SUPPLEMENT

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Comparison of intrathecal plain articaïne and levobupivacaine with fentanyl for Caesarean section

Abstract

Purpose: Articaïne is used as a local anesthetic for outpatient surgery because it offers rapid onset of anesthesia and short duration motor block. Levobupivacaine is often preferred for Caesarean section. We evaluated the anesthetic characteristics of fentanyl-supplemented plain articaïne and levobupivacaine for Caesarean section under combine spinal epidural anesthesia.

Methods: Patients undergoing Caesarean section received in random order plain articaïne 40 mg (Group A, n=50) or plain levobupivacaine 10 mg (Group L, n=50) mixed with fentanyl 20 µg intrathecally. The onset and duration of sensory and motor block, first analgesic request, and hemodynamic parameters were recorded.

Results: Onset times of maximum motor block were longer in Group L than Group A (P=0,001). Time to two-segment regression of sensory block were 70 min for Group A and 90 min group L (P=0.001). Times to complete regression of motor blockade were significantly longer in group L than group A (P =0,001).

Conclusion: To have a faster onset and shorter duration of spinal anesthesia, we recommend the use of plain articaïne for Caesarean section.

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Neuraxial anesthesia is currently the gold standard of practice for obstetric anesthesia and it is now the preferred method in many countries. In clinical practice for spinal anesthesia, levobupivacaine is increasingly popular as a replacement for bupivacaine because of its equipotency, lower cardiovascular and central nervous system side effects, more specific effects on sensorial pathways rather than motor fibres and faster onset for sensorial block [1]; however, the long acting duration may be its disadvantage similar to bupivacaine for Caesarean section.

Articaine, an amide-type local anesthetic, is another agent that may be preferred in clinical anesthesia practices. It has been showed that it is not only non-toxic and short acting, appropriate for the procedures including dentistry and for regional and neuraxial anesthesia, including spinal anesthesia [2, 3]. These optimal features of articaine have been demonstrated by many researchers [4-6]. Opioids are often combined with local anesthetics for Caesarean section as they increase both the quality of the analgesia and the hemodynamic stability [7]. Improved analgesia and hemodynamic stability result in early mobilization - important after Caesarean section as this provides the mother with opportunities for mother-child bonding and leads to greater overall patient satisfaction.

To date, there have been no published studies on the intrathecal use of the combination of articaine with fentanyl for Caesarean section. We hypothesized that articaine provides faster onset and even an early recovery of sensory-motor block characteristics, and would therefore be an appropriate agent for Caesarean section under spinal anesthesia. Specifically, we designed this prospective randomized study to evaluate the anesthetic characteristics of plain articaine and levobupivacaine in combination with with fentanyl (20 µg) for Caesarean section under combine spinal epidural anesthesia.

Methods

Study population

After institutional review board approval and written informed consent, a prospective randomized study was performed in ASA I -II, 100 women at term pregnancy (≥ 36 weeks), aged 18-45 years, who were scheduled for elective Caesarean section delivery. Exclusion criteria included obesity (≥ 115 kg), preeclampsia, eclampsia, contraindications to regional anesthesia and a history of allergic reactions to amide-type local anesthetics.

Data collection and study parameters

All received 20 ml/kg of warmed lactated Ringer's solution intravenously (IV) over a period of 15 min prior to regional anesthesia. Monitoring included continuous electrocardiography (lead II), pulse oximetry and arterial blood pressure (noninvasive measurement) cycled at 3 min interval (Datex Engstrom AS/3 Anaesthesia Monitor; Helsinki, Finland).

All patients received combined spinal epidural anesthesia. The blocks were performed at L₃₋₄ or L₄₋₅ interspace with the parturients in the sitting position. A 18-gauge Tuohy needle (Espocan; B.Braun, Melsungen, Germany) was introduced with loss of resistance technique, and the dura was punctured with a 27-gauge Quincke needle oriented with the orifice facing cephalad using the needle-through-needle technique. After confirming the subarachnoid space by viewing free flow of cerebrospinal fluid; as determined by a table of random numbers, patients received one of the following intrathecal solutions: 2% plain articaine (Ultracaine®, Aventis, Frankfurt am Main, Germany, 20 mg/ml) 40 mg (Group A), and 0.5% isobaric levobupivacaine (Chirocaine®, Abbott, USA) 10 mg (Group L). In each group, fentanyl (20 µg) was added to the local anesthetics. The intrathecal drugs were injected over approximately 60 sec without barbotage. After withdrawal of the spinal needle, a 20-gauge epidural catheter was inserted through the epidural needle 3-4 cm into the epidural space and firmly fixed. Following the injection of prepartate to epidural space, the patients were immediately turned to supine position with 15° left uterine tilt and oxygen (4 litre min⁻¹) was administered via a facemask.

