\), median difference 8.5, 95% confidence interval \((CI) 0–20, P=0.09\) or the worst pruritus score \([3 (2–7) vs 5 (2–6)]\), median difference 1, 95% CI 0–2, \(P=0.24\). The incidence of pruritus was 84% in the MNTX group and 88% in the placebo group \((P=0.48)\). Analgesic and gastrointestinal outcomes did not significantly differ between the groups.

Conclusions. A single dose of subcutaneous methylnaltrexone bromide 12 mg did not reduce the overall severity or incidence of pruritus. In this study, treatment with a peripherally acting \(\mu\)-opioid antagonist was generally ineffective against intrathecal morphine-induced pruritus, but a small clinical effect cannot be excluded.

Clinical trial registration. Australian New Zealand Clinical Trials Registry (ACTRN12611000345987).

Keywords: analgesics, opioid, morphine; antipruritics; quaternary ammonium compounds, methylnaltrexone

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Intrathecal (subarachnoid or spinal) morphine provides excellent postoperative analgesia after abdominal surgical procedures, including after Caesarean delivery.\textsuperscript{1} One of the major limitations to this highly effective method of analgesia is the high incidence of morphine-induced pruritus. This common (number needed to harm of two to three) side-effect is dose-dependent and is a frequent complaint and concern for parturients.\textsuperscript{1–6} In the post-partum setting, the incidence of pruritus after intrathecal morphine (with doses of 100–200 \(\mu g\)) is 70–90%. Intrathecal morphine-induced pruritus is described as moderate to severe in intensity by up to 50% of women, and up to 25% of patients request treatment.\textsuperscript{2,5–9} Although pruritus is believed to be predominantly of central origin, peripheral mechanisms also appear to be present.\textsuperscript{2,10}

Pruritus induced by intrathecal morphine is difficult to prevent or treat. There is a moderate but short-lived response to mixed

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opioid agonists/antagonists or antagonists such as nalbuphine or naloxone, but these centrally acting μ-opioid antagonists have the potential to adversely affect analgesia. Treatment of opioid-induced pruritus does not respond or shows a weak response to antihistamines, serotonin antagonists, and propofol.

Methylnaltrexone bromide (RELISTOR, Link Healthcare, Australia and Salix Pharmaceutical, USA) is a peripherally acting μ-opioid receptor antagonist which was developed to antagonize the peripheral side-effects of opioids while preserving centrally mediated analgesia. Treatment of opioid-induced constipation unresponsive to laxatives among patients with advanced illness or receiving palliative care with methylnaltrexone has regulatory approval in several countries, including Australia, Singapore, and the USA. Methylnaltrexone is a quaternary ammonium derivative of the opioid antagonist naloxone, which limits its transfer across the blood–brain barrier. It does not impact on analgesia or affect postoperative pain. Methylnaltrexone bromide is likely to be of minimal benefit for the management of centrally mediated pruritus. However, in a small clinical trial among 10 volunteers, an incidental finding was that methylnaltrexone appeared to reduce the severity of skin pruritus induced by systemic morphine. This study suggests that morphine-induced pruritus may have a peripheral mechanism.

The primary aim of the study was to determine if a peripherally acting μ-opioid antagonist would reduce the severity of morphine-induced pruritus. We hypothesized that subcutaneous methylnaltrexone would significantly reduce the severity and incidence of intrathecal morphine-induced pruritus after spinal anaesthesia for Caesarean delivery.

**Methods**

The trial received institutional ethical approval from the Women and Newborn Health Service, Australia; Stanford University School of Medicine, USA, and Singhealth Centralised Institutional Review Board, Singapore. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000345987). All participants gave written informed consent. The study was a randomized, blinded, parallel-group, placebo-controlled, multicentre trial that was conducted at three centres (King Edward Memorial Hospital for Women in Australia, Lucile Packard Children’s Hospital in the USA, and KK Women’s and Children’s Hospital in Singapore) between June 2012 and February 2013.

