Original Article

Effects of perineural administration of dexmedetomidine in combination with bupivacaine in a femoral-sciatic nerve block

ABSTRACT

Background and Aim: Perineural administration of dexmedetomidine, a α2-adrenoceptor agonist, prolongs the duration of analgesia. We hypothesized that adding dexmedetomidine to bupivacaine would prolong postoperative analgesia after below knee surgery.

Materials and Methods: After ethical approval, 60 patients scheduled for below knee surgery under combined femoral-sciatic nerve block were randomly allocated into two groups to have their block performed using bupivacaine 0.5% alone (group B) or bupivacaine 0.5% combined with 100 μg bupivacaine-dexmedetomidine (group BD). Motor and sensory block onset times; durations of blockades and analgesia were recorded.

Results: Sensory and motor block onset times were shorter by 20% in group BD than in group B ($P < 0.01$). Sensory and motor blockade durations were longer in group BD (+45% and +40%, respectively) than in group B ($P < 0.01$). Duration of analgesia was longer in group BD by 75% than in group B ($P < 0.01$). Systolic, diastolic arterial blood pressure levels, and heart rate were significantly less in group BD, six patients in group BD, and no patients in group B developed bradycardia ($P < 0.05$).

Conclusion: The addition of dexmedetomidine 100 μg to bupivacaine 0.5% during ultrasound-guided combined femoral and sciatic block for below knee surgery was associated with a prolonged duration of analgesia. However, this may be associated with significant bradycardia requiring treatment.

Key words: Analgesia; below knee surgery; combined femoral-sciatic nerve block; dexmedetomidine; ultrasound

Introduction

Below knee surgery often results in severe and long-lasting postoperative pain that requires large doses of opiates.[1] Few studies have evaluated peripheral nerve blocks for lower extremity surgery and compared them with spinal anesthesia.[2,3] These studies showed that combined sciatic-femoral nerve block for lower extremity surgery offers satisfactory anesthesia with a clinical profile similar to that of spinal anesthesia. However, the sciatic-femoral nerve blocks were associated with significantly lower pain scores during the early postoperative hours.[4]

Several perineural adjuvant medications were used to increase the duration postoperative analgesia including.

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However, only a few of these studies examined the effect following femoral-sciatic nerve block.[5-7]

Dexmedetomidine is a highly specific and selective α2-adrenoceptor agonist.[8] Systemic administration of dexmedetomidine has been the focus of interest for their sedative, analgesic, perioperative sympatholytic, and cardiovascular stabilizing effects with reduced anesthetic requirements.[9] Some recent investigations have studied the effects of mixing dexmedetomidine with local anesthetics during peripheral nerve and nerve plexus block in humans. All these studies have shown that the perineural dexmedetomidine as an adjuvant to local anesthetics for peripheral nerve blocks can prolong the duration of the blockade and postoperative analgesia.[10-12] To the best of the authors' knowledge, no previous study examined the effect of adding dexmedetomidine to bupivacaine 0.5% during femoral-sciatic nerve blocks.

We hypothesized that adding of dexmedetomidine 100 μg to bupivacaine 0.5%, would lengthen the time to the first request for postoperative analgesia, shorten sensory and motor block onset time, and increases the duration of sensory and motor blockade. This prospective, randomized, double-blind study aimed to investigate the effect of adding dexmedetomidine to bupivacaine 0.5% on the onset and duration of femoral-sciatic nerve block, as well as its effect in prolonging postoperative analgesia.

Materials and Methods

After obtaining the approval of the Ethical Committee and a written informed patients' consent, 60 patients with American Society of Anesthesiologists physical status I or III, who were scheduled for below knee surgery under combined femoral-sciatic block, were included in this prospective, randomized, controlled double-blind study.

