ORIGINAL PAPER

Effects of fentanyl added to a mixture of intrathecal bupivacaine and morphine for spinal anaesthesia in elective caesarean section

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Abstract

Background: The use of either fentanyl or morphine intrathecally as adjuncts to bupivacaine for spinal anaesthesia in caesarean deliveries is commonplace. However, the use of fentanyl in combination with morphine and bupivacaine in elective caesarean section is debatable. We hypothesized that while the addition of intrathecal fentanyl to morphine and bupivacaine increases side effects, it does not improve the clinical quality of anaesthesia or analgesia in elective caesarean deliveries.

Methods: In this case-controlled, double-blinded study, women undergoing elective caesarean deliveries received intrathecal fentanyl plus morphine with bupivacaine (Group 1) or intrathecal morphine with bupivacaine alone (Group 2). Patients were assessed at 4 hours for pain at rest and on movement using the visual analog scale (VAS), time taken for sensory block to T6 and side effects.

Results: Fifty patients were randomized into Group 1 (n = 25) and Group 2 (n = 25). There was no difference in the mean VAS scores at rest or on movement between the two groups. At 4 hours, the mean (SD) VAS scores at rest were 13.2 (13.7) mm and 12.0 (11.5) mm in Group 1 and 2, respectively (P = 0.739). The mean (SD) VAS scores on movement in Group 1 were 38.0 (18.2) mm, and in Group 2 were 28.4 (12.4) mm (P = 0.349). Group 1 took 7.34 hours to the first request for postoperative opioid analgesia while Group 2 took 7.08 hours (P = 0.749). Correspondingly, patient satisfaction ratings were comparable for both groups, the mean (SD) rating in Group 1 at 84.4 (11.11) compared to Group 2 at 87.6 (9.02), (P = 0.269). Patients in both groups had similar onset of T6 block. The incidence of side effects was higher in Group 1 than Group 2.

Conclusion: Our study found that the addition of intrathecal fentanyl to morphine and bupivacaine did not have an advantage for short-term postoperative analgesia, but increased the incidence of opioid-related side effects and thus cost of care in a maternal population attending for elective caesarean section.

Keywords: intrathecal, fentanyl, morphine, caesarean section, pain

Introduction

Fentanyl has been used as an adjunct to bupivacaine for spinal anaesthesia for elective caesarean section as it has been shown both to improve the quality of block and reduce the need for intraoperative supplementation of opioids [1].

The use of either fentanyl or morphine intrathecally as adjuncts to bupivacaine for spinal anaesthesia in caesarean deliveries is commonplace. Intrathecal morphine has been shown to improve postoperative analgesia in caesarean sections. However, the role of fentanyl in improving quality of analgesia in elective caesarean sections is debatable. There is an incongruity of evidence to suggest that this provides superior anaesthesia. Furthermore, there is limited data to suggest whether or not fentanyl could potentially increase the incidence of side effects associated with intrathecal opioids. The use of both fentanyl and morphine intrathecally has been shown to cause significant
pruritus, nausea and sedation in the maternal population [2, 3] as well as to reduce the Apgar scores in neonates [4]. This not only decreases maternal satisfaction of the anaesthetic experience but would also add to increased hospital costs.

This double-blinded randomized case-control study was conducted to assess the clinical advantage of intrathecal fentanyl use when added as an adjunct to intrathecal morphine and bupivacaine for caesarean sections. We hypothesized that while the addition of intrathecal fentanyl to intrathecal morphine increases side effects associated with intrathecal opioids, it does not contribute to the improved clinical quality of anaesthesia or analgesia when combined with bupivacaine in spinal anaesthesia for elective caesarean deliveries.

Methods

Upon institutional clinical research Ethics Committee approval, pregnant women 19 years of age or older presenting for elective caesarean delivery were recruited for participation in this study. Informed consent was taken on arrival to hospital by one of the study investigators.

Patients excluded from this study were women who had contraindications to neuraxial anaesthesia or analgesics used in the study, chronic pain, systemic diseases such as neuromuscular disorders, women with a complicated pregnancy such as preeclampsia, HELLP syndrome or multiple pregnancies, high body mass index of more than 35 and women who were not able to read or understand oral or written English.

Patients were blinded to the treatment allocation administered by a staff anaesthetist. The anaesthetists performing the spinal anaesthesia were separate to study investigators. Investigators interviewing patients post-operatively were hence blinded to treatment.