Surgery was allowed to start if the upper dermatome level of loss of discrimination to pinprick was at or above T6. The sensory block was assessed at the midclavicular line of both sides of the body with pinprick testing using a 25-gauge needle protruding 2 mm through a guard and the motor block was assessed by a modified Bromage scale (modified Bromage scale: 0, full movement; 1, inability to raise extended leg, can bend knee; 2, inability to bend knee, can flex ankle; and 3, no movement).

Pinprick testing was performed at 2 min intervals until 15 min, then at 5 min intervals until 30 min, and thereafter at 15 min intervals until complete regression of sensory block had been attained. The motor block was assessed at 5 min intervals until 30 min and, then every 10 min at the end of surgery and after surgery it was performed every 20 min until full recovery of motor function (Bromage grade 0).

For assessment of the onset of anesthesia, the time for sensory block to develop to maximum block height and the

time to achieve maximum Bromage score were recorded. To assess the duration of the sensory block, the two-segment regression time from the maximum block height and time for regression to L1 were used. Duration of motor block was assessed by recording the time elapsed from the maximum to the lowest Bromage score.

Hypotension (defined as 20% decrease of systolic blood pressure compared with preoperative control levels) was treated with 5 mg increments of ephedrine and 200 ml boluses of lactated Ringer's solution. Bradycardia (heart rate <50 beats/min) was treated with atropine 0.5 mg IV.

Intraoperative adverse events were also recorded, and included hypotension, bradycardia, nausea, vomiting and shivering. After the operation, patients' ECG, respiratory rate and blood pressure were monitored. The measured values were recorded every ten minutes during the first hour, then every 30 min until discharging from PACU. Side effects such as itching, nausea, vomiting and hypotension were also recorded. Following the arrival to 1 score of Bromage Scale (which happened in the majority of patients at the end of surgery), patients were discharged from PACU.

In all patients, the epidural catheter was used for postoperative analgesia. Postoperative pain was managed by patient-controlled epidural analgesia (Abbott PMP) with fentanyl because of its propriety by mobilization. All patients remained in the hospital until the morning after the operation. Patients were interviewed by one of the investigators before leaving the hospital and were interviewed again over the next 2 days by telephone about adverse effects, including post-dural puncture headache (PDPH) and transient neurological symptoms (TNS), which was defined as pain, dysesthesia, or both, in the buttocks, thighs or lower limbs occurring after recovery from the anesthetic and outside the surgical area. If any TNS were present, the patient was contacted again the one week after spinal anesthesia.

Statistical analyses

The SPSS 13.0 program was used to analyse the statistical data (SPSS Inc., Chicago, IL). Numerical variables were examined for normality by Kolmogorov-Smirnov tests. Patient characteristics data and surgery time were analysed using Student's t-test, and sensory and motor block variables were compared using Mann-Whitney U-test. The incidence of TNS was compared using the Chi-square test. The results are shown as means (SD), medians (25th/75th percentiles), exact numbers or proportions expressed as a percentage. $P < 0.05$ was considered statistically significant.

TABLE 1. Demographic data

	Group A (n=50)	Group L (n=50)
Age (year)	31±4	29±4
Height (cm)	163±6	165±7
Weight (kg)	78±9	79±12
Time from injection to the end of surgery (min)	44±12	43±17

Values are means ± SD. No significant differences were observed.

Results

There were not significant differences between the two groups for demographic and surgical characteristics Table 1.

Sensory block

The sensory block to the T10 dermatome spread faster and T10 was maintained at least longer in Group A than in Group L (4 *vs.* 5 min, $P=0.002$). Maximal level of the sensory block was not different between the two groups (T4 *vs.* T3, $P=0.08$); however, articaine produced a median spread of analgesia with a range of T3–T5; levobupivacaine had a median spread with a range of T2–T4 (Figure 1). Times to reach maximal sensory block were similar in both groups (10 min). Two segment regression time (70 *vs.* 90 min, $P=0.04$) was significantly shorter in Group A than in Group L. The duration of sensory block, from injection to the recovery of L1 dermatome, was significantly shorter in Group A than in Group L (239 *vs.* 368 min, $P=0.001$, respectively). First analgesic request was significantly shorter in Group A than in Group L (110 *vs.* 183 min, $P=0.001$, respectively) (Table 2).

