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ORIGINAL ARTICLE

Analgesia and side effects of the addition of 10 or 20 μg fentanyl to articaine in spinal anesthesia for knee arthroscopy: a randomized and observer-blinded study

Paula Stenman[1] · Merja Salonen[1] · Pekka Tarkkila[1] · Per Rosenberg[2]

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Abstract
Objectives Articaine, a popular and rapidly acting local anesthetic in dentistry, has been also found to be beneficial in ambulatory spinal anesthesia. Analgesia in the intraoperative and immediate postoperative period may be further improved by adding fentanyl to the local anesthetic solution for spinal anesthesia. The aim was to evaluate dose-dependency of analgesia and side effects associated with intrathecal fentanyl additive to articaine for spinal anesthesia in knee arthroscopy patients.
Methods In this randomized, observer- and patient-blinded study, 90 adult patients scheduled for elective ambulatory knee arthroscopy under spinal anesthesia were randomized into three groups: plain articaine 60 mg with saline (group AF0), articaine 60 mg with fentanyl 10 μg (group AF10) or 20 μg (group AF20) in a total volume of 1.9 ml. The blinded observer tested the sensory and the motor block, and performed telephone interviews on the first and seventh postoperative days.
Results The median (IQR) duration of sensory block at the dermatomal level of T10 was significantly longer in groups AF10, 69 min (56) and AF20, 69 min (45) than in group AF0, 41 min (35) ($p = 0.013$). Motor block duration was similar in all groups (median 120 min). Group AF20 patients experienced pruritus significantly more often than patients in the other groups ($p = 0.039$). No acute or late anesthetic side effects occurred, and satisfaction with the anesthetic technique was the same in all groups (97% satisfied).
Conclusions Fentanyl 10 or 20 μg as additive to articaine for spinal anesthesia prolonged the duration of sensory block significantly and similarly. Fentanyl 20 μg was more often associated with pruritus than fentanyl 10 μg.

Keywords Day-case spinal anesthesia · Local anesthetic articaine · Subarachnoid fentanyl additive · Postoperative pruritus

Introduction

Articaine is an amide-type local anesthetic [1, 2] with a low degree of toxicity [1, 3, 4]. It has been found useful in spinal anesthesia for ambulatory surgery of the lower parts of the body [5–7]. Among the doses of articaine studied, it seems that in adults 60 mg provides an onset (<5 min) and duration (approximately 60 min at the T10-dermatomal level) suitable for routine day-surgery of the lower extremities.

Low-dose bupivacaine is nowadays popular for day-case spinal anesthesia and its analgesic effect can be enforced and prolonged by mixing small doses of fentanyl in the intrathecal solution [8]. The fentanyl adjunct (10–20 μg) does not prolong the duration of motor block [9, 10]. In the higher dose range, fentanyl often causes irritating pruritus [11]. In the only published study on open inguinal hernia repair performed under spinal anesthesia with articaine combined with fentanyl [12], the need for intraoperative and postoperative analgesics was less with than without intrathecal fentanyl, but the duration of the spinal block was similar in both groups. This lack of an effect on

✉ Pekka Tarkkila
pekka.tarkkila@hus.fi

[1] Department of Anesthesiology and Intensive Care Medicine, Töölö Hospital, Helsinki University Hospital, PO Box 266, 00029 Helsinki, Finland

[2] Department of Anesthesiology and Intensive Care Medicine, Helsinki University, Biomedicum Helsinki 2C, PO Box 705, 00029 Helsinki, Finland

the duration of sensory block by the addition of fentanyl prompted us to perform a spinal anesthesia study comparable to those where fentanyl has been shown to prolong the sensory block of bupivacaine and lidocaine [9, 10], i.e., using a smaller local anesthetic dose and applying it in patients undergoing knee arthroscopy. A prolongation of articaine spinal anesthesia or analgesia, which otherwise ends rather quickly, would turn beneficial in cases of unexpected increased duration of surgery or when surgery is performed by trainees. Our aim was to investigate the effects and side effects of two intrathecal fentanyl doses, 10 and 20 μg, added to 60 mg articaine. We hypothesized that the sensory block would be dose-dependently prolonged by fentanyl.

Patients and methods

The Ethics Committee §19 (24.4.2009, 47/13/03/02/05, and the National Agency for Medicines (25.03.2009 KLnro 21/2009) approved the study protocol and all patients gave their written informed consent. The study was registered in the EU clinical trial register (EudraCT 2009-010696-24).

