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CLINICAL RESEARCH

Spinal anesthesia for elective cesarean section. Bupivacaine associated with different doses of fentanyl: randomized clinical trial

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Abstract
Objective: Assess patients submitted to elective cesarean section under spinal anesthesia, and the efficacy of different doses of fentanyl associated with bupivacaine.
Methods: The study included 124 pregnant women randomly distributed into 4 groups (n = 31) according to different doses of fentanyl (15 μg, 10 μg, 7.5 μg), Groups I, II, and III, respectively, and control group IV, associated with 0.5% hyperbaric bupivacaine (10 mg). An epidural catheter was inserted in case epidural top-up was required. We assessed the anesthetic blockage characteristics, negative maternal and neonatal outcomes, and maternal side effects. Statistical analysis was performed using Kruskal-Wallis, Fisher's exact and chi-square tests. The level of significance was 5% ($p < 0.05$).
Results: The quality of analgesia, time for the first complaint of pain and motor block recovery time were significantly better for groups that received fentanyl in comparison to controls ($p < 0.001$). None of the groups had negative maternal-fetal outcomes. Nausea was significantly more frequent in patients in Groups II (10 μg) and III (7.5 μg) when compared to Groups I (15 μg) and IV (no fentanyl). Vomiting was more frequent in Group III than in Group I ($p = 0.006$). The incidence of pruritus was significantly higher in the groups receiving fentanyl ($p = 0.012$).

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Conclusions: Among the solutions studied, the spinal anesthesia technique using 15 μg of fentanyl associated with 10 mg of hyperbaric bupivacaine provided satisfactory analgesia and very low incidence of adverse effects for patients submitted to cesarean section.
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REBEC: RBR-5XWT6T.

Introduction

Spinal anesthesia with hyperbaric bupivacaine is the most commonly used anesthetic technique for elective cesarean section and in urgent and emergency scenarios due to its simplicity and ease of performance, low cost and quick installation of anesthesia, providing adequate analgesia and muscle relaxation for the surgery.[1–3] However, when used alone, 12 to 15 mg doses are required to obtain satisfactory levels of sensory blockage for surgery and to avoid visceral pain resulting from intraoperative peritoneal traction, and consequently, major adverse events will be circulatory, such as arterial hypotension and fetal distress.[3] Doses of local anesthetics can be reduced to avoid the spinal anesthesia hemodynamic adverse events probably due to excessive doses of local anesthetic, although this approach may be associated with a greater need for analgesia complementation intraoperatively.

The association of low doses of bupivacaine with fentanyl, a lipophilic opioid, has been proposed to improve the quality of the blockade, prolong duration of analgesia, and reduce the incidence of intraoperative nausea and vomiting.[1,3]

Several doses of fentanyl (from 2.5 to 50 μg) have been described in the literature for spinal block for cesarean section, and the 25 μg dose was used in most studies.[1,2,4–6] However, intrathecal fentanyl has been associated with increased postoperative opioid requirements, possibly due to a fast-onset opioid tolerance or opioid-induced hyperalgesia. In addition, a ceiling effect was observed with intrathecal doses above 0.25 $\mu g.kg^{-1}$, revealing that high doses of intrathecal fentanyl do not improve the quality of analgesia and increase adverse effects.[1] Therefore, the results regarding the efficacy of fentanyl in association with local anesthetics vary, and a significant dose-effect relationship has not been established yet. The present study evaluated pregnant women undergoing cesarean section under spinal anesthesia and aimed to compare the effectiveness of different doses of fentanyl associated with hyperbaric bupivacaine regarding the quality of the blockade and maternal and neonatal outcomes.

Methods

The present study is a prospective, double-blind, randomized trial. The study was approved by the institution's research and ethics committees and carried out from November 2017 to December 2018. After signing an informed consent, full-term pregnant participants were included, and submitted to cesarean section under spinal anesthesia.