Patients were excluded if they have significant cardiac, pulmonary, renal, hepatic, neurological, neuromuscular, or psychiatric disorders, coagulopathy. Pregnant women, patients with body mass index >35 kg/m^2, those receiving adrenoceptor agonists or antagonists, anticoagulants, antiplatelets other than acetylsalicylic acid, patients with a history of hypersensitivity to any of the study medications, and those who refused to participate in the study, were also excluded.

Standard anesthesia monitors including a three-lead electrocardiogram, pulse oximeter, and noninvasive blood pressure were attached, and baseline measurements were recorded. Supplemental oxygen was administered through a nasal cannula at a flow rate of 1-2 L/min. Intravenous (IV) access was achieved using 20 gauges cannula. Patients were given 1-2 mg of midazolam IV as a premedication 10-15 min before the start of the block in addition to 50 μg of fentanyl prior to block needle insertion.

Patients were randomly allocated using the closed envelope method into two groups (30 patients each): In group BD, bupivacaine-dexmedetomidine hydrochloride (Precedex®, Hospira, Lake Forest, IL, USA) one mL, containing100 μg, was added to 39 mL of bupivacaine 0.5%. In group B; 1 mL of normal saline was added to the same volume of bupivacaine 0.5%. In both groups, the 40 mL of the mixture was used for both femoral and sciatic block. The study solutions looked identically and were prepared by an anesthesiologist who did not participate in the study.

Patients were placed in the supine position, with the operative lower limb in the neutral position. After skin disinfection with povidone iodine and sterile drapes were applied. A lubricated high-frequency, 8-12 MHz, straight array ultrasound (US) probe covered with a sterile plastic sheath of Sonoscape A5 portable US machine (Guangdong, China) was placed perpendicular to the skin just beneath the inguinal crease to identify the femoral artery, using a two-dimensional ultrasonographic scanning. The femoral nerve was visualized as a hyperechoic structure, 1-2 cm lateral to the femoral artery. Infiltration with 3 mL of lidocaine 1% was performed at the needle insertion site. A short bevel 40 mm, 21 gauges insulated nerve block needle (Stimuplex A, B. Braun Melsungen AG, Germany), was inserted parallel and in line (in the plane) with the US transducer probe. The needle was advanced slowly until it approached the femoral nerve under the US guidance. After a negative aspiration of blood, 15 mL of the prepared study solutions were deposited around the femoral nerve according to group assignment by an anesthesiologist who was unaware of the nature of study drug solution. The satisfactory spread of the drug around the brachial plexus was observed sonologically in real time.

Patients were, then, positioned in the lateral decubitus, with the operative side uppermost with flexed hip and knee. The lateral prominence of the greater trochanter and the ischial tuberosity were identified with palpation, and a line was drawn between them. After skin disinfection with povidone iodine and sterile drapes were applied, a lubricated low-frequency, 5-2 MHz, curved array US probe covered with a sterile plastic sheath was used to scan the sciatic nerve at depth between 6 and 8 cm. The "subgluteal space" appeared as a hypoechoic line between the gluteus maximus and the

quadratus femoris muscles. At this level, the sciatic nerve was seen as a hyperechoic triangle with an approximate diameter of 1.5-2 cm within the subgluteal line. A short bevel 100 mm, 21 gauges insulated nerve block needle (Stimuplex A, B. Braun Melsungen AG, Germany) was inserted parallel and in line (in the plane) with the US transducer. The needle was advanced slowly until it became close to the sciatic nerve under the US guidance, after a negative aspiration of blood, 25 mL of the study solutions were deposited around the sciatic nerve in real time, according to the group assignment.

An independent third investigator who was not involved in patient's care collected outcome data. The primary outcome was the duration of postoperative analgesia. Secondary outcomes included; the onset and duration of both sensory and motor blockade, postoperative analgesic requirements, and evidence of any adverse drug reactions.