Adult patients [18–75 years old, American Society of Anesthesiologists (ASA) class I–II] scheduled for day-case knee arthroscopy under spinal anesthesia in the day-surgery center of the university hospital were recruited. Exclusion criteria were patient's refusal, body mass index (BMI) >30 kg/m^2, pregnancy, low back pain, neuropathy of the lower extremities, chronic use of analgesics, self-medication with an analgesic in the morning before surgery, problems with communication, and generally accepted contraindications to neuraxial anesthesia.

Randomization into three groups was performed using a sealed envelope method, stratified to blocks of 30. The anesthesiologist performing the intrathecal block prepared all the solutions according to the allocation in the operating room immediately prior to administration. In group AF0, plain articaine (slightly hyperbaric, i.e., density of articaine 4% at 37 °C 1.0035 g/ml; National Standards Laboratory, Centre for Metrology and Accreditation, Espoo, Finland) 60 mg and 0.9% NaCl 0.4 ml were drawn and mixed in a syringe.

In group AF10, plain articaine 60 mg 1.5 ml and fentanyl 10 μg (0.2 ml) and 0.9% NaCl 0.2 ml were drawn and mixed in a syringe. In group AF20, plain articaine 60 mg 1.5 ml and fentanyl 20 μg (0.4 ml) were drawn and mixed in a syringe. The final volume of the solutions in each group was thereby 1.9 ml and thus the concentration of articaine was 32 mg/ml (3.2%). Only the anesthesiologist who prepared the local anesthetic solution was aware of which anesthetic solution the patient would receive.

Premedication was given approximately 1 h before surgery and consisted of oral etoricoxib 60–120 mg (<60 kg 60 mg, 60–70 kg 90 mg, >70 kg 120 mg), or alternatively oral acetaminophen 0.5–1 g (<65 kg 0.5 g ≥65 kg 1 g) if there was a contraindication for etoricoxib. Diazepam 5–10 mg was given orally if the patient requested a sedative when reporting for surgery at the outpatient clinic.

Spinal anesthesia

Before the spinal anesthetic administration, 200–300 ml of Ringer's acetate solution was given intravenously. Intraoperative monitoring included ECG, heart rate, and pulse oximetry. Non-invasive arterial blood pressure was recorded in the operating room at 5-min intervals.

For spinal anesthetic injection, the patient was placed horizontally in the lateral decubitus position with the side of intended surgery facing down. After the skin was infiltrated with 1% lidocaine, the intrathecal puncture was performed in the midline using a 27-gauge pencil-point needle at the L3–4 interspace. On obtaining a free flow of cerebrospinal fluid and with the needle aperture facing downwards, the anesthetic solution was injected at a constant rate of approximately 0.1 ml/s. At the end of the injection of the total volume, an aspiration was made, and the aspirate was reinjected. When the intrathecal injection was started, a research assistant who was not aware of this allocation entered the operating room.

After injection, the patient was immediately turned supine, and the operating table was tilted head-end 10° up to prevent from extensive cephalad spread of the block. The head-up tilt was retained if the block had spread more cephalad than to the T10 dermatome; otherwise the table was placed in the horizontal position before the start of surgery.

Assessment of the blocks

The dermatomal assessment of the block was always performed by the same research assistant. Dermatomal sensory block was assessed by pin-prick with a 27-gauge short bevel needle in caudad to cephalad bilaterally in the anterior axillary line at 2-min intervals for 10 min, then at 5-min intervals until 30 min, and then at 15-min intervals until recovery of sensation of the S2 dermatome posteriorly at knee joint.

Motor block was assessed on a three-grade scale (grade 0 = no motor block, grade 1 = reduced ability to bend the knee or flex the ankle, grade 2 = complete motor block) at 5-min intervals for 30 min and, thereafter, at 15-min intervals until the full recovery. During surgery, the motor block was only assessed on the non-operative side.

Supplemental intraoperative medication

Arterial hypotension was treated with ephedrine 5 mg intravenously using clinical judgment, or if mean arterial blood pressure (MAP) was <60 mmHg. Bradycardia was treated with atropine 0.5 mg intravenously at the discretion of the attending anesthesiologists, or if the heart rate was <40 beats/min. Midazolam in 1-mg doses was given for anxiety by the patient's request or as judged by the attending anesthesiologists, and ondansetron 4 mg for nausea and vomiting. For painful sensations during surgery, fentanyl 1 μg/kg IV was given, maximally twice, and thereafter, if needed, general anesthesia was administered using propofol, remifentanil, and laryngeal mask airway.