Inclusion criteria were age equal to or above 18 years; ASA (American Society of Anesthesiologists) physical status II and III; BMI less than 40 $kg.m^2$; pregnancy equal to or above 37 weeks; with a live and single fetus. Exclusion criteria were pregnant women with psychiatric disorders; history of drug addiction; diagnosis of acute or chronic fetal distress; contraindication for regional anesthesia; history of hypersensitivity to the study drugs; previous administration of opioids and/or other central nervous system depressants during current hospital admission.

We calculated the sample size based on findings of Dahlgren et al.,[6] reporting a total 140-minute duration of analgesia for the bupivacaine (12.5 mg) + fentanyl (10 μg) combination. Using a dose of bupivacaine (10 mg) lower than that recommended by Dahlgren et al.,[6] was justified by the relevance of reducing maternal and neonatal hemodynamic events. By considering a difference in analgesia duration of approximately 30 minutes around the reported mean (140 minutes) for each comparison group, assuming this difference by the Student's *t*-test, and considering a 5% significance level ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$), the estimated sample was 124 patients (31 cases in each group), randomly allocated into one of four groups using a computer-generated table of numbers (SAS software version 9.2). The sealed envelope technique was used and the anesthesiologist who performed the spinal anesthesia and assessed the study variables was blind to the solution used.

The four groups received a 10 mg (2 mL) dose of 0.5% hyperbaric bupivacaine, associated with different doses of fentanyl. A 0.9% NaCl solution was added to complete a total volume of 3 mL in all groups. All drugs used were from the same manufacturer.

The four groups of the study were: Group I, fentanyl (15 μg – 0.3 mL) + 0.9% NaCl solution (0.7 mL); Group II, fentanyl (10 μg – 0.2 mL) + 0.9% NaCl solution (0.8 mL); Group III, fentanyl (7.5 μg – 0.15 mL) + 0.9% NaCl solution (0.85 mL); and Group IV, 0.9% NaCl solution (1.0 mL). Combined to the spinal anesthesia all patients had an epidural catheter placed prior to the spinal anesthesia, in case epidural top-ups with local anesthetic would be required to ensure adequate anesthesia for surgery for participants with intraoperative discomfort.

Participants were fasting and did not receive preanesthetic medication. In the operating room, all were continuously monitored with continuous ECG DII derivation tracing, noninvasive blood pressure monitor, and pulse oximeter. After venous access with an 18 cannula, 500 mL to 750 mL of Ringer's lactate solution was infused before performing the blockade. With the patient in the sitting position, an epidural puncture was initially performed with a 16G Tuohy needle, in the L2–L3 interspace, and the epidu-

ral catheter was inserted introduced in the cranial direction. The spinal anesthesia was performed with a Whitacre 27G or 25G Quincke needle in the L3–L4 interspace, and the anesthetic solution was manually injected at a rate of 1 mL.15s^{-1}, without barbotage. After the block, participants were placed in supine position and a Crawford wedge installed to displace the uterus to the left until fetal extraction. Oxygen supplementation (2 to 3 L.min^{-1}) was provided by a nasal cannula.