This study investigated two groups of subjects presenting for elective caesarean section. Patients were randomized using sealed envelopes to either Group 1 or Group 2. Subjects in Group 1 received both intrathecal morphine 100 μg and intrathecal fentanyl 10 μg with 2.3 ml of 0.5% hyperbaric bupivacaine as a spinal anaesthetic. Subjects in Group 2 received intrathecal preservative free morphine 100 μg with 2.3 ml 0.5% hyperbaric bupivacaine for their spinal anaesthetic.

Spinal anaesthesia was administered under aseptic conditions, with the patient in the sitting position, using a 25 G Whitacre pencil point spinal needle introduced at the level of L3-4 interspace. After the free flow of clear cerebrospinal fluid was observed, the drug mixture was given over 10-15 s with cephalad orientation of the spinal needle bevel.

The sensory block was tested with ice and the time taken to reach a sensory level of T6 noted.

All subjects were given a co-loading of 500 millilitres of Hartmann’s solution. All patients received 50 μg of intravenous phenylephrine immediately after administration of the spinal anaesthetic. Subsequently, hypotension was treated accordingly at the discretion of the supervising anaesthetist. Intra-operatively, patients requiring rescue analgesia would have received intravenous fentanyl in 25 μg aliquots. Additionally, post-delivery they received intravenously ondansetron 4 mg and a prophylactic antibiotic as per standard care. After delivery, patients would have been started on an oxytocin infusion of 40 IU in 1 liter Hartmann’s solution as per standard practice at our institution. At the end of surgery, patients received routine analgesia of rectal paracetamol 1.5 g and diclofenac 100 mg unless otherwise contraindicated. Postoperative analgesia consisted of standard doses of oral paracetamol, diclofenac around the clock and oxycodone as required.

Maternal demographics were recorded and patients were assessed at 4 hours after induction of spinal anaesthesia. Postoperative pain was assessed using a visual analog scale (VAS) of 0 to 100 mm, with 0 being no pain and 100 being the worst possible pain. Patients rated their pain at rest and on movement. Time to first request of postoperative opioid, patient satisfaction rating (on a verbal rating scale of 0 to 100) and any side effects reported were recorded.

The primary end point for this study was the effect of intrathecal fentanyl on pain scores at 4 hours when added to intrathecal morphine and bupivacaine in spinal anaesthesia for elective caesarean deliveries. Secondary end points included time taken for the sensory block to reach a level of T6, patient satisfaction, the incidence of side effects such as nausea, vomiting and pruritus, as well as time to first request for postoperative opioid analgesia.

To the best of our knowledge, the mean VAS at 4 hours post caesarean section under spinal anaesthesia with intrathecal morphine and bupivacaine has not been reported. Therefore, a pilot study was carried out on ten patients in order to establish this parameter. Assuming a clinically significant reduction of 20% in VAS when fentanyl is added, this information was used to calculate the standardized effect size and subsequently was used to estimate the sample size (alpha 0.05, beta 0.2), which was expected to be no more than 40 patients.

Statistical analysis was performed with SPSS Statistics 17.0.1. Demographics were examined with basic descriptive analysis. Continuous variables such as time taken to onset of block, VAS scores, time taken to first request for postoperative opioid and patient satisfaction ratings were analysed for significance using...
unpaired t-test analysis. The side effect profiles were analysed using Fischer’s exact test.

Results

Fifty patients met the inclusion criteria and were randomized to either Group 1 (n = 25) or Group 2 (n = 25) (Figure 1). The maternal characteristics of age, weight, height and body mass index were similar for both groups (Table 1).

Table 1. Maternal characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.08 (4.4)</td>
<td>31.08 (5.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.44 (8.4)</td>
<td>79.12 (9.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.6 (6.7)</td>
<td>166.3 (7.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2 (1.0)</td>
<td>28.6 (0.8)</td>
</tr>
</tbody>
</table>

BMI = body mass index
Data are mean (SD)

Time taken for onset of T6 sensory block was similar in both groups. Group 1 achieved a T6 block after a mean (SD) of 5.05 (2.02) min while Group 2 achieved same after 6.3 (2.46) min, (P = 0.056). None of the patients required intra-operative rescue analgesia.

There was no difference in the mean VAS scores at rest or on movement between the two groups. At 4 hours, the mean (SD) VAS scores at rest were 13.2 (13.7) mm and 12.0 (11.5) mm in Group 1 and 2, respectively (P = 0.739). The mean (SD) VAS scores on movement in Group 1 were 38.0 (18.2) mm and in Group 2 were 28.4 (12.4) mm (P = 0.349) (Figure 2). Group 1 took on average 7.34 hours to the first request for postoperative opioid analgesia while Group 2 took 7.08 hours (P = 0.749). Correspondingly, patient satisfaction ratings were comparable for both groups, with a mean (SD) rating in Group 1 at 84.4 (11.11) compared to Group 2 at 87.6 (9.02) (P = 0.269).

