Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance

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ABSTRACT

Background: Previous studies have demonstrated that the addition of intrathecal fentanyl to a spinal anesthetic for cesarean delivery improves intraoperative analgesia. However, intrathecal fentanyl may induce acute tolerance to opioids. The objective of this study was to investigate whether the addition of intrathecal fentanyl to spinal anesthesia with intrathecal morphine increases postoperative analgesic requirements and pain scores.

Methods: In this randomized, double-blinded study, 40 women having elective cesarean delivery were enrolled. Patients received spinal anesthesia with hyperbaric bupivacaine 12 mg, morphine 200 µg, and fentanyl 0, 5, 10 or 25 µg. Each patient received intravenous patient-controlled analgesia morphine for 24 h postoperatively. Outcome measures included postoperative morphine usage and pain scores, as well as intraoperative pain, nausea, hypotension and vasopressor use.

Results: Total morphine use over the 24-h post-spinal study period was similar among the study groups (P = 0.129). Postoperative pain scores were higher in patients receiving fentanyl 5, 10 and 25 µg compared to fentanyl 0 µg control group (P = 0.003).

Conclusions: The study results suggest that intrathecal fentanyl may induce acute tolerance to intrathecal morphine. However, because there was no difference in postoperative analgesia requirement and the difference in pain scores was small, the clinical significance of this finding is uncertain.

Keywords: Analgesic-opioids; Anesthesia-obstetric; Anesthesia-spinal; Tolerance; Spinal; Anesthesia; Intrathecal; Fentanyl; Acute; Tolerance

Introduction

Opioids are commonly added to the local anesthetic solution when administering spinal anesthesia for cesarean delivery. Intrathecal (IT) fentanyl improves intraoperative analgesia, especially during uterine exteriorization, and prolongs the sensory component of the block associated with IT local anesthetics. However, IT fentanyl provides limited postoperative analgesia with median time to first analgesia of 4 h (range 2–13 h). Neuraxial morphine has a long duration of action and provides prolonged postoperative analgesia compared to other routes of administration. Using a lipophilic opioid such as fentanyl, is helpful because the onset time for neuraxial morphine may be too slow for it to contribute to intraoperative analgesia.

A potential problem is that patients may experience more postoperative pain if intraoperative opioids are administered due to opioid-induced hyperalgesia. Animal and human volunteer data suggest that administration of high doses of intravenous (i.v.) opioids induces acute tolerance to subsequently administered opioids, whereas clinical studies have yielded inconsistent and inconclusive results. To our knowledge, only one previous study has investigated whether administration of IT fentanyl with a spinal anesthetic for cesarean delivery induces acute tolerance to opioids. Cooper et al. showed that when patients were given a large dose of IT fentanyl (25 µg) with their spinal anesthetic, they had an increased requirement for i.v. morphine postoperatively. However, in contrast to common clinical practice, IT morphine was not given in their study.

The primary aim of this study was to determine if the addition of IT fentanyl to a spinal anesthetic solution...
containing IT morphine induces acute opioid tolerance, quantified by increased postoperative morphine requirements and pain scores. The secondary aim was to determine if there is a dose–response associated with this phenomenon. Our null hypothesis was that the addition of IT fentanyl would not change postoperative analgesic use or pain scores.

**Methods**

A total of 40 patients were enrolled (10 per group) in this randomized, double-blinded, controlled, dose-ranging study after obtaining Institutional Review Board approval and written informed consent. We enrolled healthy women (American Society of Anesthesiologists physical status 1 or 2) with term singleton pregnancies (>37 weeks of gestation) undergoing elective cesarean delivery under spinal anesthesia before noon. Patients were excluded from study participation if they met any of the following criteria: morbid obesity (body mass index >40 kg/m²), planned postpartum tubal ligation, previous adverse reaction to opioid medications or history of chronic opioid use.

The spinal anesthetic was administered with a 25-gauge Whitacre needle (B. Braun Medical, Bethlehem, PA, USA) at the L2–3 or L3–4 intervertebral space with the patient in the sitting position. Each participant received IT hyperbaric bupivacaine 12 mg and preservative-free morphine sulfate 200 µg (Astramorph PF, APP Pharmaceuticals LLC, Schaumburg, IL, USA) with an added randomized dose of 0, 5, 10 or 25 µg IT fentanyl (Baxter Healthcare Corporation, Deerfield, IL, USA). Randomization was by computer-generated random-number allocation. The mixture was diluted to a total of 2.5 mL with sterile saline. The investigator, patient, anesthesiologist treating the patient, and all study staff remained blinded to the assigned treatment. An anesthesiologist not involved in the study or patient care prepared the fentanyl doses.