Postoperative evaluation

In the postanesthesia care unit (PACU1 = recovery room), the patient's head-end was tilted up 30° and lower limbs elevated. Pain intensity was assessed on a numeric rating scale (NRS 0–10: 0 = no pain, 10 = worst imaginable pain). The patients received fentanyl 1 μg/kg IV, if NRS was ≥4, and the dose was repeated once when necessary. In the day-surgery ward (PACU2), patients received 5–10 mg oral oxycodone when the intensity of pain on the NRS was ≥4. For milder pain (NRS <4) oral acetaminophen was given as required. Pruritus, nausea, time to tolerate fluid intake by mouth, time to voiding were recorded until discharge. A glass of water or clear fruit juice was offered to the patients as soon as they were moved to the PACU2. The time when the patient would be ready for discharge was also recorded.

The criteria for discharge were stable vital signs, no bleeding, ability to drink, no severe pain (NRS 0–3) or nausea, ability to ambulate without support, and ability to urinate.

Telephone interviews

Telephone interviews were performed by a group-blinded research assistant on the first and the seventh postoperative day using standardized questions. Possible side effects, complications, pain, nausea, itching, headache (position dependent or not), back or leg pain (pain in the gluteal region radiating to the legs), as well as the patient's satisfaction with the anesthetic technique were recorded. In case of any signs of a serious complication, the patient was called back to the hospital for medical examination and treatment.

Power analysis

The primary aim of this study was to compare the effect of addition of fentanyl 0, 10, and 20 μg to articaine 60 mg on the duration of the spinal analgesia and secondly on the occurrence of possible anesthesia-related side effects in day-case knee arthroscopy. The power analysis was based on the spinal anesthesia study by Chung et al. [13] who found that fentanyl 10 μg added to ropivacaine 18 mg prolonged sensory analgesia at the T10 dermatome from 119.3 ± 19.7 to 143.0 ± 34.1 min (mean, SD) (i.e., by 20%). Assuming a power of 80%, (α 0.05) the sample size of 3 × 26 (ANOVA-sample size) was needed to detect a statistically significant difference in the median duration of sensory block at T10.

Statistics

Statistical analysis was performed with SPSS (version 19.0; IBM Corp., Armonk, NY, USA). For continuous normally distributed variables, median or mean ± SD were reported and tests between the groups were analyzed using one-way ANOVA with post hoc multiple comparisons (Tukey). Repeated measures ANOVA was used for analysis of the duration of the sensory and motor block. If the data were not normally distributed, Kruskal–Wallis test with pairwise post hoc comparison was used, when appropriate. Ordinal variables were reported as median (with IQR) and differences between the groups were analyzed using Mann–Whitney *U* test.

Results

One of the 90 randomized patients in group AF0 was excluded from the analysis due to protocol violation; he had received a combination formulation of acetaminophen and codeine for premedication. The remaining 89 patients received the allocated intervention. One patient in group AF20 required general anesthesia because the sensory block was insufficient, and his data are included until the induction of general anesthesia (Fig. 1). For premedication, 84 patients received etoricoxib and five patients received acetaminophen. The patients and the surgical characteristics were similar in the three groups (Table 1).

During spinal needle insertion, a paresthetic sensation was registered in three group AF0 patients, six group AF10 patients, and four group AF20 patients, but these patients did not report any neurological sequelae afterwards.