Inclusion criteria included ASA class I or II women, aged 18 yr or more undergoing elective Caesarean delivery via Pfannenstiel incision under spinal anaesthesia (with or without epidural catheter insertion) but including intrathecal morphine. Exclusion criteria were preoperative use of opioid medication or a drug with antipruritic activity; preoperative pruritus for any reason; current weight outside the range 62–114 kg, as approved for the dose of methylnaltrexone; renal impairment, gastrointestinal disease, or diarrhoea; conversion to another method of anaesthesia; administration of epidural opioid; and failure to administer intrathecal morphine.

Women were recruited at antenatal pre-admission clinics, the maternal–fetal assessment unit, birthing unit, or ward before their Caesarean delivery. A randomization sequence for two groups in a 1:1 ratio was generated for each centre, in blocks of four, using a computer-generated random number sequence. After patient screening and randomization, intraoperative allocation was by means of a sealed, number-coded envelope. The envelope contained either the study drug (of identical appearance to saline and prepared by a staff member who had no further study involvement) or the normal saline 0.6 ml placebo. Patients, the attending anaesthetist, postoperative staff, and data collectors were blinded to group allocation. The study drug was either methylnaltrexone 12 mg in 0.6 ml solution for subcutaneous injection into the anaesthetized anterolateral thigh (MNTX group) or a similar volume of 0.6 ml normal saline (placebo group). The study drug or placebo was given during skin closure near the end of surgery.

Intraoperative anaesthetic and postoperative care was standardized. Spinal anaesthesia was established using hyperbaric bupivacaine 10–12 mg, fentanyl 15 μg, and morphine 100 μg. When intraoperative pain was reported by the patient, it was treated with nitrous oxide, i.v. fentanyl, or local anaesthetic (epidural, intraperitoneal, or wound infiltration) as per treating clinician preference. All women received prophylactic i.v. metoclopramide 20 mg. Nausea and vomiting experienced intraoperatively, after operation, or both was treated with ondansetron 4 mg. Additional treatment for nausea and vomiting was according to clinician preference and local practice. Supplementary postoperative analgesia was provided by regular paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs, plus oral oxycodone, or i.v. morphine if necessary. Postoperative pruritus was treated on request, provided it was rated by the patient as moderate or severe [a verbal numerical rating score (VNRS) ≥ 4 on a 0–10 scale, with 0, no pruritus, and 10, worst pruritus imaginable]. Treatment of pruritus was according to preferred local practice, using nalbuphine, ondansetron, naloxone, or an antihistamine (such as chlorpheniramine).

Baseline data such as patient age, characteristics, physical, and obstetric status were collected within 24 h of the scheduled time of surgery. The time from intrathecal drug injection until study drug administration, the incidence of intraoperative pain or nausea/vomiting, and the baseline pruritus score at the time of study drug injection were noted. In the postoperative period, a VNRS was used to measure the presence and severity of pruritus, nausea, and pain (at rest and dynamic, with sitting up), with most parameters recorded at 2, 4, 8, 12, and 24 h post-surgery. At 24 h post-delivery, the patient was reviewed to determine the overall incidence pruritus; the incidence of a VNRS ≥ 4; whether treatment for the pruritus had been required; their satisfaction with the control of pruritus (0–100, 0, totally unsatisfied, and 100, totally satisfied); the global 0–50 intensity of postoperative nausea and vomiting (PONV) score; the quality of recovery score (QoR, range 0–18); and the overall benefit of analgesia score (OBAS, range 0–28). The OBAS assesses pain intensity and opioid-related
adverse effects. Possibly side-effects of methylnaltrexone, such as gastrointestinal cramping, flatulence, or defaecation, were sought by direct questioning.