Hydration was maintained with Ringer's lactate solution (10 mL.kg^{-1}.hour^{-1}). The following variables were studied: 1) Sensory block latency: time elapsed between end of the spinal injection of anesthetic solution and absence of pain to pinprick stimuli at T10 level (assessed every minute); 2) Maximal level of sensory block: assessed 20 minutes after the end of the spinal injection of anesthetic solution; 3) Maximal degree of motor block: assessed 20 minutes after the end of the spinal injection of anesthetic solution, according to the modified Bromage score: 0 = free movement of the lower limbs (null), 1 = ability to flex knees and move feet, 2 = ability to only flex feet, 3 = complete inability to move lower limbs, 4) Time to full recovery of motor block: interval between the end of the spinal injection of anesthetic solution and the free movement of the lower limbs (0, nil); 5) Total duration of analgesia: interval between the end of the spinal injection of anesthetic solution and spontaneous complaint of pain (VNS $\geq$ 3) reported by the patient; 6) Quality of intraoperative analgesia evaluated according to the method proposed by Lee et al.[7] distributed in 4 levels: Excellent, no complaints, comfortable; Good, little discomfort, no need for additional medication; Fair, uncomfortable, but manageable with the medication such as intravenous benzodiazepines and/or opioids; Poor, impossible to control with intravenous drugs, requiring epidural lidocaine through the catheter. Patients who reported excellent and good quality of analgesia were classified as satisfactory analgesia, and as unsatisfactory when analgesia was considered fair and poor; 7) Maternal hemodynamic and respiratory variables: Mean Arterial Pressure (MAP, mmHg), heart rate (HR, bpm), peripheral oxygen saturation (SpO_2, %) were evaluated at the following moments: before block (M0), immediately after block (M1), every 5 minutes during surgery (M2), at the end of surgery (M3). 8) Neonatal outcomes: neonate's Apgar score was registered at the 1stand 5thminutes. Newborns were evaluated at birth in the delivery room, and when they presented normal tonus, breathing or crying, they were placed in skin-to-skin contact, according to the standard routine of the hospital's neonatology service; 9) Maternal side effects: nausea, vomiting, pruritus; 10) Duration of surgery (minutes), time between skin incision and wound suture; and time for fetal extraction (minutes), time between skin incision and umbilical cord clamping.

Arterial hypotension was defined as decrease in Mean Arterial blood Pressure (MAP) more than 20% below baseline in the first 30 minutes after spinal block. Whenever present, arterial hypotension was initially treated with increase in Ringer's lactase infusion, and if persistent, with IV boluses of 5–10 mg of ephedrine; Bradycardia: defined as decrease in heart rate below 50 beats per minute and when present treated with 0.02 mg.kg^{-1} of atropine; respiratory depression: when SaO_2< 90% and respiratory rate < 10 rpm.

During stay at the PACU, as per protocol intravenous tenoxicam (40 mg) and dipyrone (30 mg.kg^{-1}) were administered, only after patient's first complaint of pain (VNS $\geq$ 3).

Statistics

Statistical analysis was performed for intention to treat. The Kruskal-Wallis test was used to analyze the characteristics of patients, time for recovery of motor block, duration of analgesia and cardiorespiratory parameters. Fisher's exact test was used for patient distribution according to physical status (ASA), sensory block latency, quality of analgesia, level of sensory block, degree of motor block. The chi-square test was used to compare the quality of analgesia (satisfactory or unsatisfactory) among different groups, for requirement of vasopressors and maternal adverse events. For the statistical analysis of maternal cardiocirculatory and respiratory parameters, moment M2 was considered the mean of the mean values obtained at 5-minute intervals during the first 30 minutes of surgery, and every 15 minutes thereafter. The level of significance was 5% (p < 0.05). All analyses were performed using the software SAS System for Windows (Statistical Analysis System), version 9.2. SAS Institute Inc, 2002–2008, Cary, NC, USA.

Results

We included 124 patients, randomly and equally distributed into the four groups previously described. Among cases, five patients had block failure, two from group IV and one patient from each of the other groups. The procedure on these patients was performed after epidural catheter injection of 2% lidocaine. No participant required general anesthesia. The analysis included 119 participants (Fig. 1). Due to the loss of five cases, a new sample power was calculated using the comparison between groups, setting the level of significance alpha or type I error at 5% (α = 0.05), with a 95% confidence interval, using the size of the groups (n = 119) and the proportions obtained from the outcomes (quality of analgesia, pruritus, nausea, and vomiting) in the 4 study groups. A power of 99.9% was obtained for quality of analgesia, 93.0% for pruritus, 82.8% for nausea and 80.8% for vomiting.

There was no significant difference among groups regarding weight, age, height, BMI, and physical status (ASA). Comparative analysis among the groups for duration of surgery and time for fetal extraction presented no significant difference, thus reducing the possible bias associated with the surgical procedure (Table 1).