All incidences of side effects such as nausea, vomiting and pruritus were higher in Group 1 than in Group 2, although only of significance in those with pruritus (Table 2).

Fig. 1. Flowchart. Group 1 – intrathecal fentanyl, morphine and bupivacaine; Group 2 – intrathecal morphine and bupivacaine
Fig. 2. Static and dynamic pain scores (mm) 4 hours post induction of spinal anaesthesia; data are mean (SD); VAS = visual analog scale

Table 2. Incidence of side effects

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 25)</th>
<th>Pearson Chi Square</th>
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<tbody>
<tr>
<td>Nausea n (%)</td>
<td>13 (52)</td>
<td>7 (28)</td>
<td>0.326</td>
</tr>
<tr>
<td>Vomiting n (%)</td>
<td>5 (20)</td>
<td>2 (8)</td>
<td>0.543</td>
</tr>
<tr>
<td>Pruritus n (%)</td>
<td>12 (48)</td>
<td>4 (16)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

n – number of patients

Twelve parturients in Group 1 encountered pruritus while only four did in Group 2. The analysis of nominal data using the Fischer’s exact test found its significance to be 0.008.

Discussion

Since the first clinical reports using intrathecal morphine for analgesia were published in 1979, neuraxial opioids have gained widespread popularity for postoperative pain. Spinal opioids have adopted a place as effective adjuncts to local spinal anaesthesia in the maternity population presenting for caesarean delivery, with common use of a combination of both lipophilic and lipophobic opioids intrathecally.

While intrathecal morphine is known to be an effective opioid for intraoperative spinal anaesthesia and postoperative analgesia, its slow onset of action can be a limiting factor. Therefore, the addition of intrathecal fentanyl as a lipophilic opioid to spinal anaesthesia was suggested to confer such benefits as improved quality of anaesthesia, better postoperative analgesia and less side effects [5-7]. However, the evidence for advantages of combined intrathecal fentanyl and intrathecal morphine with bupivacaine versus intrathecal morphine alone and bupivacaine in elective caesarean sections has been inconsistent to date.

The results of this study indicate that the addition of fentanyl to intrathecal morphine does not result in better postoperative analgesia based on similar resting and movement VAS scores at 4 hours post spinal administration. Indeed, these findings are supported by a placebo controlled trial [2]. Our secondary outcome, time of onset to T6 sensory block as well as time to first request for postoperative opioid analgesia, did not differ between the two groups. Our results may have contrasted with studies [8, 9] that propose a postoperative analgesic advantage of intrathecal fentanyl due to our use of a low dose of 10 μg intrathecal fentanyl. Some studies [10, 11] seem to indicate a dose of 20 μg intrathecal fentanyl for maximizing postoperative analgesia while minimizing side effects. Arguably, Hunt et al. [3] suggested that even a low dose of 6.25 μg intrathecal fentanyl with hyperbaric bupivacaine significantly extended post-caesarean section analgesia duration from 71 to 192 minutes.

Intrathecal fentanyl has a high lipid solubility (580:1 lipid solubility compared to morphine), which allows its rapid clearance from the cerebrospinal fluid (CSF). This increased clearance is postulated to cause less cephalad spread of fentanyl, and thus fewer side effects compared to intrathecal morphine [12-14].

However, our study showed a lower incidence of maternal side effects when intrathecal fentanyl was not added to intrathecal morphine and bupivacaine.

The mechanism for intrathecal opioid-induced nausea and vomiting is thought to be a result of cephalad migration of the opioid in CSF to opioid receptors in the area postrema and chemotactic trigger zone in the medulla [15]. The incidence of nausea and vomiting in our study in association to combined fentanyl and morphine was higher than with morphine alone, although not significant. This indifference despite our low dose of intrathecal fentanyl is in contrast with studies [16-18] suggesting that intrathecal fentanyl decreases nausea and vomiting. A possible explanation is that fentanyl may in fact result in hypobaricity of the injectate as shown in an in vitro study [19], despite suggestions that fentanyl increases baricity.

