Egyptian Journal of Anaesthesia (2014) **30**, 149–153

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Dexmedetomidine as supplement to low-dose levobupivacaine spinal anesthesia for knee arthroscopy

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Received 8 August 2013; revised 6 November 2013; accepted 25 November 2013
Available online 24 December 2013

KEYWORDS

Intrathecal dexmedetomidine;
Spinal levobupivacaine;
Knee arthroscopy

Abstract *Aim:* To evaluate efficiency of dexmedetomidine compared to fentanyl as supplements to low-dose levobupivacaine spinal anesthesia in patients undergoing knee arthroscopy.
Materials and methods: Sixty adult patients (ASA I or II) scheduled for knee arthroscopy were randomized to receive plain levobupivacaine (4 mg) plus dexmedetomidine (3 μg) in group D or fentanyl (10 μg) in group F.
Results: Dexmedetomidine shortened time to surgery ($P = 0.002$), time to highest sensory level ($P = 0.001$), and time to highest Bromage score ($P < 0.001$). The highest sensory level was comparable in both groups ($P = 0.969$), but the duration of sensory block was significantly longer in group D ($P = 0.009$). The highest Bromage score was 2 in both groups. This score was attained in significant higher number of patients in group D ($P = 0.038$) that showed better muscular relaxation ($P = 0.035$). At the end of surgery, a residual motor block (Bromage score 1) was observed in significant higher number of patients ($P = 0.033$) and time to ambulation was significantly longer in group D ($P = 0.001$). There was no difference in the number of patients bypassed post-anesthesia care unit (PACU) ($P = 0.761$) or time to hospital discharge ($P = 0.357$) between groups. The pain free period was more prolonged ($P < 0.001$), and the visual analog scale (VAS) for pain was lower at the 2nd, 4th, 6th, and 8th postoperative hours ($P < 0.001$, < 0.001, 0.013, 0.030 respectively) in group D.

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.egja.2013.11.003

Conclusion: Dexmedetomidine is a good alternative to fentanyl for supplementation of low-dose levobupivacaine spinal anesthesia for knee arthroscopy.

1. Introduction

Spinal anesthesia provides an excellent mean of postoperative pain control following ambulatory procedures [1]; however, these advantages may be offset by an increased likelihood of delayed recovery of motor power and, hence, delayed ambulation and prolonged hospital stay [2,3]. The development of the ''low-dose spinal'' technique involving the use of low-doses of local anesthetics, often in association with fentanyl, improved the utility of spinal anesthesia in ambulatory surgical setting through increasing the sensory without increasing motor block or time to micturition. Nevertheless, inadequate anesthesia and risks of intrathecal opioids still remain the main problems of this technique [4,5].

Intrathecal α_2-adrenoceptor agonists as adjuvant drugs have been shown to decrease the required doses of local anesthetics [6,7]. Dexmedetomidine is highly selective α_2-adrenoceptor agonists. It potentiates local anesthetics effects, prolongs postoperative analgesia, and has a dose-dependent sedative effect without respiratory depression [8]. The mechanism of action of intrathecal α_2-adrenoceptor agonists is not well understood; they may have an additive or synergistic effect to local anesthetics through binding to the pre-synaptic C-fibers and postsynaptic dorsal horn neurons producing analgesia by depressing the release of C-fiber neurotransmitters and hyperpolarization of postsynaptic dorsal horn cells [9,10]. The prolongation of motor block of spinal anesthetics may result from hyperpolarization of ventral horn motoneurons of the spinal cord that facilitate local anesthetic action [11].

The purpose of the present study is to evaluate efficiency of low-dose dexmedetomidine compared to fentanyl as supplements to low-dose levobupivacaine spinal anesthesia in patients undergoing knee arthroscopy.

2. Materials and methods

After obtaining an institutional review board approval (code number: 1901) and written informed consent, 60 consecutive adult patients (ASA I or II) of both sexes scheduled for day case knee arthroscopy by the same surgeon were included in this prospective, randomized, double-blind study. Uncooperative patients and those with diabetes mellitus, body mass index >35 kg/m^2, height <150 cm or >185 cm, contraindication to spinal anesthesia, allergy to amide type local anesthetics, or history of chronic analgesic therapy were excluded from the study.