**Sample size calculation and statistical analysis**

The primary outcome was the severity of pruritus with co-endpoints being 0–24 h area under the curve (AUC) VNRS and the worst 0–24 h VNRS pruritus score. Key secondary outcomes were the incidence of pruritus and the need for antipruritic treatment. An *a priori* sample size calculation found that a total sample size of 130 (*n* = 65 per group) was required to demonstrate a 25% change in the intensity of pruritus (power of 88%; *α* error rate of 0.05; 10% loss of subjects). Owing to the absence of AUC data, the sample size calculation was based on previously reported data where the mean (SD) pruritus score over 24 h was 6 (2.5). The sample size also had more than 80% power to demonstrate a one-third reduction in the incidence of pruritus from a (conservative) estimate of 75% in the control group.

Descriptive statistics were summarized using the median with inter-quartile range (IQR) and range (R). Categorical outcomes were summarized using percentage frequency distributions. AUC for pruritus scores to 24 h was calculated using the trapezoidal rule. Univariate comparisons of continuous data were made using the Mann–Whitney test and the \( \chi^2 \) or Fisher exact test was used for categorical comparisons. The median difference and 95% confidence intervals for worst pruritus and 24 h AUC were calculated using the Hodges–Lehmann method. \( P \)-values of < 0.05 were considered statistically significant. The intention-to-treat analysis was performed using SPSS.
v.18 (SPSS, Chicago, IL, USA) and Stata Statistical Software: Release 12 (StataCorp LP, College Station, TX, USA).

**Results**

A total of 137 patients were recruited into the study (MNTX group \( n = 69 \), placebo group \( n = 68 \)) across three study sites (Australia \( n = 18 \), Singapore \( n = 79 \), and USA \( n = 40 \)). There were five major protocol violations (Fig. 1).

The baseline patient characteristics were similar except that women in the MNTX group were significantly older compared with the placebo group (Table 1). Intraoperative data (Table 2) showed no significant differences between groups in terms of anaesthesia care, intraoperative treatment, duration from anaesthesia to study drug administration, or duration of surgery. Intraoperative vomiting (after delivery) was more common in the MNTX group (15\% vs 4\%, \( P = 0.04 \)).

The primary outcome measures of severity of pruritus were not significantly different between groups (Table 3 and Fig. 2). The secondary pruritus incidence and severity measures are shown in Table 3 and significantly differed for percentage with moderate or high pruritus score and for treatment, in favour of the MNTX group. In the MNTX group, three of nine women required more than one treatment for pruritus (ondansetron \( n = 1 \), antihistamine \( n = 1 \), naloxone \( n = 1 \)) and one woman required 3 doses of ondansetron. Of those who required rescue medication for pruritus in the placebo group, four of 19 women required a second dose (antihistamine \( n = 1 \), naloxone \( n = 2 \), or ondansetron \( n = 1 \)), and one woman required 4 doses (1 dose ondansetron and 3 doses of naloxone).

The incidence of nausea and vomiting in the first 24 h was 26\% and 31\% in the MNTX and placebo groups, respectively (\( P = 0.53 \)). The use of antiemetic agents, overall quality of pain relief (OBAS), maternal satisfaction scores, and quality of recovery (QoR) were not significantly different between the groups (Table 4). Postoperative pruritus, nausea, vomiting, or pain scores at rest, recorded at 2, 4, 8, 12 and 24 h, did not show significant differences between groups at any follow-up point (Table 3 and Figs 3 and 4). The incidence of cramps,

### Table 1 Patient characteristic, obstetric, and baseline clinical data.

<table>
<thead>
<tr>
<th>Data representation</th>
<th>Methylaltrexone (( n = 69 ))</th>
<th>Placebo (( n = 68 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34 (22–46)</td>
<td>32 (21–40)*</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (67–87; 62–113)</td>
<td>78 (69–83; 55–113)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>30 (27–35; 22–44)</td>
<td>30 (27–32; 20–47)</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>14 (20%)</td>
<td>13 (19%)</td>
<td></td>
</tr>
<tr>
<td>Primary CS</td>
<td>18 (26%)</td>
<td>18 (27%)</td>
<td></td>
</tr>
<tr>
<td>Preop QoR (0–18)</td>
<td>18 (17–18; 8–18)</td>
<td>18 (17–18; 11–18)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Operating theatre data. Data represent median (IQR; R) or \( n \) (\%). For duration of surgery calculated from time of surgical incision to the time surgery ended.