Patients were immediately placed supine with left uterine displacement after the spinal anesthetic was administered. The height of the spinal block was assessed by pinprick and touch every 2 min until the block reached the T4 dermatome bilaterally. Intraoperative vital-sign measurements included: mean arterial pressure measured with a non-invasive blood pressure monitor, heart rate, respiratory rate and oxygen saturation. Ephedrine was given in 5-mg increments to treat systolic arterial pressure <80% of the preanesthetic value. Patient complaints of intraoperative pain or nausea were treated as needed at the discretion of the anesthesiologist. Pain was assessed with a 100 mm visual analog pain scale (VAPS, 0 = no pain, 100 = worst pain imaginable). Intraoperative pain scores were assessed at the time of spinal placement, skin incision, uterine incision, delivery, and skin closure. The quality of intraoperative anesthesia was assessed by the presence or absence of any patient request for supplemental anesthesia. Postoperative pain scores, oxygen saturation, and respiratory rate were assessed on arrival to the post-anesthesia care unit (PACU), and at 30 min and 60 min, 4, 8, 12, and 24-h following the end of surgery.

In the PACU, each patient received i.v. morphine patient-controlled analgesia (PCA) for the first 24-h. The settings were as follows: bolus 1 mg, lockout interval 8 min, hourly maximum 8 mg. No background infusion was utilized. The interval dose and cumulative dose of morphine were recorded at 4, 8, 12 and 24-h following the administration of spinal anesthesia. No other forms of analgesia were administered.

**Statistical analysis**

Based on a pilot study, *a priori* power analysis predicted that we required 10 patients in the control group and 30 patients in the treatment group to detect a mean difference of 30% in postoperative morphine use in the first 24 h (expected mean 17.7 mg, standard deviation 5.5 mg, power 0.8, alpha 0.05).

Descriptive statistics were used to summarize demographic and outcome data. Normal distribution was determined using QQ plots and the Kolmogorov–Smirnov test. The area under the VAPS × time curve (AUC) was calculated using the trapezoid rule to assess the pain burden over the 24-h study period. The Kendall Correlation test was used to assess the effect of increasing fentanyl doses on postoperative pain AUC and morphine (mg) consumption. One-way ANOVA was used to analyze normally distributed continuous variables with the post-hoc Tukey test if an overall difference was found. The Kruskal–Wallis test was utilized for ordinal and non-parametric continuous data with post-hoc comparisons using the Mann–Whitney U test. Associations among categorical variables (requirement for supplemental intraoperative anesthesia or treatment of nausea) were investigated using the χ² test and Fisher’s exact test as appropriate. The association between pain (VAPS × time AUC) and analgesic consumption (total 24-h IV morphine use) was performed using Spearman’s rho. A *P*-value <0.05 was considered statistically significant for the primary outcome measure of analgesic use, as well as for pain scores, in the control group compared to the fentanyl groups combined. For the between-groups secondary analysis, to account for multiple comparisons, a *P*-value <0.017 was used to reject the null hypothesis. Data were analyzed using NCSS version 17 for Windows (NCSS, LLC, Kaysville, UT, USA).

**Results**

Forty patients were recruited and enrolled. One patient in the control group dropped out secondary to pruritus...
after 12 h. Two patients dropped out because of postoperative pain: one in the fentanyl 5 μg group who had complete data until 8 h, and another in the fentanyl 25 μg group who had complete data until 12 h. Therefore, partial data for three patients and complete data for 37 patients were analyzed. There were no statistically significant differences in the demographics among groups with respect to age, height, weight, gestational age and parity (Table 1).

Total postoperative PCA morphine consumption did not differ among the groups (Fig. 1). Postoperative pain scores during the study period are outlined in Fig. 2. There was a significant difference between the postoperative pain AUC with increasing fentanyl doses (Tau 0.38, \( P = 0.003 \), Kendal correlation test). The median [interquartile range] pain AUC in the fentanyl 0 μg control group was 267 [120–360] mm.h, compared with 487 [367–760] mm.h in the fentanyl 5 μg group (\( P = 0.018 \)), 520 [381–647] mm.h in the fentanyl 10 μg group (\( P = 0.007 \)), and 608 [483–757] mm.h in the fentanyl 25 μg group (\( P = 0.023 \)). There was a poor correlation between pain, AUC and total morphine consumption (\( r = 0.194; P = 0.265 \)).

There were no significant differences in postoperative oxygen saturation or respiratory rate between the groups. At no time did any patient have an oxygen saturation <96%. One patient in the fentanyl 25 μg group had a respiratory rate of 8–10 breaths/min from 30 to 50 min after the spinal anesthetic. Otherwise, respiratory rates in all patients varied from 14–24 breaths/min during the intraoperative and postoperative periods.