Patients were randomized using a computer generated random numbers table into groups: D and F; 30 patients each. Allocation to each group was concealed using opaque sealed sequentially numbered envelopes. All patients received 4 mg plain levobupivacaine [Chirocaine®, Abbot Laboratories; 5 mg/ml] combined with 3 μg dexmedetomidine (Precedex, Hospira, USA; 100 μg/ml) in group D, or 10 μg fentanyl (Fentanyl, Hameln pharmaceutical gmbh, Germany, 50 μg/ml) in group F. The spinal solutions were prepared by an anesthesiologist, who was blinded to the study, to a total volume of 3 ml with sterile water. The patient, surgeon, and anesthesiologist who performed the block and recorded the data were blind to the study solutions. Before lumbar puncture, the patients were monitored for electrocardiography, pulse oximetry, and non-invasive blood pressure. They were preloaded with Ringer's solution (250 ml) followed by an infusion of 2 ml/kg/h. Lumber puncture was performed in the sitting position at L_{4-5} or L_{3-4} using a midline approach with a 25-G spinal needle with the hole pointing upwards. The spinal solutions were injected over 10 s with no barbotage followed by placing the patients in the supine position. In case of intraoperative discomfort or pain, they were administered general anesthesia and excluded from the study. The sensory and motor blocks were assessed every 2 min till their upper levels were attained, and then every 15 min till they returned to normal. The sensory block was tested bilaterally along the mid-clavicular lines by pin prick, while the motor block was assessed according to the Bromage scale (0: no motor loss, 1: inability to flex hip joint, 2: inability to flex knee joint, 3: inability to flex ankle). When no motor block could be detected (Bromage scale 0) and when the patients were ready, they were asked to walk.

At the end of surgery, the patients were bypassed the post-anesthesia care unit (PACU), if PACU bypass score was 10 [12], no pain, nausea, vomiting, pruritus, or shivering [13]. In the ambulatory surgery unit, they were discharged home when the Post-Anesthetic Discharge Scoring System was $\geqslant 9$ [14].

The times to surgery (loss of pin prick sensation at T_{12}), highest sensory level, highest Bromage score, ambulation, and hospital discharge measured from intrathecal injection were determined. The highest sensory level, duration of sensory blockade (measured from intrathecal injection till regression of the sensory level to S_1), highest Bromage score, Bromage score at end of surgery, intraoperative adequacy of muscular relaxation evaluated as good or poor by the surgeon, intraoperative level of sedation according to Ramsay sedation score [15], number of patients bypassed the PACU, and side effects including nausea, vomiting, shivering, respiratory depression (oxygen saturation $<96\%$ and respiratory rate <10/min), hypotension (mean arterial blood pressure $<20\%$ of preoperative value or systolic blood pressure less than 100 mmHg; treated by increasing the fluid infusion rate and IV 3–6 mg ephedrine), bradycardia (heart rate <50/min; treated by IV 0.6 mg atropine) were recorded.

The patients were contacted by telephone, after discharging home, in order to determine the pain free period (measured from intrathecal injection to the first analgesic requirement) and the severity of pain according to a visual analog scale (VAS: 0–10) at the following times: 1st, 2nd, 4th, 6th, 8th, 10th, and 12th postoperative hour. Rescue analgesia, oral diclofenac sodium 50 mg/12 h, was started when the VAS was $\geqslant 3$.

The sample size was estimated using data from a previous pilot study performed at our institution. A difference of 7 min in the mean (M) value of times to ambulation between

the two groups and a standard deviation (SD) of 9 was used for calculation. Twenty-six patients were required per group using a cutoff for statistical significance of 0.05% and a power of 80%. Thirty patients per group were included. Data were analyzed using SPSS (version 20) for windows and presented as M ± SD, median (range), or number (%) where appropriate. Independent *t*-test was used for comparison of age, weight, height, body mass index (BMI), surgery time, time to surgery, the duration of sensory block, time to highest Bromage score, time to ambulation, time to hospital discharge, and the pain free period. Mann–Whitney *U* test was used for analysis of the highest sensory level and the VAS values. Fisher's exact test was used for comparison of gender, ASA status, the highest Bromage score, Bromage score at end of surgery, adequacy of relaxation, and the number of patients bypassed PACU. $P < 0.05$ was considered statistically significant.

3. Results

The spinal technique was easy and uneventful in all patients. One patient was administered general anesthesia and excluded after recruitment because of intraoperative pain complaint after successful intrathecal injection, leaving 29 patients, in group F. Therefore, the statistical analyses were based on 29 patients in the dexmedetomidine group and 30 patients in the fentanyl group. Demographic data (Table 1) were comparable in both groups ($P < 0.05$).