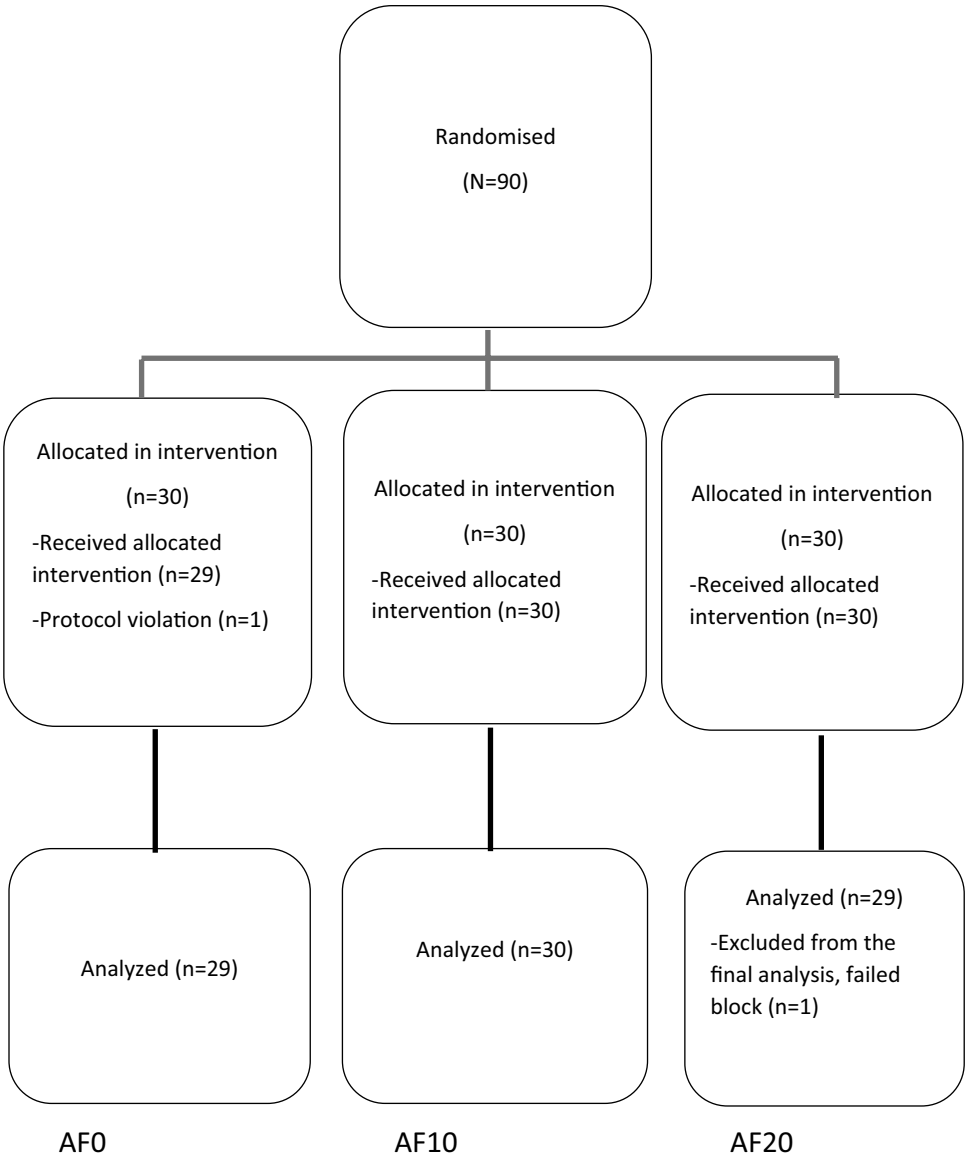

Fig. 1 Flow diagram of screened, excluded, and recruited patients

Table 1 Patient characteristics and surgical data for the three groups

	AF0 ($n = 29$)	AF10 ($n = 30$)	AF20 ($n = 30$)	p
Age (years)	47 ± 12	46 ± 12	49 ± 13	0.69
Weight (kg)	77 ± 11	76 ± 11	75 ± 13	0.83
Height (cm)	175 ± 9	174 ± 9	171 ± 11	0.35
ASA I/II (*n*)	21/8	20/10	19/11	0.75
Male/female (*n*)	16/13	15/15	14/16	0.81
Duration of surgery (min)	32 (20)	38 (15)	32 (16)	0.24
Time from intrathecal injection to the end of surgery (min)	53 (23)	59 (26)	50 (16)	0.10

Group AF0, articaine 60 mg; group AF10, articaine 60 mg + fentanyl 10 μg; group AF20, articaine 60 mg + fentanyl 20 μg

Data are presented as number (%), mean (range) for age, mean ± SD, or median (IQR). No significant differences between the groups were found

Sensory and motor block

Sensory analgesia to the T10 dermatome was reached in 21 of 29 patients in group AF0, in 21 of 30 in patients group AF10 and in 25 of 29 patients in group AF20 in a median (IQR) time of 6–8 min (4–6) in all groups. The median maximum cephalad spread of sensory block did not differ between the three groups (Fig. 2).