Sensory block was assessed by pinprick using a 23 gauge needle across the dermatomal areas innervated with the common peroneal and tibial nerves (namely; lateral aspect of the leg and plantar aspect of the foot) and femoral nerve (namely; anterior aspect of the thigh at the level of the patella and medial part of the leg for saphenous distribution). Sensory blockade was assessed using a 3-points numerical rating scale: 0 = sharp pin felt (normal sensation), 1 = dull sensation felt that is, loss of sensation to pinprick only (analgesia), 2 = no sensation felt that is, loss of sensation of pain and touch (anesthesia).

Motor blockade was assessed across the distributions of the common peroneal and tibial nerves through assessing the dorsiflexion and plantar flexion of the foot, respectively, against a manual resistance. The femoral nerve motor block was assessed by the ability to elevate the leg outside the bed or to extend the leg at the knee while the hip is semi-flexed. The degree of motor blockade was assessed using a 3-points numerical scale: 0 = normal motor function, 1 = reduced motor strength, but with reserved perceptible movement, 2 = complete motor block.

Sensory onset time was defined as the time interval between the end of study solution administration (T0) and a loss of sensation to pinprick (Grade 1) along the distribution of any of either femoral or sciatic nerves. Motor onset time was defined as the time interval between the T0 and a reduced motor strength (Grade 1) either at knee or ankle levels. Time to surgical anesthesia was defined was defined as the onset time for readiness for surgical procedures that represent by the time interval between the T0 and the complete sensory blockade at the distribution of both of sciatic and femoral nerves with inability to move the ankle and toes of the operated leg (Grade 2).

Patients who did not achieve a complete block through the two nerves, defined as Grade 2 sensory and motor blocks, within 30 min were excluded from the study.

Hemodynamics parameters including heart rate (HR), systolic arterial blood pressure (SAP), and diastolic arterial blood pressure (DAP) were recorded at 0 (baseline), 5, 10, 15, 30, 45, 60, 90, and 120 min after completion of the blockade.

Intraoperative complications including hypotension (defined as a 20% decrease below the baseline value), bradycardia (defined as HR lower than 50 bpm), hypoxemia (defined as peripheral oxygen saturation [SpO_2] <90%), or nausea and vomiting were recorded. Any side effects relate dexmedetomidine such as bradycardia, hypotension, hypertension, hypoglycemia or hyperglycemia were recorded. Furthermore, any evidence of clinical criteria suggesting local anesthetic toxicity (lightheadedness, dizziness, tinnitus, disorientation, drowsiness, generalized muscle twitching, and convulsions) was recorded.

Durations of sensory and motor blockades were defined as the time interval between the T0 and the complete resolution of either sensory or motor blockades (Grade 0) across the distribution of the two blocked nerves, respectively.

Postoperative analgesia was accomplished with 6 hourly interval IV paracetamol 1 g irrespective of pain status, starting after arrival to the ward. Rescue analgesia (tramadol 100 mg) was administered when patients report visual analog pain scales score ≥4. The time between the end of local anesthetic administration T0 and the first analgesic request was recorded as the duration of the analgesia. Furthermore, the total amount of tramadol consumed during the postoperative 24 h was recorded.

Statistical analysis

Power analysis was based on a pilot study of five patients in the control group that showed a main duration of analgesia of 420 min (±80). Twenty-seven patients were required in each group to detect 1 h difference in the duration of analgesia, with an alpha error of 0.05 and a power of 80%. To compensate for dropout cases and shifting from normality in data distribution, 30 patients were studied in each group.

Data were tested for normality using Kolmogorov-Smirnov test. Unpaired Student's *t*-test was used to compare the continuous data between the two groups. The chi-square

test was used for analysis of categorical data. Repeated measure analysis of variance was used for comparison of differences between the groups. Data were expressed as mean ± standard deviation or number (%). A $P \leq 0.05$ was considered to be statistically significant.

Results

All patients completed the study as shown in Table 1, there were no differences between the two study groups in patients' or surgical characteristics. Table 2 shows the block variables and postoperative analgesia. The onset of sensory and motor block and the time to surgical readiness were significantly shorter in group BD than in bupivacaine (group B). In addition, the durations of sensory and motor blockade were longer in group BD than in group B ($P < 0.01$). Similarly, the time to first analgesic request was 462.5 ± 54.3 in group B and 807.7 ± 112.9 in group BD ($P < 0.01$).