The incidence of pruritus was significantly higher in Group 1 using a combination of intrathecal fentanyl and morphine. Again, this is in contrast to previous studies [2, 8, 20], which found that the incidence of pruritus was comparable with use of both fentanyl and morphine or morphine alone. A study by Herman et al. [21] regarding the effects of intrathecal fentanyl on analgesia and ventilation during labor found that there
was a dose-response relationship between the dose of fentanyl and the incidence of pruritus.

The precise mechanism of pruritus after intrathecal opioids is not completely clear.

Fan [22] reported that morphine could activate serotonin Type 3 receptors by a mechanism independent of opioid receptors. Therefore, a direct stimulation of serotonin Type 3 receptors in the dorsal horn of the spinal cord and in the medulla by intrathecal injection of opioids may be a possible mechanism for the pruritus. It may be that fentanyl could activate 5-HT3 receptors to a larger extent than morphine. Although there have been studies with the use of prophylactic ondansetron (5-HT3 antagonist) leading to the reduction in incidences of pruritus in morphine [23, 24] or fentanyl [25] individually compared to placebo, to the best of our knowledge there are no studies comparing the efficacy of a 5-HT3 antagonist on either fentanyl or morphine. Our use of intravenous ondansetron as a routine practice post-delivery should be noted. Although its significance for reduction in pruritus is not certain, it was used for all the patients in the study and thus should not have a bearing on the results.

A limitation of our study was that oxytocin infusions initiated after delivery, as is routine practice at our institution, was not standardized to a set flow rate intraoperatively. This might potentially influence discomfort and VAS scores in patients experiencing cramps from increased flow rates.

In summary, the addition of 10 μg of intrathecal fentanyl in combination with 100 μg intrathecal morphine to hyperbaric bupivacaine for spinal anaesthesia confers no intra- or post-operative advantage, while leading to an increase in side effects and hence associated cost of care, in a maternal population attending for elective caesarean section.

Conflict of interest

Nothing to declare

References

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Rezumat

Introducere. În anestezia spinală, administrarea intratecală a fentanylului sau a morfinei ca adjuvanți ai bupivacainei pentru operația cezariană este în prezent o practică comună. Totuși este încă controversată administrarea combinației de fentanyl și morfină, ca adjuvanți ai bupivacainei pentru operația cezariană de elecție. Am pornit de la ipoteza că atât timp cât asocierea intratecală a fentanylului la morfină cu bupivacaină determină creșterea incidenței efectelor secundare, nici nu îmbunătățește calitatea anesteziei sau analgeziei în cazul nașterilor prin operație cezariană efectivă.

Material și metodă. În acest studiu case-control, dublu orb femeile supuse cezarienei de elecție au primit anestezie spinală cu fentanyl plus morfină și bupivacaină (Grup 1) sau cu morfină și bupivacaină (Grup 2). S-au evaluat la 4 ore scorurile de durere în repaus și la mișcare utilizând scala analog vizuală (VAS), timpul necesar pentru instalarea blocului la T6 și efectele secundare.

Rezultate. Cincizeci de pacienți au fost randomizate în Grupul 1 (n = 25) și Grupul 2 (n = 25). Nu au existat diferențe în ce privește media scorurilor de durere VAS în repaus sau la mișcare, între cele două grupuri. Media (SD) scorurilor de durere VAS, în repaus, la 4 ore a fost 13,2 (13,7) mm în Grupul 1 și 12 (11,5) mm în Grupul 2 (P = 0,739). Media (SD) scorurilor de durere VAS, la mișcare a fost în Grupul 1 de 38 (18,2) mm iar în Grupul 2 de 28,4 (12,4) mm (P = 0,349). Primul analgezic la cerere a fost solicitat la 7,34 ore în Grupul 1 și la 7,08 ore în Grupul 2 (P = 0,749). Corespunzător, cotele de satisfacție ale pacienților au fost comparabile între cele două grupuri, cu o medie (SD) în Grupul 1 de 84,4 (11,11) în comparație cu Grupul 2 de 87,6 (9,02) (P = 0,269). Durata de instalare a blocurilor la T6 a fost similară între cele două grupuri. Incidența efectelor secundare a fost mai mare la Grupul 1 comparativ cu Grupul 2.

Concluzii. Rezultatele studiului nostru au arătat că asocierea de fentanyl la amestecul de morfină și bupivacaină nu a oferit avantaje pe termen scurt, privind analgezia postoperatorie, dar a crescut incidența efectelor secundare, asociate opioidelor și astfel a ridicat costul îngrijirii populației materne supuse operației cezariene de elecție.

Cuvinte cheie: intratecal, fentanyl, morfină, operație cezariană, durere