As shown in Table 2, intrathecal dexmedetomidine fastened the time to surgery (onset of neuraxial block) ($P = 0.002$), time to highest sensory level ($P = 0.001$), and time to highest Bromage score ($P < 0.001$). The highest sensory level was comparable in both groups ($P = 0.969$), but the duration of sensory blockade was significantly longer in group D than group F ($P = 0.009$). The intensity of motor block was superior in the dexmedetomidine group. Although the highest Bromage score was 2 in both groups, this score was attained in significant higher number of patients in dexmedetomidine group compared to fentanyl group (19 vs. 10 patients; $P = 0.038$). At the end of surgery, the Bromage score equaled 1 in significant higher number of patients in group D (16 vs. 7 patients in groups D and F respectively; $P = 0.033$) and the adequacy of muscular relaxation as evaluated by the surgeon (good in 22 vs. 13 patients in groups D and F respectively; $P = 0.035$) were significantly better in group D. There was no significant difference between the number of patients who bypassed the PACU (22 vs. 23 patients in groups D and F respectively; $P = 0.761$). The time to ambulation was significantly longer in group D (the mean difference equaled 9.1 ± 2.7 min; $P = 0.001$), and there was no significant difference between groups concerning the time to discharge from hospital ($P = 0.357$).

The pain free period was significantly longer in group D ($P < 0.001$), and the VAS was significantly lower in dexmedetomidine than fentanyl groups at the 2nd, 4th, 6th, and 8th postoperative hours ($P < 0.001$, < 0.001, 0.013, 0.030 respectively) (Table 3).

None of patients developed nausea, vomiting, shivering, pruritus, or respiratory depression. Only two patients developed intraoperative hypotension in group F, and one developed bradycardia in group D; and they were managed successfully. One patient in group F fell asleep during surgery and was easily aroused by simple verbal command (Ramsay sedation score 2).

4. Discussion

This is the first study testing intrathecal levobupivacaine in association with dexmedetomidine for knee arthroscopy. In comparison with intrathecal fentanyl adjuvant, dexmedetomidine fastened the onset of spinal anesthesia; it prolonged and intensified levobupivacaine sensory and motor blocks. Although the time to ambulation was increased (the mean difference between the groups equaled 9.1 ± 2.7 min), it did not affect the ratio of patients who bypassed the PACU or the time to discharge home. Dexmedetomidine prolonged the pain free period and improved postoperative analgesia. Different studies [8,16–18] are consistent with these findings.

In the present study, although the statistically significant difference in the anesthetic characteristics, particularly the duration of sensory and motor blocks, between the groups are really insubstantial, this is likely to be advantageous in knee arthroscopic surgery that requires early ambulation and discharge. Kanazi et al. [16], showed dexmedetomidine potentiates the anesthetic characteristics of hyperbaric bupivacaine without serious side effects in patients undergoing transurethral resection of prostate or bladder tumor. Dexmedetomidine produced valuable differences in the duration of sensory and motor blocks (averaged 100 and 90 min; respectively) between patients received bupivacaine (12 mg) and those received bupivacaine (12 mg) and dexmedetomidine (3 μg) which is contradictory to our results. However, this could be attributed to the use of low-dose of local anesthetic in our study (4 mg of levobupivacaine).

Levobupivacaine and bupivacaine are equally effective local anesthetics for spinal anesthesia; however, the decreased cardiovascular and central nervous system toxicity make levobupivacaine an interesting choice for spinal anesthesia despite

Table 1 Demographic data.

Variables	Group F no = 29	Group D no = 30	*p*
Age; year	40.1 ± 6.1	39.1 ± 5.5	0.481
Weight; kg	81.3 ± 7.4	79.4 ± 7.2	0.319
Height; cm	176.7 ± 3.9	175.8 ± 4.5	0.385
BMI; m/kg^2	26 ± 1.8	25.7 ± 1.9	0.592
Gender; male/female	14/15	17/13	0.606
ASA; I/II	19/10	18/12	0.789
Surgery time; min	55.1 ± 11.4	52.8 ± 10.9	0.443

Table 2 Anesthetic characteristics'.

Variables	Group F no = 29	Group D no = 30	*P*
Time to surgery; min	5.1 ± 1.5	3.9 ± 1.2*	0.002
Highest sensory level[a]	T8 (6–11)	T8 (5–11)	0.969
Time to highest sensory level; min	13.8 ± 4.4	10.7 ± 2.3*	0.001
Duration of sensory blockade; min	64.9 ± 11.3	73.9 ± 13.9*	0.009
Highest Bromage score (0/1/2/3); n	0/19/10/0	0/11/19/0*	0.038
Time to highest Bromage score; min	18.9 ± 4.1	14.1 ± 2.3*	<0.001
Bromage score at end of surgery (0/1/2/3); n	22/7/0/0	14/16/0/0*	0.033
Adequacy of relaxation (good/poor); n	13/16	22/8*	0.035
Patients bypassed PACU; n%	23(79.3%)	22(73.3%)	0.761
Time to ambulation; min	64.2 ± 11.9	73.3 ± 8.5*	0.001
Pain free period; min	70.2 ± 8.4	126.6 ± 12.9*	<0.001
Time to hospital discharge; min	254 ± 19.3	266 ± 25.2	0.357

[a] Data presented as Median (range).
* Statistically significant difference ($P < 0.05$).