As shown in Figures 1 and 2, SAP and HR were significantly lower in group BD than those in group B from 10 to 90 min after the initiation of block ($P < 0.05$). DAP was similarly lower in group BD at 45, 60, and 90 min following initiation of block.

Bradycardia was observed in six patients in group BD and no patient in group B ($P = 0.02$). Bradycardia was treated with atropine and did not recur later. Hypotension occurred in two patients in group BD and no patients in group B ($P = 0.5$). Side-effects including nausea, vomiting, and hypoxemia were not reported in both groups. All patients recovered without evidence of sensory or motor deficit. No patient had hypertension, hypoglycemia or hyperglycemia.

Table 1: Demographic data and surgical characteristics

Variable	Group B ($n = 30$)	Group BD ($n = 30$)	*P*
Age (years)	37.3±10.39	39.57±10.64	0.62
Height (cm)	169±5.58	173±8.68	0.23
Weight (kg)	74.2±10.5	77.57±7.99	0.42
Gender (female/male)	12/18	9/21	0.41
Duration of surgery (min)	124±24.97	126.78±34.72	0.83
Type of surgery			
Orthopedic	18	20	0.592
Plastic	7	6	0.756
Vascular	5	4	0.999

Data are expressed as mean and SD (mean ± SD) or numbers; SD: Standard deviation

Discussion

This study examined the effect of adding dexmedetomidine 100 μg to bupivacaine 0.5% used for US-guided combined sciatic and femoral nerve block for below-knee surgery. The addition of dexmedetomidine enhanced postoperative analgesia through lengthening the time to the first analgesic request and reducing the postoperative analgesic consumption. It also resulted in the more rapid onset of motor and sensory block with increased duration of block.

This study has clinically importance that the addition of dexmedetomidine 100 μg to bupivacaine for combined sciatic-femoral nerve block during US-guided for below knee surgery was associated with +75% longer duration of analgesia, −20% shorter onset times for sensory and motor block, −25% faster time for surgical readiness, and longer duration of sensory and motor block (+45% and +40%, respectively) despite it would be more importantly to consider the cumulative tramadol consumption 24 h as a primary outcome. However, the reported statistical differences of 4 min in the onset time of sensory and motor blockades would not have medical importance, particularly the study was not deign to test the cost of healthcare like operating room stays.

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a highly specific and selective α2-adrenoceptor agonist. It has α2:α1 binding selectivity ratio of 1620:1 as compared to 220:1 for clonidine, thus decreasing the unwanted side effects of α1 receptors.[13] Presynaptic

Table 2: Characters of the block and postoperative analgesia in both groups

Variable	Group B ($n = 30$)	Group BD ($n = 30$)	*P*
Onset time of sensory block (min)	19.8±1.98	16.5±2.19	0.0011
Onset time of motor block (min)	24.3±2.49	20.14±2.64	0.0011
Surgical anesthesia time (min)	29.1±1.37	23.57±2.49	0.0000
Duration of sensory block (min)	412.5±54.26	594.67±104.69	0.0001
Duration of motor block (min)	247±39	335±38.54	0.0001
Duration of analgesia (min)	462.5±54.26	807.67±112.85	0.0001
Total analgesia requirements over 24 h	240±51.64	100±81.65	0.0002
Number of patients needed analgesia (%)	30 (100%)	19 (63%)	0.0002
Number of patients developed bradycardia (%)	0	6 (20%)	0.0048
Number of patients developed hypotension (%)	0	2 (6.6%)	0.1503