Although there was no significant difference in the time to two-segment regression of sensory block (Table 2), the median (IQR) duration of sensory block at the dermatomal level of T10 was significantly longer in group AF10, 69 (56) min, and group AF20, 69 (45) min, than in group AF0, 41 (35) min, ($p = 0.013$) (Table 2).

The motor block was complete (grade 2) in 99% of patients at 10 min after the intrathecal injection. All patients had a complete motor block 15 min after injection on the dependent side, and all but one patient in group AF0 (who had grade 1) had a complete motor block on the non-dependent side, too. There were no difference in the duration of motor block between the groups (Table 2). All the patients had a full recovery from motor block 195 min after spinal injection.

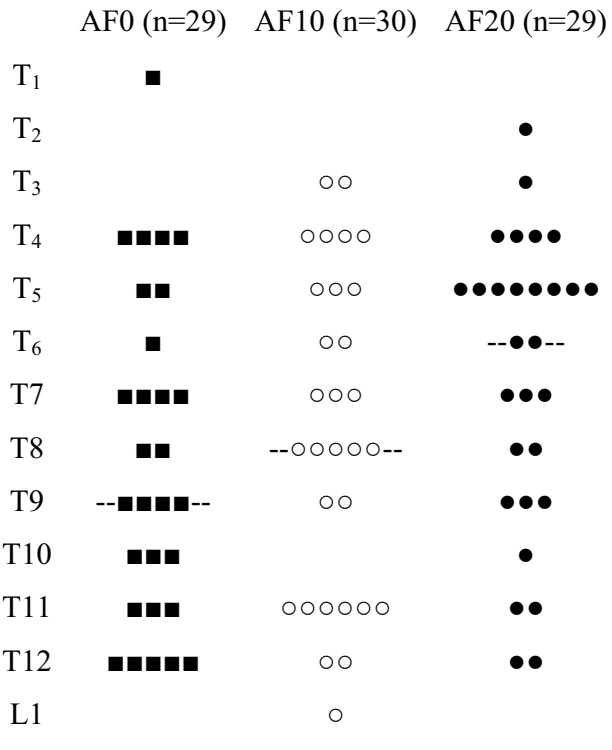

Fig. 2 Maximum cephalad extent (dermatomes) of sensory block of each patient in groups AF0, AF10, AF20. The median level is indicated with a *horizontal broken line*

Intraoperative and in-hospital postoperative variables and medications

During surgery, three patients in group AF10 received fentanyl (0.075, 0.05, and 0.1 mg after 29, 100, and 105 min from the intrathecal local anesthetic injection, respectively). Their sensory block level was at dermatome T12, L1, and Th12 on the non-dependent side, respectively, when intravenous fentanyl was administered. In groups AF0 and AF20, intravenous fentanyl was not required intraoperatively. None of the patients complained of pain from the tourniquet.

The intraoperative hemodynamics was similar in the three groups (Table 3). Atropine was given to three, three, and four patients, and ephedrine to five, five, and four patients in groups AF0, AF10, and AF20, respectively (Table 3).

Intraoperative nausea was infrequent in all groups (Table 3). One patient in group AF0, with extension of sensory block to dermatome T10, received ondansetron 4 mg intravenously for mild nausea. The requirements for supplementary sedation (doses of midazolam 1–2 mg IV) were similar in all groups. One patient in both group AF0 and group AF10, and two patients in group AF20 experienced pruritus intraoperatively, but no medication was required.

Table 2 Data on spinal block and the immediate postoperative (in PACU1 and PACU2) period and on the 1st postoperative day

	AF0 ($n = 29$)	AF10 ($n = 30$)	AF20 ($n = 29$)	p
Duration of sensory block at higher than T10 (min)	41 (35)	69 (56)	69 (45)	0.013*
Two segment regression of sensory block (min)	60 (45)	60 (30)	60 (30)	0.30
Duration of full motor block (grade 2) (min)	94 ± 15	90 ± 17	89 ± 17	0.68
Patients experiencing pruritus in PACU1, *n* (%)	1 (3)	3 (10)	7 (24)*	0.046*
Patients experiencing pruritus, 1st POD, *n* (%)	3/27 (11)	3/28 (10)	9/26 (35)*,§	0.039
Median time to first voluntary urinary voiding (min)	230 (68)	222 (54)	210 (90)	0.77
Oral oxycodone consumption in PACU2, *n* (%)	3 (10)	4 (13)	3 (10)	0.95