Motor block

The onset times of motor block in terms of 3 score of Bromage scale (5 *vs.* 10 min, $P=0.001$) and mean times to full recovery of motor function (140 *vs.* 215 min, $P=0.001$) were shorter in Group A than Group L (Table 2). The results of articaine and levobupivacaine for spinal anesthesia compared with the results from other authors (Table 3, 4). Intraoperative blood pressure and heart rate values were found to be statistically similar ($P>0.05$) (Figure 2, 3). Seven patients in articaine group and four patients in levobupivacaine group developed hypotension ($P=NS$). One patient (T3 level of anesthesia) in the articaine group developed hypotension accompanied by bradyarrhythmia, which improved after the application atropine (0.5+0.5 mg) and lidocaine (1 mg/kg). Mean

Articaine	Peak anaesthesia	Levobupivacaine
ooo	T1	oooo
ooooo	T2	oooooooooooo
oooooooooooooooooooo	T3	oooooooooooooooooooo
oooooooooooooooooooo	T4	oooooooooooooooooooo
ooooooo	T5	o
ooooooo	T6	oooo

FIGURE 1. Maximum extension of sensory block in all patients of both groups (each circle represents one patient).

FIGURE 2. Mean heart rates (bpm) in patients receiving intrathecal levobupivacaine or articaine intraoperatively.

ephedrine doses were found to be statistically similar (8.3 *vs.* 7.8 mg, $P>0.05$) in Group A and Group L, respectively.

Three patients in the articaine group developed mild TNS that were limited to the 3rd postoperative day. None of the patients in levobupivacaine group developed TNS. Urinary retention could not be assessed because of an indwelling urinary catheter was present for at least 24 hours. None of the patients had respiratory depression, desaturation or pruritus

FIGURE 3. Average mean arterial pressures (mmHg) in patients receiving intrathecal levobupivacaine or articaine intraoperatively.

during intraoperative and postoperative periods. On the second day, two patients in the articaine group and one patient in levobupivacaine group suffered from PDPH. Two patients were adequately treated with acetaminophen plus caffeine; however, other patient needed epidural blood patch. PONV (four *vs.* three patients) and pruritis (one *vs.* two patients) did not differ significantly between in Group A and Group L, respectively. Any other unwanted events were seen between groups.

Discussion

In this study, plain articaine and levobupivacaine with fentanyl was compared with respect to hemodynamic effects, sensory and motor block and complications for Caesarean section. The results of this study indicated that both groups produced similar quality spinal anesthesia, but the onset and recovery times of the sensory-motor blocks were significantly shorter in Group A although side-effects were not different. Our findings are comparable to previous studies of spinal anesthesia with articaine and levobupivacaine for spinal anesthesia (Tables 3, 4).

Only a few studies have investigated obstetric spinal anesthesia using plain levobupivacaine. There is still a belief that plain local anesthetics give unpredictable blocks [8, 9], but in our study, using a 10 mg dose of plain levobupivacaine, a predictable anesthesia was achieved and the success rate was high. Similar results were found by Gori *et al.* [10] using isobaric levobupivacaine for Caesarean section. Hunt *et al.* [11] reported that fentanyl given intrathecally in conjunction with 0.5% levobupivacaine improved the quality of intraoperative analgesia, prolonged the duration of postoperative analgesia and retarded the sensory anesthesia

regression without delaying motor regression. In contrast, Lee *et al.* [12] found that no significant differences between 0.5% levobupivacaine with or without fentanyl in the quality of sensory and motor block and the addition of fentanyl has a dose-sparing effect with 0.5% levobupivacaine for spinal anesthesia in urological surgery. Kuusniemi *et al.* [13] studied the effect of adding fentanyl 25 µg to bupivacaine for spinal anesthesia. They found that the addition of fentanyl 25 µg to 10 mg of bupivacaine increased the intensity and duration of motor block in comparison to bupivacaine 10 mg alone.

Similarly, the addition of fentanyl to levobupivacaine also extended the duration of motor block in our study.