Table 2 shows spinal block characteristics. There were no significant differences among the groups for sensory latency time, maximal level of sensory block and degree of motor block. The maximum level of sensory block ranged from T2 to T6, with a predominance of level T4 in the four groups, with no significant difference (p = 0.496). The degree of motor block ranged from 0 to 3, with a predominance of degree 3 in all groups. Duration of analgesia and time to full recovery of motor block (BROMAGE = 0) were significantly longer (p < 0.001) for all participants receiving spinal anesthesia solution that contained fentanyl (Groups I, II and III), compared to participants receiving only local anesthetic

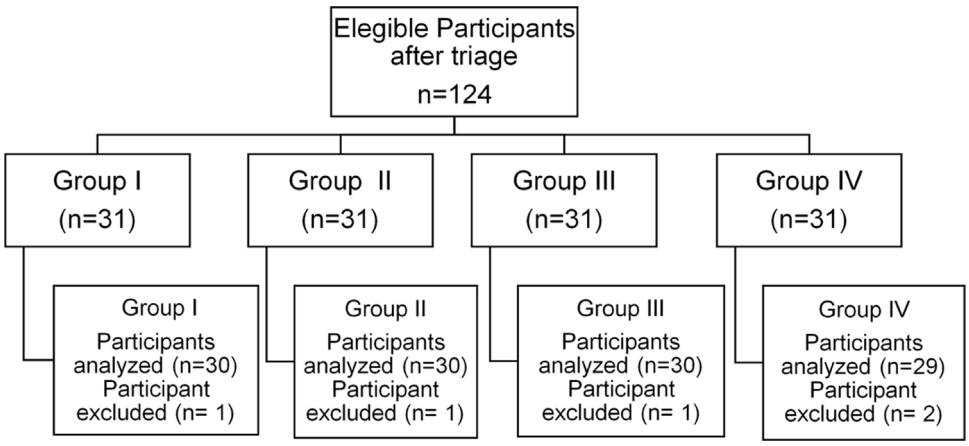

Figure 1 Flow chart of patients (CONSORT).

Table 1 Demographic data and surgical parameters.

Variables	Group I	Group II	Group III	Group IV	*p*
Age (years)[a]	31.52 ± 5.76	31.32 ± 6.48	30.77 ± 7.39	26.97 ± 7.03	0.23
Weight (kg)[a]	87.39 ± 16.04	83.74 ± 13.46	86.50 ± 14.16	83.80 ± 14.61	0.69
Height (m)[a]	1.63 ± 0.07	1.63 ± 0.08	1.62 ± 0.06	1.63 ± 0.07	0.92
BMI ($kg.m^{-2}$)[a]	33.03 ± 5.55	31.42 ± 5.00	32.75 ± 4.95	31.40 ± 5.18	0.395
Duration of surgery (min)[a]	83.0 ± 20.17	79.42 ± 20.55	70.39 ± 18.0	74.60 ± 19.61	0.125
Time to fetal extraction time (min)[a]	22.63 ± 9.29	21.16 ± 7.26	28.97 ± 7.10	21.50 ± 8.24	0.936

Values presented as Mean ± SD.
[a] Kruskal-Wallis test.

Table 2 Spinal anesthesia variables.

Variables	Group I	Group II	Group III	Group IV	*p*
Sensory block latency (min)[a]	1.65 ± 0.71	1.65 ± 1.08	1.90 ± 1.04	2.06 ± 0.96	0.125
Degree of motor block[a]	2.94 ± 0.25	2.87 ± 0.43	2.87 ± 0.43	2.83 ± 0.59	0.949
Level of sensory block[a]	4.13 ± 1.02	4.00 ± 1.26	3.94 ± 0.96	4.33 ± 1.06	0.49
Time to full motor function recovery (min)[a]	134.47 ± 50.23	119.07 ± 36.88	115.83 ± 50.99	71.45 ± 38.07	<0.001 I, II, III ≠ IV
Duration of analgesia (min)[a]	142.50 ± 69.99	117.27 ± 37.09	112.03 ± 49.99	67.00 ± 35.37	<0.001 I, II, III ≠ IV

Values presented as Mean ± SD.
[a] Kruskal-Wallis test.