Data are expressed as mean and SD (mean±SD) or numbers; SD: Standard deviation

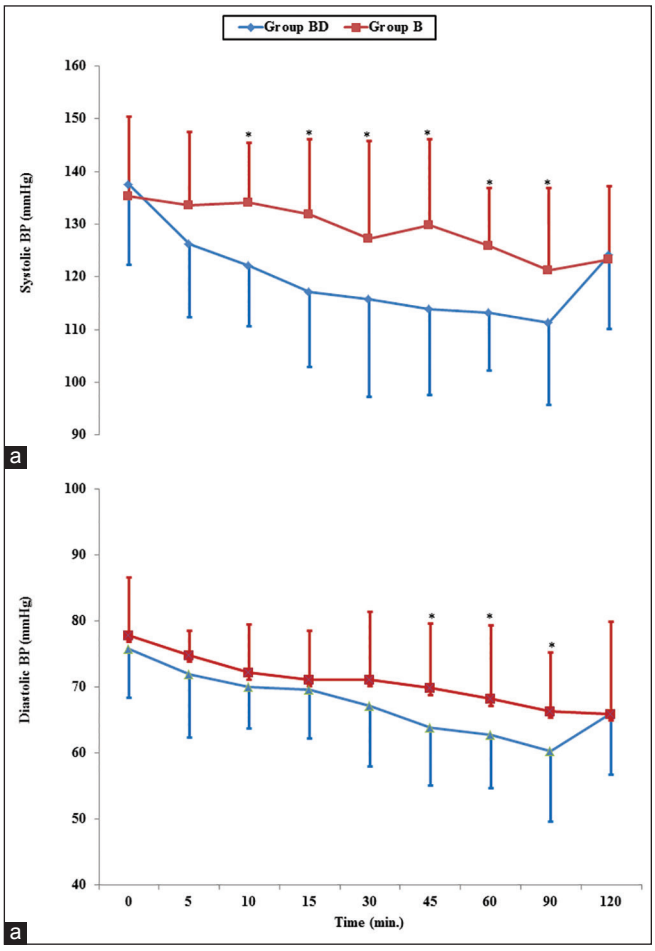

Figure 1: Systolic arterial pressure and diastolic arterial pressure changes in groups bupivacaine (B) and bupivacaine-dexmedetomidine (BD) at different observation times after initiation of the block (T0). *$P \leq 0.05$ significant difference between the two groups

activation of α2-adrenoceptor in central nervous system inhibits the release of norepinephrine through activation of locus coeruleus, which inhibits the propagation of pain.[14]

In various experimental studies, dexmedetomidine had been reported to enhance sensory and motor blockade along with increased duration of analgesia when it added to local anesthetics solution.[15,16] In addition, it has a dose-dependent increase in the duration of thermal antinociception and analgesia.[17] The beneficial effects of adding dexmedetomidine to local anesthetics for peripheral nerve block procedures have proved to be efficacious in humans.[10-12]

The peripheral effects of α2-adrenoceptor agonist appear to be less obvious because α2-adrenoceptors are not present on the axon of the normal peripheral nerve.[18] There have been four proposed mechanisms for the action of α2-adrenoceptor agonist in peripheral nerve blockades. These mechanisms are centrally mediated analgesia, α2B-adrenoceptor mediated

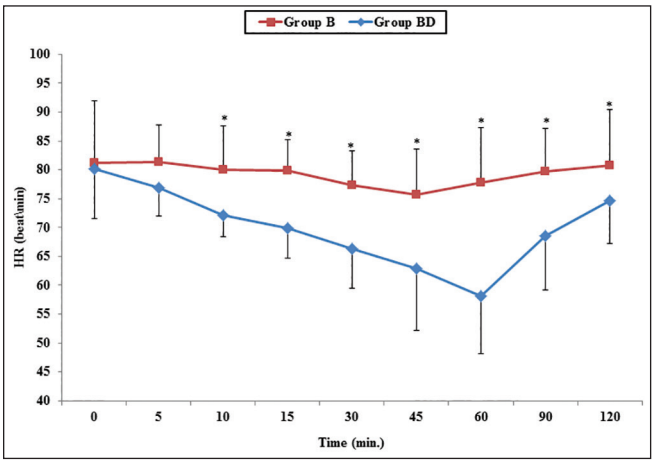

Figure 2: Heart rate changes in groups bupivacaine (B) and bupivacaine-dexmedetomidine (BD) at different observation times after initiation of the block (time 0). *$P \leq 0.05$ significant difference between the two groups

vasoconstrictive effects, attenuation of the inflammatory response, and direct action on a peripheral nerve. Central analgesia, vasoconstriction, and anti-inflammatory properties do not fully explain the efficacy of dexmedetomidine in peripheral nerve blockades.[19]