No patient reported pain at spinal placement, skin incision, uterine incision, or skin closure. However, some patients spontaneously reported pain at other times during the surgery and were treated at the discretion of the anesthesiologist providing clinical care. Four patients in the control group versus two patients in all the fentanyl groups combined required treatment for intraoperative nausea (\( P = 0.031 \), Table 2). Interventions to treat intraoperative pain were similar in the control group compared to the fentanyl groups combined (\( P = 0.164 \), Table 2). There were no differences in blood pressure (minimum or average) or ephedrine use among the study groups (Table 3).

Table 1 Patient demographics and obstetric characteristics

<table>
<thead>
<tr>
<th>Fentanyl dose</th>
<th>0 μg (n = 10)</th>
<th>5 μg (n = 10)</th>
<th>10 μg (n = 10)</th>
<th>25 μg (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34 ± 6</td>
<td>36 ± 4</td>
<td>30 ± 7</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 8</td>
<td>163 ± 5</td>
<td>163 ± 5</td>
<td>158 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88 ± 7</td>
<td>93 ± 14</td>
<td>82 ± 23</td>
<td>92 ± 18</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38 ± 1</td>
<td>38 ± 1</td>
<td>40 ± 1</td>
<td>39 ± 1</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No differences among groups except for gestational age (\( P = 0.046 \)).
Discussion

Our primary objective was to investigate if clinically significant acute tolerance to opioids developed with the addition of IT fentanyl to a bupivacaine spinal anesthetic solution containing IT morphine. This was assessed by measuring the postoperative i.v. morphine requirement and postoperative pain for patients who had received IT fentanyl in doses 5, 10, and 25 μg compared to a no-fentanyl group. We expected that if acute tolerance occurred, the amount of morphine consumed and postoperative pain experienced would be greater for the patients who were given fentanyl versus no fentanyl, assuming subjects in each group used the PCA to treat their pain to the same level. In addition, morphine usage and pain would likely increase successively with increasing doses of IT fentanyl if there was a dose response associated with IT fentanyl dose and acute tolerance.

Our study did not find any significant difference in postoperative morphine usage with increasing fentanyl dosages. However, pain scores over the first 24 h after surgery, as measured by AUC, were increased in the groups receiving IT fentanyl. We expected that if acute tolerance occurred, the amount of morphine consumed and postoperative pain experienced would be greater for the patients who were given fentanyl versus no fentanyl, assuming subjects in each group used the PCA to treat their pain to the same level. In addition, morphine usage and pain would likely increase successively with increasing doses of IT fentanyl if there was a dose response associated with IT fentanyl dose and acute tolerance.

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Four patients in the control group versus two patients in all the fentanyl groups combined required treatment for intraoperative nausea ($P = 0.031$). A number of other studies have shown less intraoperative pain and nausea when fentanyl is added to the local anesthetic for spinal anesthesia. Intrathecal fentanyl blunts the noxious input from visceral afferents that are stimulated by pulling on the peritoneal structures and exteriorization or manipulation of the uterus. Intrathecal fentanyl may induce acute opioid tolerance when IT morphine is included in the spinal anesthesia solution. One limitation with our study design is that it does not allow us to definitively differentiate if IT fentanyl results in tolerance to the IT morphine administered in the spinal solution or the i.v. PCA morphine used to treat postoperative pain. Differentiation between IT and i.v. morphine tolerance could have occurred if only non-opioids were administered for postoperative analgesia, however, we felt that non-opioids (non-steroidal anti-inflammatory drugs, acetaminophen) would provide inadequate post-cesarean analgesia and could not be ethically justified at our institution.

Table 2  Incidence of intraoperative pain and nausea requiring treatment

<table>
<thead>
<tr>
<th>Fentanyl dose (μg)</th>
<th>Patients requiring treatment for pain</th>
<th>Patients requiring treatment for nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 10)</td>
<td>2</td>
<td>4*</td>
</tr>
<tr>
<td>5 (n = 10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 (n = 10)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>25 (n = 10)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of patients per group. There was a significant difference compared to the fentanyl groups combined ($P = 0.031$).

Table 3  Intraoperative hemodynamic data

<table>
<thead>
<tr>
<th>Fentanyl dose (μg)</th>
<th>Mean BP (mmHg)</th>
<th>Minimum BP (mmHg)</th>
<th>Ephedrine dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 10)</td>
<td>70 ± 5</td>
<td>59 ± 7</td>
<td>17 ± 10</td>
</tr>
<tr>
<td>5 (n = 10)</td>
<td>71 ± 7</td>
<td>57 ± 11</td>
<td>13 ± 11</td>
</tr>
<tr>
<td>10 (n = 10)</td>
<td>77 ± 26</td>
<td>55 ± 9</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>25 (n = 10)</td>
<td>70 ± 15</td>
<td>56 ± 20</td>
<td>19 ± 15</td>
</tr>
</tbody>
</table>

Data are mean ± SD. There were no significant differences among the groups. BP: blood pressure.