(Group IV). Boxplot Figure 2 illustrate the analysis of values observed for these variables.

Table 3 presents the quality of analgesia. More participants in the groups receiving a solution containing fentanyl (Groups I, II and III) rated analgesia as ''Excellent'', 25 (83.33%), 22 (73.33%), 18 (60%), respectively. In Group IV, 7 participants (24.13%) reported excellent analgesia. There was a significant difference between the groups that received fentanyl when compared to the control group ($p < 0.001$). The statistical analysis comparing the groups that received fentanyl showed: I vs. II ($p = 0.792$); I vs. III ($p = 0.187$); II vs. III ($p = 0.618$), with no significant difference.

Statistical significance was obtained for Groups I, II and III compared to Group IV ($p < 0.001$) for satisfactory analgesia (excellent and good); unsatisfactory analgesia (fair and poor) was observed in 21 (72.41%) patients in the group without fentanyl. All patients who classified anesthesia as ''Fair'' received intravenous fentanyl and/or midazolam. Patients whose anesthesia was classified as ''Poor'', required epidural top-up with 2% lidocaine (100 mg) via catheter.

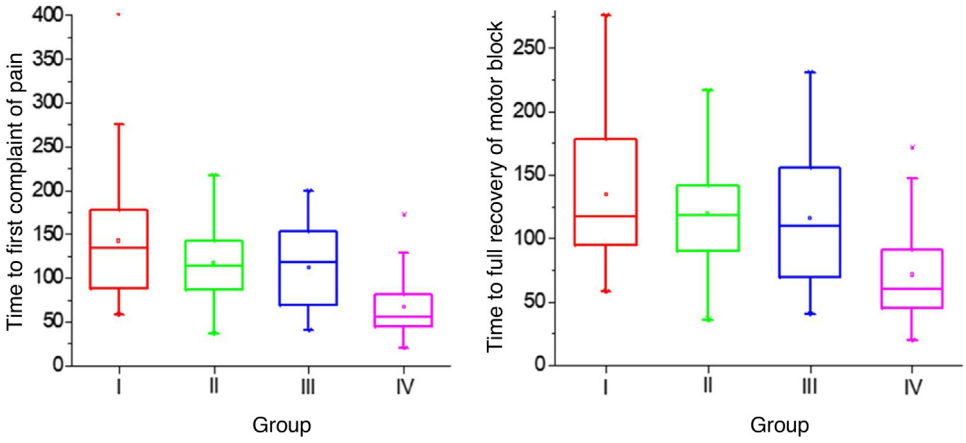

Figure 2 Analgesia duration and time to full recovery of motor block (minutes).

Table 3 Quality of analgesia.

	Group I	Group II	Group III	Group IV	Total
Excellent	25 (83.33%)	22 (73.33%)	18 (60.00%)	7 (24.13%)	72
Good	1 (3.33%)	2 (6.66%)	3 (10.00%)	1 (3.44%)	7
Fair	2 (6.66%)	3 (10.00%)	7 (23.33%)	9 (31.03%)	21
Bad	2 (6.67%)	3 (10.00%)	2 (6.66%)	12 (41.37%)	19
Total	30	30	30	29	119

Values presented as total number (n°) and frequency (%).
[a]Fisher's exact test: $p < 0.001$.

There were no maternal-fetal events related to anesthesia in any of the groups. In the individual analysis of MAP values, hypotension was observed, at some point during the intraoperative period, in 19, 19, 17 and 20 patients in Groups I, II, III, and IV, respectively, corrected with increased infusion of Ringer's lactate and vasopressor drug. Vasopressor requirements were similar among groups ($p = 0.879$). No episodes of bradycardia were observed. The mean values for respiratory rate and peripheral oxygen saturation remained 10 movements per minute and between 95 and 100%, respectively, and were similar in the four groups. For all groups, Apgar scores ranged from 7 to 10 and 8 to 10 in the 1st and 5th minutes, respectively.