Despite the higher dosages of levobupivacaine that were used in the study by Gori *et al.* [14], maximum block levels were lower by comparing to ours and Gauter. The reason for this discrepancy may be the use of combined spinal-epidural anesthesia technique. The times of two segment regressions were shorter than ours in the studies designed by Gauter *et al.* and Gori *et al.* Thus, we think the addition of fentanyl can prolong the time of sensory and motor blocks.

TABLE 2. Sensory and motor block characteristics

	Group A (n=50)	Group L (n=50)
Puncture level L3–4/L4–5 (n)	32/18	30/20
Maximal extension of sensory block	T4 [3–5]	T3 [2–3]
Time to maximal sensory block (min)	10 [4–10]	10 [3–15]
Time T10 (min)	4 [3–5]	5 [4–6]*
Time (max-2) (min)	70 [50–90]	90 [69–120]*
Time to regression to L1 (min)	189 [103–237]	238 [185–288]*
Time to maximum motor blockade (min)	5 [5–10]	10 [5–15]*
Time to complete regression of motor blockade (min)	140 [120–165]	215 [180–270]*
First analgesic request (min)	110 [65–135]*	183 [136–205]

Data are median [range] or count; time max: time taken for sensory block to reach maximum; time T10: time taken for sensory block to reach T10; time(max-2): time taken for two-segment regression of sensory block from its highest level. *P < 0.05 compared to Group A and Group L

TABLE 3. Articaine for spinal anesthesia

Author (year)	Bachmann ⁽²⁰⁰⁸⁾	Hendriks ⁽²⁰⁰⁹⁾	Demircioglu
Number of patients	30	30	50
Solution	2% plain	2% plain	2% plain+fentanyl
Articaine (mg)	84	50	40
Block height	T8–T7 (L3–T3)	T10 (T3–L1)	T4 (3–5)
Time to maximal sensory block (min)	15 (4–60)	10 (2–40)	10 (4–10)
Time T10 (min)	6 (2–30)	NA	4 (3–5)
Time to two dermatome regression (min)	75 (45–180)	61 (24–104)	70 (60–90)
Time to regression to L1 (min)	NA	NA	239 (223–255)
Duration of motor block (min)	180 (90–240)	140 (33)	140 (120–165)
TNS (number of patients)	0	1	3

TABLE 4. Levobupivacaine for spinal anesthesia

Author (year)	Gori ⁽²⁰¹⁰⁾	Gautier ⁽²⁰⁰³⁾	Demircioglu
Number of patients	23	30	50
Solution	0.5% plain	0.5% plain	0.5% plain+fentanyl
Levobupivacaine (mg)	2.5	8	10
Block height [median (range)]	T6	T2 [T1–2]	T3 [2–4]
Time to maximal sensory block (min)	NA	17 (9)	10 [3-15]
Time T10 (min)	NA	NA	5 [4-6]
Time to two dermatome regression (min)	80 (28)	69 (14)	90 [49-120]
Time to regression to L1 (min)	176 (37)	NA	348 [255-438]
Duration of motor block (min)	150 (48)	120 (75±190)	215 [180-270]
TNS (number of patients)	NA	NA	0

Early mobilization is important after Caesarean section to provide the mother with opportunities for mother-child bonding, hence, leading to greater overall patient satisfaction. Articaine, with its faster onset and shorter elimination time, seems to be an appropriate agent for Caesarean section under spinal anesthesia. Because of lower incidence of TNS with articaine than lidocaine is preferable for Cesarean surgery. Semenikhin *et al.* and Kaukinen *et al.* [15, 16] reported that articaine epidural analgesia and anesthesia for labour were safe for mother and exerted no depressive effect on the baby. Kaukinen *et al.* [17] compared articaine and lidocaine for urological procedures in spinal anesthesia and found that there were no differences in duration of sensory and motor block. Kozlov *et al.* [18] compared 5% hyperbaric articaine with 0.75% hyperbaric bupivacaine and 0.5% isobaric bupivacaine in 152 patients on the lower part of the body with spinal anesthesia. Onset of sensory and motor block was faster with articaine but the duration of operative analgesia was not shorter than with hyperbaric bupivacaine. Kallio and *et al.* [19] and Dijkstra *et al.* [20], using hyperbaric articaine and hyperbaric bupivacaine solutions, reported a shorter duration of motor block with hyperbaric articaine than with hyperbaric bupivacaine. To date, no study had been published on the intrathecal use of 2% articaine in combination with fentanyl, but our results compared well with other studies for articaine without fentanyl (Tables 4). Hendriks *et al.* [21], using plain articaine solutions for spinal anesthesia in day-case knee arthroscopy, reported was slightly longer two segment regression time compared with our result. The reason may be that we added fentanyl into articaine. However, the other