The direct action of α2-adrenoceptor agonists on the nerve can be explained on the basis of a study conducted by Dalle *et al*. on the C nerve fibers of rabbit nerves.[20] The authors concluded that α2-adrenoceptor agonist enhances activity-dependent hyperpolarization by inhibiting the hyperpolarization-activated cation (Ih) current. The Ih current plays a key role in cell excitability, especially the firing frequency, in both the central and peripheral nervous systems. The Ih current is activated during the hyperpolarization phase of an action potential and normally acts to reset a nerve for subsequent action potentials. Therefore, by blocking the Ih current, α2-adrenoceptor agonist enhances hyperpolarization and inhibits subsequent action potentials.

The analgesic effect of adding α2-adrenoceptor agonist to local anesthetics for combined sciatic-femoral nerve block remains unclear. Casati *et al*. reported that addition of 1 mg/kg clonidine to 0.75% ropivacaine had no effect on onset time and quality of combined sciatic-femoral nerve block, but prolonged nerve block duration, providing a 3 h prolongation in postoperative pain relief, and no hemodynamic side effects.[5] On the other hand, Helayel *et al*. did not find an advantage in the quality and the duration of block in their sciatic block that was formed with the addition of 2 g/kg clonidine to 0.5% 40 mL ropivacaine.[6]

Dexmedetomidine may lead to side effects such as a hypertension, hypotension, bradycardia, and hyperglycemia.

No patient had hypertension, hypoglycemia or hyperglycemia. Unfortunately, the present study found that the addition of 100 μg dexmedetomidine to bupivacaine during combined femoral-sciatic nerve block for below knee surgery was associated with bradycardia and hypotension (20% and 6.7%, respectively). Similarly to the present study, Esmaoglu *et al*. reported bradycardia in 23.5%.[21] Hyperglycemia was not recorded, interestingly the dexmedetomidine group showed lower serum glucose levels.

The decrease in pulse rate and blood pressure might be related to the postsynaptic activation of central α2-adrenoceptors, leading to decreased sympathetic activity that decrease the blood pressure and slower HR.[22] Baroreceptor reflex is well preserved with the use of dexmedetomidine. Thus, bradycardia is easily treatable conferring hemodynamic stability.[23]

This study has some limitations. First, the beneficial effects of dexmedetomidine may be explained by systemic absorption rather than the peripheral effect on the nerve itself. The recruitment of a control group, for which the same dose of dexmedetomidine is administered systemically, would help to differentiate between systemic and local mechanisms of action. Second, in similar to others,[21] we have considered using of 100 μg of dexmedetomidine, despite the effective dose of perineural dexmedetomidine has not been identified yet. Further studies are required to determine the optimum dose of dexmedetomidine needed to enhance the action of local anesthetic without producing side-effects. Third, it would be better to indicate the dose of dexmedetomidine on patient body weight rather than a fixed dose to avoid the heterogeneity that can be raised from dividing the dose between the femoral and sciatic nerve (37.5%: 62.5%). In addition, the present study was not designed to test the onset of sensory and motor blockades individually.

Conclusion

The addition of dexmedetomidine 100 μg to bupivacaine 0.5% during US-guided combined femoral and sciatic block for below knee surgery was associated with a prolonged duration of analgesia. However, this may be associated with significant bradycardia requiring treatment.

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Conflict of interest

There are no conflicts of interest.

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