The incidence of pruritus was significantly higher ($p = 0.012$) in the groups that received fentanyl compared to the group that did not receive fentanyl.

Nausea occurred more frequently in Groups II (18 patients) and III (20 patients), in comparison to Groups I (9 patients) and IV (12 patients). Statistical analysis showed a significant difference between Groups I and II ($p = 0.02$) and I and III ($p = 0.005$). Vomiting was more frequent in Group III (9 patients), with a significant difference ($p = 0.006$) compared to Group I (1 patient).

Discussion

It is very important to provide adequate and safe maternal-fetal anesthesia by choosing the anesthetic technique for cesarean section. Typically, C-section is performed under spinal anesthesia and several combinations of local anesthetics and analgesics are used. As this study was performed at a teaching hospital, where surgeries are often performed by training physicians and have longer surgical times, we decided, in addition to performing spinal anesthesia, to insert an epidural catheter. This approach aimed to administer top-up with local anesthetic for patients spontaneously complaining of pain (VAS > 3) intraoperatively.

Bupivacaine is the local anesthetic commonly used for spinal anesthesia in pregnant women, however, its isolated use in low doses (7. 5–10 mg) has been shown to be insufficient to promote adequate surgical analgesia, with the incidence of pain around of 71%, requiring, therefore, higher doses to avoid visceral pain, nausea, and vomiting, resulting from the peritoneal traction that may occur during Csection.[1–3,7–10] However, high dose of bupivacaine is one of the main factors responsible for the high incidence of hypotension (50–85%), as well as other factors promoting subarachnoid cephalic dispersion of local anesthetics and the infusion of oxytocin.[7,8,10]

Although several studies have evaluated the benefits, risks and adequate doses of fentanyl associated with bupivacaine in spinal anesthesia for obstetric procedures, their results are still controversial. Adding opioids to bupivacaine administered intrathecally may show clinical advantages, such as improving the quality of intraoperative analgesia and prolonging postoperative analgesia. However, the potential disadvantages of opioid, such as pruritus, sedation, urinary retention and respiratory depression should be considered.[1,11–13] Fat-soluble opioids, such as fentanyl, despite their lower rostral diffusion compared to water-

soluble ones, may be responsible for cases of respiratory depression when used intrathecally in pregnant women, which can be explained by their effects being potentiated by progesterone and endogenous opioids, which are high in these patients.[13] In this study, the four groups behaved similarly in relation to respiratory function, with no cases of respiratory depression, similar to results described by other authors.[1,6,7]

There was more frequent nausea and/or vomiting in the groups that received the lowest doses of fentanyl, compared to the one that received the highest dose of opioid. This finding agrees with what was described by other authors who observed that the addition of intrathecal fentanyl reduces the incidence of these intraoperative effects.[1,6] However, in our study, despite the higher dose of spinal fentanyl (15 μg) having resulted in lower incidence of nausea and vomiting, this was also observed for the placebo group, which can be attributed to the use of lidocaine via epidural catheter, improving the quality of analgesia, a relevant protecting factor against these adverse events.

Given that the presence of nausea and vomiting during C-section is considered important and mainly related to uterine exteriorization and peritoneal traction, there have been current descriptions that intrathecal opioids can provide protection against these adverse effects.[1,6,14,15] Dahl et al.[15] showed that the incidence of nausea and vomiting did not increase with the use of fentanyl and sufentanil, and other authors described that the use of antiemetics was only necessary in patients when using local anesthetic alone.[6]

Although the relationship between the occurrence of pruritus and the dose of fentanyl is not sufficiently evident, it has been a frequent complaint among patients who received this drug intrathecally.[1,6,10–13,16–27] Approximately 80% of patients receiving fat-soluble opioid intrathecally report pruritus, which in some cases is described as severe and stressful.[27–30] In this study, the occurrence of pruritus was similar in the groups receiving different doses of fentanyl, therefore, it was not a dose-dependent effect as described by many authors.[1,6,10,15] Dahl et al.[15] demonstrated in a retrospective study that included 485 patients, a high incidence of pruritus, but similar with different doses of opioids.