results were close to each other in terms of time. Backman *et al.* [22] used 84 mg plain articaine solutions in spinal anesthesia for open inguinal hernia repair and reported a longer duration of motor block and delaying two segment regression time than hyperbaric 84 mg articaine solution. The reason may be that Backman and colleagues used higher doses of articaine than our study and Hendriks *et al.* In our study, these two studies in compared with, the sensory block spread significantly more extensively. Although we used a smaller amount of local anesthetic to Bachmann and Hendriks *et al.*, our patients were pregnant for the T10 and maximal sensory block level to achieve a shorter time, peak sensory block level could have been higher. This increases sensory block level higher than another reason of may be following co-administration of fentanyl.

All local anesthetics are potentially neurotoxic, and so is articaine. In previously published studies on articaine in spinal anesthesia, there was no description of any symptoms resembling TNS [17, 19, 23, 24]; however, Timmerman L *et al.* [25] (two patients, 5%), Hendriks *et al.* (one patient, 2.7%) and Dijkstra *et al.* (one patient, 2.6%) their studies on articaine in spinal anesthesia there was description of any symptoms resembling TNS. In our study, three patients (6%) in Group A developed mild pain in the buttocks, thighs and/or lower limbs limited to the 3th postoperative days. The study population was not large enough to discover any difference in the occurrence of rare side-effects such as TNS. After lidocaine spinal anesthesia, the reported incidence of TNS has varied from 0% to 40% [26, 27]. Although the anesthetic characters are quite similar with articaine and lidocaine, TNS rate was lower in

articaine than lidocaine and the Cesarean section in such a short operation may be preferred. But more and larger randomised, double-blind studies are needed to confirm the benefits of articaine in obstetrics. There was no evidence that articaine is superior to lidocaine or prilocaine, nor is there any information on TNS after its use in spinal anesthesia. TNS were evaluated in very few of the studies with levobupivacaine. In our recent study [28] using plain levobupivacaine solutions for spinal anesthesia, one patient (3.3%) developed symptoms resembling TNS. Breebaart *et al.* [29] did not report TNS any patients in the levobupivacaine group (n=30) in day-case spinals for arthroscopy. In our study, none of the patients developed symptoms resembling TNS after spinal anesthesia with levobupivacaine.

Hemodynamic parameters were similar in both groups during the operation, but seven patients in the articaine group (14%) and four patients in levobupivacaine group (4%) developed hypotension. One patient (T3 level of anesthesia) in the articaine group developed hypotension accompanied by bradyarrhythmia. The maximum levels of sensorial block, partly higher in Group L, although hypotension more developed in Group A (the highest sensory levels achieved were T4 [3–5] and T3 [2–3], Group A and Group L, respectively). Following co-administration of fentanyl and local anesthetic, the increased incidence of hypotension may be related to the higher sensory level achieved, as reported by Addlsson *et al.* [30]; however, animal studies have shown that fentanyl does not potentiate the effect of bupivacaine on efferent sympathetic pathways. Therefore, this difference in highest sensory levels may not fully explain the increased incidence of episodes of hypotension [31]. The incidence of PDPH did not differ significantly between the groups (4% *vs.* 2% in Group A and Group L, respectively). These values are accordance with the literature. Only in one patient the headache was severe enough to indicate treatment with an epidural blood patch. The potential side-effects of spinal fentanyl such as the pruritus, nausea and vomiting did not occur in our patients.

Previous studies had limitations. Articaine provides satisfactory anesthesia for about 1 hour; when operation time exceeds one hour, the quality of anesthesia may decrease and anesthesia may require to be supported. The anesthetists do not commonly use articaine for CSE technique, and more and larger randomised, double-blinded studies are needed to confirm the benefits of articaine in obstetrics.

In conclusion, the faster onset of spinal anesthesia, satisfactory anesthesia for Cesarean section and duration of sensory and motor dermatomes was clearly shorter block with

plain articaine than with a plain levobupivacaine. And fentanyl, the addition of both local anesthetics was prolonged the duration of sensory block; however, fentanyl added to levobupivacaine was prolonged the duration of motor block.

We conclude that, plain articaine is a feasible drug for Caesarean section in spinal anesthesia and a good alternative, with a favorable recovery profile, to levobupivacaine.

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