<table>
<thead>
<tr>
<th></th>
<th>Methylaltrexone (( n = 69 ))</th>
<th>Placebo (( n = 68 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal anaesthesia only</td>
<td>49 (71%)</td>
<td>50 (73%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Pre-delivery nausea</td>
<td>4 (6%)</td>
<td>9 (13%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Pre-delivery vomiting</td>
<td>0</td>
<td>2 (3%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Pre-study drug pruritus</td>
<td>13 (19%)</td>
<td>9 (13%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Time from anaesthesia to study drug (h)</td>
<td>1.2 (0.9–1.5; 0.4–4.5)</td>
<td>1.2 (1.0–1.4; 0.6–3.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Duration of surgery (h)*</td>
<td>0.9 (0.6–1.1; 0.2–3.6)</td>
<td>0.8 (0.7–1.1; 0.3–2.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Post-delivery nausea</td>
<td>22 (32%)</td>
<td>13 (19%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Post-delivery vomiting</td>
<td>10 (15%)</td>
<td>3 (4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Intraoperative fentanyl given</td>
<td>4 (6%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Primary and secondary pruritus outcomes. Data represent median (IQR; R) or \( n \) (\%). CI, 95\% confidence interval; AUC, area under the curve.

<table>
<thead>
<tr>
<th></th>
<th>Methylaltrexone (( n = 69 ))</th>
<th>Placebo (( n = 68 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 h AUC score</td>
<td>24 (9–47), 0–204</td>
<td>36 (11–68), 0–191</td>
<td>0.09</td>
</tr>
<tr>
<td>Median difference</td>
<td></td>
<td>8.5, 0–20</td>
<td></td>
</tr>
<tr>
<td>Worst score</td>
<td>3 (2–7), 0–10</td>
<td>5 (2–6), 0–10</td>
<td>0.24</td>
</tr>
<tr>
<td>Median difference</td>
<td></td>
<td>1.0, 0–2</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>58 (84%)</td>
<td>60 (88%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Pruritus scores ( &gt;4 )</td>
<td>28 (41%)</td>
<td>41 (60%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment of pruritus</td>
<td>9 (13%)</td>
<td>19 (28%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
flatulence, and defaecation after MNTX did not differ from placebo (Table 4).

**Discussion**

The subcutaneous injection of methylnaltrexone bromide 12 mg after Caesarean birth did not reduce the incidence or severity of intrathecal morphine-induced pruritus to a clinically important extent in this study. The suggestion of a late effect, with reduction in pruritus severity based on a lower percentage of high pruritus scores and lower need for treatment, needs further exploration.

We believe this is the first study to address the effect of methylnaltrexone on pruritus resulting from administration of an intrathecal opioid. Pruritus commences 25–180 min after intrathecal morphine, and peaks between 3 and 9 h post-injection. This pruritus peak coincides with peak cerebrospinal fluid concentration at the level of the cistern magna. Studies have found opioid-induced pruritus to be dose-dependent and located on the face, neck, and upper thorax. Pruritus is common in pregnant women, possibly because of an interaction of oestrogen with opioid receptors.

The mechanisms underlying pruritus are complex. Potential mechanisms include: peripheral TRPV1 positive neurones that respond to itch and nociception; small myelinated nerve fibres that react to pruritogens but not algogens; a peripheral and/or central role of prostaglandins, serotonin, dopamine and opioids; and multiple central pathways including an important centre in the medullary dorsal horn where there are connections to the spinal trigeminal nucleus.