PACU1 immediate post-anesthesia care unit, recovery room, *PACU2* day-surgery ward, *1st POD* first postoperative day

Values are expressed as mean ± SD, or median (IQR) and number (%) of patients

* $p < 0.05$ compared with AF0 and § $p < 0.05$ compared with AF10

Table 3 Intraoperative data

Group	AF0 ($n = 29$)	AF10 ($n = 30$)	AF20 ($n = 29$)	p value
Intraoperative lowest MAP, mmHg	81 ± 17	83 ± 13	78 ± 14	0.57
Intraoperative lowest heart rate, beats/min	56 ± 11	53 ± 7	54 ± 10	0.46
Intraoperative ephedrine, *n* (%)	5 (17)	5 (17)	4 (14)	0.93
Intraoperative atropine *n* (%)	3 (10)	3 (10)	4 (14)	0.88
Intraoperative nausea, *n* (%)	3 (10)	2 (7)	4 (14)	0.66
Intraoperative midazolam, *n* (%)	8 (28)	7 (23)	9 (31)	0.80
Patients experiencing pruritus intraoperatively, *n* (%)	1 (3)	1 (3)	2 (7)	0.76

Group AF0, articaine 60 mg; group AF10, articaine 60 mg + fentanyl 10 μg; group AF20, articaine 60 mg + fentanyl 20 μg. MAP 0 mean arterial pressure

Values are expressed as mean ± SD and number (%) of patients

In PACU1, postoperative pain at rest was mild in all groups (NRS <4); in 24 patients (83%) in group AF0, 29 patients (97%) in group AF10 and 28 patients (97%) in group AF20 there was no pain (NRS 0) or the pain was mild (NRS 1–3). No pain at all (NRS 0) was reported by 11, 14, and 18 patients in groups AF0, AF10 and AF 20, respectively (NS). Moderate pain (NRS 4–6) was reported by five (17%), one (3%), and one patient (3%) in groups AF0, AF10, and AF 20, respectively. None of the patients in any group had severe pain (NRS ≥7) in PACU1. The need for postoperative oral oxycodone was slightly lower in group AF20 than in the other groups (NS) (Table 3). One patient in groups AF0 and AF20 received acetaminophen orally.

During the stay in PACU1 and PACU2, nausea did not occur. Pruritus was more common in Group AF20 than in Group AF0 or in Group AF10 (Table 3); the difference between Groups AF0 and AF20 was statistically significant ($p = 0.046$) (post hoc analysis). No significant differences were found between the groups in time to voiding (Table 2) and in the mean time to discharge readiness.

Three patients remained in hospital overnight: one in group AF10 because of a surgical complication (hemarthron) and another in group AF10 because of inability to move safely on crutches. One patient in group AF0 remained in the hospital overnight because of missing instructions for immediate postoperative care and rehabilitation.

Postoperative interviews

On the first postoperative day, median NRS at rest was 1.8 in group AF10, and 0 in groups AF0 and AF20. Median NRS on movement was 2.0, 2.8, and 1.0 in groups AF0, AF10 and AF20, respectively. When moving the operated leg, the NRS score in group AF10 was significantly higher than in group AF0 ($p = 0.015$) with no other differences between the groups. In group AF10, one patient temporarily experienced severe pain (NRS = 10) because of a surgical complication (hemarthron).

Nine patients in group AF20 reported occurrence of pruritus during some period on the 1st POD compared to three patients in both groups AF0 and AF10 ($p = 0.039$) (Table 2). The information about pruritus was missing in two, two, and three patient interview recordings in groups AF0, AF10, and AF20, respectively.

In the 7th postoperative-day interview, 97% of the patients in each group responded that they were satisfied with their spinal anesthesia. There was one dissatisfied patient in each group. One patient in group AF0 suffered from a conservatively treated postdural puncture headache during the first week, one patient in group AF10 was dissatisfied because of an extensive spread of sensory block (T3) and associated nausea, and one patient in group AF20 was not satisfied because of the sensation of being paralyzed and nauseated during surgery. Postoperative voiding difficulties were not encountered in any of the study patients. On the 7th postoperative day, pain was absent or negligible. Symptoms of neurological sequaleae were not reported.