Hemodynamic changes during cesarean section under spinal anesthesia with hyperbaric bupivacaine can be attributed to the dispersion of bupivacaine in the subarachnoid space, which may be facilitated by the physiological changes associated with pregnancy. These changes can cause significant maternal morbidity and mortality and deleterious effects on the concept, and the incidence and severity depend on the blockage extension, circulating blood volume and aortocava compression.[9,10] In our study, despite the high levels of sensory block (T4) obtained, these changes were not significant, and when they occurred, they were controlled by displacement of the uterus to the left, volume expansion and intravenous ephedrine, strategies used to prevent arterial hypotension related to spinal anesthesia.[3,10] In the doses used, fentanyl did not change the vitality of newborns, confirmed by Apgar score above 7 in the 1stand 5thminutes, results previously observed, and that confirm the safety of the association of drugs used.[10,17,20,23]

Even though the high liposolubility of fentanyl is associated with high affinity for μ receptors, constituting pharmacokinetic characteristics capable of explaining the decrease in latency time of local anesthetics and the fast onset of sensory blockade, studies show conflicting results. In this study, the time to sensory block did not differ among groups, a finding already revealed by other authors.[1,2,16]

The time for full motor block recovery was similar in all patients whose anesthetic solution contained fentanyl, but significantly longer in comparison to patients in the group that only received local anesthetic, demonstrating the importance of opioids when using lower doses of bupivacaine.[9]

As previously found by other authors, fentanyl proved to be significantly important to improve the quality of anesthesia, as well as to prolong the time of analgesia in all patients in which it was used.[1,2,6] The best quality of anesthesia in patients who received opioids, as described by other authors, may result from synergism between the two drugs by acting at different sites. Opioids, when administered intrathecally, in addition to acting on specific spinal cord receptors, have weak local anesthetic activity, but can increase local anesthetics' antinociceptive activity.[13,20] Mean analgesia times in the groups in which opioids were used were similar, with an increase of almost 100% in the duration of analgesia compared to that found in the group that did not receive fentanyl.

Therefore, unlike what has been described by other authors who did not obtain adequate analgesia with doses of less than 10 μg of fentanyl,[4] our study revealed that doses as low as 7.5 μg of this opioid provided satisfactory analgesia in patients undergoing cesarean section under spinal anesthesia, which was also described by other authors.[2] We observed that of the 30 patients receiving this lower dose of fentanyl, 21 classified quality of anesthesia as ''excellent'' and ''good'' and the duration of analgesia was similar to that obtained in the two other groups that received the highest doses of opioid. However, although the quality of anesthesia was shown to be satisfactory, in the groups that received lower doses of fentanyl, the occurrence of nausea and vomiting was more significant in relation to the group that received the highest dose of this opioid.

In our study, we did not use the intrathecal fentanyl 25 μg dose in another group because the literature has already described that a lower dose of intrathecal fentanyl could provide effective analgesia associated with fewer adverse effects such as nausea, vomiting and pruritus. Moreover, it has been described that intrathecal fentanyl would be implicated in the increase of opioid requirements postoperatively, possibly due to sudden tolerance or hyperalgesia induced by opioids, and to a probable ceiling effect observed with intrathecal doses greater than 0.25 $\mu g.kg^{-1}$, highlighting that high doses of intrathecal fentanyl do not improve the quality of analgesia and increase adverse effects.[1] The ideal, therefore, would be an adequate dose of intrathecal fentanyl that provides an effective quality of analgesia with fewer adverse effects.

The results of this study demonstrate that fentanyl at a dose of 15 μg associated with 10 mg of hyperbaric bupivacaine intrathecally for patients submitted to C-section was effective, providing adequate anesthesia, with low occurrence of nausea and vomiting and greater maternal-fetal safety.

Conflicts of interest

The authors declare no conflicts of interest.

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