PCA use, showed that we would require 170 patients (control group 42: fentanyl group 128) to have enough power to have shown a difference in analgesic use (SD 10.75 mg, power 0.8, alpha 0.05). Although the higher postoperative pain scores in patients receiving fentanyl did not result in increased analgesic use, we believe that the differences in pain scores suggests that intrathecal fentanyl may induce acute opioid tolerance when IT morphine is included in the spinal anesthesia solution. One limitation with our study design is that it does not allow us to definitively differentiate if IT fentanyl results in tolerance to the IT morphine administered in the spinal solution or the i.v. PCA morphine used to treat postoperative pain. Differentiation between IT and i.v. morphine tolerance could have occurred if only non-opioids were administered for postoperative analgesia, however, we felt that non-opioids (non-steroidal anti-inflammatory drugs, acetaminophen) would provide inadequate post-cesarean analgesia and could not be ethically justified at our institution.

Four patients in the control group versus two patients in all the fentanyl groups combined required treatment for intraoperative nausea ($P = 0.031$). A number of other studies have shown less intraoperative pain and nausea when fentanyl is added to the local anesthetic for spinal anesthesia. Intrathecal fentanyl blunts the noxious input from visceral afferents that are stimulated by pulling on the peritoneal structures and exteriorization or manipulation of the uterus. These visceral afferent stimuli can manifest clinically as nausea, vomiting or cramping and do not appear to be blocked completely with the local anesthetic block alone. Even when IT morphine 200 μg was added, as in this study, visceral stimuli appeared to be inadequately blocked in the absence of IT fentanyl. Although hypotension can cause nausea and be a potential confounder, there was no evidence in our study that patients...
treated for nausea had more hypotension than the other patients. The intraoperative benefit of using IT fentanyl suggested in this study and a number of previous studies appears to outweigh the potential for inducing acute postoperative tolerance.

An important message from the data in this study, and other studies of post-cesarean delivery pain is the variability in the postoperative analgesic use and pain scores across all groups. The phenomenon of acute tolerance that we were studying accounted for very little of the variation in the amount of pain or analgesia required. For example, the range of morphine doses used by any group was three times the median dose in the groups. Large inter-patient variability in opioid use is not unique to this study.

Although this study was underpowered to show small differences among groups, we found no apparent benefit with larger IT fentanyl doses. These findings are consistent with those of Hunt et al., who studied IT fentanyl doses, ranging from 2.5 to 50 μg in combination with IT bupivacaine for cesarean delivery. They found improved intraoperative analgesia compared to bupivacaine alone, but minimal additional benefit beyond IT fentanyl doses of 6.25 μg and interestingly also no difference in postoperative morphine use amongst the groups. Side effects from IT opioids are dose-dependent and larger doses of fentanyl may increase the risk of respiratory depression. We did not observe any significant respiratory depression in the study groups. One patient who received fentanyl 25 μg had a decreased respiratory rate intraoperatively for 20 min. Although the patient’s respiratory rate fell below 10 breaths/min, the oxygen saturation remained above 96% and the episode resolved spontaneously.

A potential limitation of this study is the multiple small-group comparisons, which were a function of the dose–response design. The strength of this design is that we obtain information over a wide range of doses. However, the multi-group design reduces the statistical power to show small differences between the groups. Due to the variability in postoperative morphine use, combined with the small sample size and multiple groups, we lacked power to show a small difference in morphine use. Although there was a statistically significant difference in postoperative pain in the fentanyl groups, the clinical effect size was small and did not lead to increased analgesic use despite a five-fold increase in fentanyl dose. However, we acknowledge that subtle differences among study groups would not have been detected due to study design limitations acknowledged above.

In conclusion, our findings suggest that IT fentanyl in doses from 5 to 25 μg co-administered with IT bupivacaine and morphine for cesarean delivery under spinal anesthesia may induce subtle acute opioid tolerance as evidenced by higher overall pain scores in patients who received fentanyl compared with the control group. However, this did not result in increased analgesic use post-cesarean delivery. Therefore the clinical importance of our findings is uncertain. Future studies with larger sample sizes are required to fully elucidate this phenomenon and determine its clinical significance before clinicians consider avoid using IT fentanyl for fear of inducing acute tolerance postoperatively, especially with in light of previous studies showing that IT fentanyl results in less intraoperative pain and nausea during cesarean delivery.

Disclosure

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