Pruritus is activated by cephalad spread of intrathecal morphine within the cerebrospinal fluid to the spinal trigeminal nucleus. Pruritus is likely mediated through an interaction with μ-opioid receptors. Methylnaltrexone is a highly polar μ-opioid antagonist derivative of naltrexone. The methyl substitution prevents it from readily crossing the blood–brain barrier.

Methylnaltrexone also has partial agonist activity at κ-opioid receptors and activates κ-opioid receptors. κ-opioid receptors are present on peripheral neurones and within the central nervous system and are believed to inhibit pruritus. In addition, most noxious mediators can produce pruritus, and TRPV1-positive neurones play a role in both nociception and pruritus induced by systemically or centrally administered opioids.

Despite these potential beneficial antipruritic effects of methylnaltrexone bromide, under conditions of the current study, the drug did not reduce the severity of intrathecal morphine-induced pruritus after Caesarean birth. These findings are in keeping with an animal study that found that methylnaltrexone administered systemically did not attenuate opioid-induced scratching in primates. However, the current study cannot exclude a weak and possibly delayed effect of methylnaltrexone on neuraxial opioid-induced pruritus. Twelve hours post-Caesarean delivery, the incidence of high pruritus scores and the need for treatment were higher in the placebo group. Administered subcutaneously, methylnaltrexone reaches peak absorption within 30 min, but the findings appear consistent with the drug’s long terminal half-life of 8 h. It is possible that the expression of TRPV1 transduction protein ion channels or yet to be determined pruritogenic factors are affected by peripherally acting opioid antagonists.

Methylnaltrexone is well tolerated by patients and volunteers. Among patients on chronic opioid therapy receiving the drug, the most common side-effects are fever, nausea (the latter less common than placebo in phase two trials), and a bowel movement response, usually within 1–4 h of administration.

**Table 4** Postoperative review at 24 h after Caesarean birth. Data represent median (IQR; R) or n (%). PONV, postoperative nausea and vomiting; OBAS, overall benefit of analgesia score; QoR score, quality of recovery. *Missing data in 12 women in the MNTX group and 13 in the placebo group.

<table>
<thead>
<tr>
<th></th>
<th>Methylaltrexone (n=69)</th>
<th>Placebo (n=68)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for PONV</td>
<td>9 (13%)</td>
<td>12 (18%)</td>
<td>0.49</td>
</tr>
<tr>
<td>PONV intensity score (0–50)</td>
<td>0 (0–1; 0–50)</td>
<td>0 (0–2; 0–50)</td>
<td>0.53</td>
</tr>
<tr>
<td>Cramping pain</td>
<td>43 (62%)</td>
<td>45 (66%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Opioid required, n (%)</td>
<td>24 (35%)</td>
<td>24 (35%)</td>
<td>0.95</td>
</tr>
<tr>
<td>OBAS (0–28)</td>
<td>4 (2–6; 0–16)</td>
<td>4 (3–7; 0–19)</td>
<td>0.58</td>
</tr>
<tr>
<td>Flatulence</td>
<td>41 (60%)</td>
<td>34 (50%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Defaecation</td>
<td>17 (25%)</td>
<td>13 (19%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>24 (35%)</td>
<td>18 (27%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Maternal satisfaction with pruritus control (0–100)</td>
<td>88 (80–97; 50–100)</td>
<td>90 (80–90; 50–100)</td>
<td>0.69</td>
</tr>
<tr>
<td>QoR score (0–18)*</td>
<td>15 (13–16; 10–18) (n=57)</td>
<td>15 (14–16; 11–18) (n=55)</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Flatulence, abdominal cramps, or diarrhoea are possible but usually mild. Methylnaltrexone reversed the opioid-induced inhibition of gut function, as measured by oral-caecal transit time. In vitro methylnaltrexone increases intestinal smooth muscle contraction by 30%, but it does not accumulate with repeat dosing or show signs of toxicity. Our study patients did not report gastrointestinal adverse events.