Table 3 VAS scale scores.

	VAS 1	VAS 2	VAS 4	VAS 6	VAS 8	VAS 10	VAS 12
Group F no = 29	0 (0–0)	2 (0–4)	3 (1–5)	3 (1–4)	4 (2–5)	4 (3–5)	4 (3–6)
Group D no = 30	0 (0–0)	0 (0–0)*	2 (1–4)*	2 (1–5)*	3 (3–4)*	4 (3–5)	4 (3–6)
P	1.00	<0.001	<0.001	0.013	0.030	0.236	0.473

Data presented as Median (range).
* Statistically significant difference ($P < 0.05$).

the fact that spinal anesthesia is achieved with small-dose regimens compared to epidural anesthesia [19,20]. A recent review of spinal anesthesia for knee arthroscopy demonstrated that bupivacaine in doses as low as 4–5 mg given in the spine position was associated with a failure rate of ~25% due to inadequate anesthesia. Low-dose bupivacaine can produce enough anesthesia with no or very low incidence of failure for knee arthroscopy, only, when hyperbaric bupivacaine is used, along with the unilateral positioning and intrathecal fentanyl [21]. Unfortunately, the unilateral spinal anesthesia added an extra time (10–15 min) required for the local anesthetic to fix [22,23]; and intrathecal fentanyl in dose of 10–25 μg produced an incidence of pruritus of 48–75% [4,24–26]. Moreover, there are reports that spinal anesthesia with plain local anesthetic has rapid onset, longer duration of action but lower height of blockade, and less cardiovascular disturbances [27,28]. Dexmedetomidine, in the present study, avoided the drawbacks of the unilateral position and intrathecal fentanyl, while preserving the benefits of plain levobupivacaine.

De Santiago et al. [13] tested three doses of plain levobupivacaine (3, 4, and 5 mg) in association with fentanyl 10 μg given in the supine position for knee arthroscopy. They showed that 4 mg is the ideal dose of intrathecal levobupivacaine. It was associated with the shortest time to ambulation, highest PACU bypass rate, fewer patients presented with altered proprioception, and higher rate of unassisted ambulation at the end of surgery. However, they reported a probability of spinal failure (~0.5%) because of inadequate block with levobupivacaine in doses of 4 or 5 mg. Similar incidences of failure (5–10%) were seen in obstetric surgical patients [29]. Our trail showed a failure rate of ~3% in levobupivacaine–fentanyl group compared to no failure in levobupivacaine–dexmedetomidine group. Weighing the capability of dexmedetomidine adjuvant to intensify anesthesia and improve postoperative pain control against the increase in motor block suggests that dexmedetomidine is a good alternative to fentanyl for supplementation of low-dose spinal anesthesia. The dexmedetomidine-associated increase in motor block could be beneficial in anxious less cooperative patients and those who require surgery of longer time.

The results of the current study are limited by the lack of United State Food and Drug Administration approval for the perineural application of dexmedetomidine because of doubts about its neurotoxicity that resulted in scant appearance of trails on this topic [30]. Indeed, relevant neurotoxicity data seem contradictory, while dexmedetomidine has been shown to cause moderate to severe demyelination in white matter when doses as high as 6.1 μg/kg were administered via an epidural route in rabbit [31], intrathecal dexmedetomidine (2.5–100 μg) produced no neurological deficits in sheeps [32], and epidural dexmedetomidine (1.5–2 μg/kg) caused no neurological deficits in humans [33,34]. In a systematic review by Abdallah and Brull [30], dexmedetomidine in doses up to 0.2 μg/kg for intrathecal and 1 μg/kg for perineural peripheral administration potentiated local anesthetics effects without producing any neurotoxic manifestations.

In conclusion, intrathecal dexmedetomidine 3 μg plus levobupivacaine 4 mg improves the quality of anesthesia and postoperative analgesia for knee arthroscopy. Low-dose dexmedetomidine is a good alternative to fentanyl for supplementation of spinal anesthesia in ambulatory surgical setting.

Conflicts of Interest

None.

Funding

This work was funded by the authors.

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