Discussion

This study showed that adding fentanyl 10 or 20 μg to articaine 60 mg for spinal anesthesia prolonged the median duration of the sensory block at the T10 dermatomal level from 41 min to 69 min as compared to plain articaine. In this study, the duration of an analgesic block seemed to be insufficient in only one patient, in whom the arthroscopic surgery was not finished until 116 min after the intrathecal local anesthetic injection. Usually, the sensory block level needs to be at least at T10 in order to avoid tourniquet cuff pain but knee arthroscopy was performed without pain even when in some patients the dermatomal block level was at T12. It is probable that this is related to the short duration of the operation or to how the knee and the intra-articular

tissues are manipulated. In a recent spinal anesthesia study in open inguinal herniorrhaphy, the addition of fentanyl 10 μg to hyperbaric articaine 72 mg significantly reduced the need for supplemental intravenous fentanyl intraoperatively [12]. Contrary to the present findings, the duration of the sensory block at the T10 dermatomal level was not affected by intrathecal fentanyl in the study on herniorrhaphy patients [12]. The reason for this contrasting result is probably mainly due to the fact that in the earlier study [12] the dose of the clearly hyperbaric articaine was larger than that of the presently used slightly hyperbaric articaine (72 vs. 60 mg), and that the spread of the intrathecal solution was deliberately influenced by protocol-based tilting up or down of the operating table. In spite of the relatively extensive cephalad spread, the associated arterial blood pressure decrease was moderate, and only a few of the patients whose maximum sensory block was at or above T4 dermatomal level needed intravenous ephedrine. In previous studies on spinal anesthesia using articaine, higher doses (72–108 mg) [7, 14] than that used in the present study (60 mg) have resulted in too wide cephalad spread of the sensory block and in arterial hypotension.

The quality and duration of motor block were unaffected by the fentanyl additive. In our study, the median duration was 120 min, which may be regarded as suitable for modern-day surgery and allows early mobilization. In earlier studies, the duration of motor block varies to some extent in response to different doses; thus, with plain articaine, 84 mg the median motor block duration was 180 min [7], with 60 mg 135 min [6] and with 40 mg 105 min [15]. In contrast to a typical partial motor block by bupivacaine in spinal anesthesia, articaine usually causes a complete motor block of the lower extremities [7, 16].

In our organization, "home-readiness" criteria are usually fulfilled when the patient has walked to the bathroom and is able to pass urine, which in our study occurred in a median time of 3.5–3.8 h. It is notable that urinary bladder catheterizations were not needed in the present study. Even in our previous spinal anesthesia studies with articaine in open herniorrhaphy patients [7, 12, 16], urinary problems have been rare, probably because of the rapid recovery of lumbar and sacral spinal nerve function after the use of articaine.

Doubling the fentanyl dose did not further improve analgesia intraoperatively and in the immediate postoperative period. This is in line with a previous spinal analgesia study on the determination of the minimal local analgesic dose of bupivacaine in labor where the intrathecal additive dose of fentanyl 5 μg provided as good bupivacaine dose-sparing effect as 15 and 25 μg [17]. However, there was a dose-dependent increase in the incidence of pruritus and duration of spinal block with increasing fentanyl doses. An increase in dose to 20 μg, or above, almost inevitably results in disturbing itching [17], while a dose of 50 μg may cause respiratory depression [18].

Limitations

The anesthesiologist specialists (either MS or PS) who performed the drug mixing, the intrathecal injection, and supervised the anesthetic management, were not blinded. However, the preparation of the solutions and the intrathecal injection were performed in a prescheduled standardized manner, and the criteria for IV administration of rescue fentanyl, atropine, midazolam, and ondansetron, stated in the study protocol, were followed. Importantly, the research assistant who assessed the spread and durations of the blocks, and registered intra- and postoperative events, was completely blinded regarding the group allocation.

Conclusions

It is concluded that both fentanyl 10 and 20 μg added to plain articaine 60 mg for spinal anesthesia similarly prolonged the median duration of sensory block at T 10 dermatome by almost 70%. The motor block duration was not affected by intrathecal fentanyl addition. There was a dose-dependent effect of fentanyl on the occurrence of pruritus, which was most frequent after fentanyl 20 μg. The degree of patient satisfaction was high (97% satisfied) and no signs of neurotoxicity were observed.

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Compliance with ethical standards

Conflict of interest None of the authors declare any conflicts of interest.

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