Peripheral opioid receptors mediate a number of other functions and peripherally mediated adverse opioid effects include nausea, vomiting, and urinary retention. There is weak evidence from clinical trial data that methylnaltrexone may have beneficial effects on opioid-induced nausea and urinary retention. A possible explanation for this is that the chemoreceptor trigger zone involved in emesis lies outside the blood-brain barrier. Urinary retention also has both central and peripheral causation. We found no difference in the incidence of PONV or urinary retention. However, the study was not adequately powered for most of these adverse outcomes.

There are no studies of methylnaltrexone bromide in pregnant women. Reproduction studies in pregnant rats and rabbits found no effect on fertility or fetal development after i.v. doses 17-fold the weight-corrected human therapeutic dose (as applied in this study). It is not known if the drug is excreted in human breast milk; however, low drug oral bioavailability would likely limit drug exposure in the breastfeeding neonate.

This study has a number of potential limitations. The findings only pertain to a single prophylactic dose of methylnaltrexone after the administration of intrathecal morphine in women undergoing Caesarean delivery. The results may differ in association with larger or repeated doses of methylnaltrexone, other neuraxial opioids, a larger or smaller intrathecal morphine dose, and/or among other patient populations. Additionally, results may have differed if the drug intervention occurred before the injection of intrathecal morphine. We opted to give the drug after delivery to minimize drug transfer to the fetus, given the paucity of information about the drug’s safety during pregnancy. In some patients, this resulted in administration several hours after injection of intrathecal morphine, at which time pruritus may have already commenced. We did not exclude women who were planning to breastfeed, because of the drug’s low oral bioavailability. Patient information before consent disclosed relevant information about the drug. A potential confounding factor was systemic (i.e. oral) opioid-induced pruritus, as intra- and postoperative pain management was not standardized. However, only one participant received intraoperative i.v. fentanyl and the requirement for postoperative i.v. or oral opioid analgesia did not differ between groups, making effects from this potential confounding very unlikely. The use of ondansetron to treat PONV could be criticized because this drug has some antipruritic effect. However, studies suggest that ondansetron does not prevent neuraxial morphine-induced pruritus and has a very modest benefit as treatment in this setting. In this study, the incidence and severity of PONV and the use of ondansetron did not differ between groups, balancing any potential effect. Finally, the study may have been underpowered to show a small clinical effect, especially considering the upper confidence interval for reduction in worst pruritus score and the possible signal of fewer high scores and a significantly lower need for treatment in the methylnaltrexone group.

Although we did not find significant between-group differences in our primary outcome measures of the intensity of pruritus, the data raised exploratory hypotheses about a possible delayed benefit. Future studies will need to address if there are dose-related effects, whether the drug shows...
efficacy against pruritus induced by other neuraxial opioids, if there is efficacy in other surgical populations including males, and if methylnaltrexone has a treatment effect.

In conclusion, under the conditions of the study, a single dose of subcutaneous methylnaltrexone bromide 12 mg did not reduce overall severity or the incidence of pruritus among an obstetric population receiving intrathecal fentanyl 15 \text{\textmu}g and morphine 100 \text{\textmu}g during spinal anaesthesia for Caesarean delivery. Prophylactic treatment with a peripherally acting \textmu-opioid antagonist was generally ineffective against intrathecal morphine-induced pruritus in this peripartum setting, although a small clinical effect cannot be excluded.

Authors’ contributions

M.P.: conception, design, and organization; interpretation of data and writing of the manuscript; and final approval; B.S.: study design and organization; interpretation of data and writing of the manuscript; and final approval; L.N.: study organization, data collection, and writing of the manuscript; and final approval; A.S.: study organization and writing of the manuscript; and final approval; E.N.: data design, analysis, and interpretation; writing of the manuscript; and final approval; B.C.: study design and organization; interpretation of data and revision of the manuscript; and final approval.

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Declaration of interest

None declared.

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