The effects of different dose levels of peri-neural dexmedetomidine on the pharmacodynamic and side effect profiles of bupivacaine-induced ultrasound-guided femoral nerve block

A Thesis Submitted For Partial Fulfillment Of The MD Degree In Anesthesiology, Surgical Intensive Care Medicine &Pain Management.

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2015

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Acknowledgement

All praise be to **Allah** and all thanks. He has guided and enabled me by **His mercy** to fulfill this thesis, which I hope to be beneficial for people.

I greatly appreciate the meticulous efforts, enthusiasm, and continuous guidance of **Prof. Dr. Mohamed Abdulatif**, for his patience, motivation, and immense knowledge.He was the person who initiated the idea and supervised closely its progress with great interest.

I would also like to express my sincere appreciation to **Prof. Dr. Maher Fawzy** for his valuable assistance and continuous guidance for completion of this work.

My deep gratitude goes to **Dr. Heba Nassar** and **Dr. Ahmed Hasanin** for their major contributions to improve my clinical and scientific writing skills.

Special thanks and appreciation to **Dr. Ahmed Hasanin**who freely gave his time, effort and experience along with continuous guidance throughout this work.

All the love and appreciation to all my **Family** members especially my dear **Father** and my **Wife** who were always supporting and encouraging me.

Dedication

This work is dedicated to the soul of my mother, who stood beside me through my entire life, gave me all the support and taught me honesty and sincerity.

To my wife and my daughter for whom I live.

List of abbreviations

DEX	Dexmedetomidine
ECG	Electrocardiogram
FDA	Food and Drug Administration
Hz	Hertz
IASP	International Association for the Study of Pain
ICU	Intensive Care Unit
IV	Intravenous
NRS	Numeric Rating Scale
PACU	Post Anesthesia Care Unit
RASS	Richmond Agitation-Sedation Score
PZT	Lead ZirconateTitanate
SD	Standard Deviation
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

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Abstract

Rationale and background:

Peri-neural administration of alpha-2 adrenoceptor agonists including dexmedetomidine extends the duration of local anesthetic-induced peripheral nerve blocks in the experimental and the clinical settings. This study was designed to explore and compare the possible effects of different dose levels of peri-neural dexmedetomidine on the clinical and side effect profiles of bupivacaine-induced femoral nerve block in patients undergoing arthroscopic knee surgery under general anesthesia.

Patients and methods:

This randomized, controlled double blinded study included 60 adult patients undergoing arthroscopic knee surgery. Ultrasound-guided femoral nerve block was initiated 30 min before induction of general anesthesia. Femoral nerve block was achieved with the use of 25 ml of bupivacaine 0.5% in all patients. Bupivacaine was combined with 1 ml normal saline (control group, n=15), 25, 50 or 75 μg (1 ml) peri-neural dexmedetomidine groups (n= 15, each). All patients received a standard general anesthetic after ensuring successful femoral nerve block. The onset and duration of sensory and motor blocks, the time to first request to postoperative rescue analgesic, Richmond Agitation-Sedation Score, perioperative hemodynamic data, resting and dynamic visual analogue pain scores, were reported at predetermined time assessment points. Total postoperative rescue intravenous morphine consumption was recorded over 24 hours.

Results:

The onset of sensory block was significantly shorter and its duration was extended with the use of 75 μg peri-neural dexmedetomidine compared to the control, 25 and 50 μg peri-neural dexmedetomidine groups. The durations of sensory block were (43.7±4.3 h, 21.6±3.0 h, 23.3±1.8 h and 30.8±3.6 h respectively). The onset of motor block was significantly shorter

with the use of 75 μg peri-neural dexmedetomidine compared to the control and 25 μg peri-neural dexmedetomidine groups. The duration of motor block was significantly longer in the 75 μg peri-neural dexmedetomidine group compared to the control and other two peri-neural dexmedetomidine groups. Time to first request to postoperative rescue analgesic was significantly longer in the 75 μg peri-neural dexmedetomidine compared to the control, 25 and 50 μg peri-neural dexmedetomidine groups (28.6±10.0 h, 10.8±1.6 h, 11.0±7.1 h and 21.8±3.0 h respectively). The total postoperative morphine consumption was significantly reduced in the 75 μg peri-neural dexmedetomidine group compared to the control and 25 μg group (1.8±2.6 mg, 7.6±5.1 mg and 6.5±3.5 mg respectively). Postoperative sedation was comparable in the four study groups. Statistically significant reductions in systolic blood pressure and heart rate were observed up to 30 minutes after induction of general anesthesia in all groups compared to the baseline values. However, there were no statistically significant differences in the haemodynamic variables among the four study groups.

Conclusion:

The use of peri-neural dexmedetomidine as an adjuvant to bupivacaine reduces the onset and prolongs the duration of ultrasound-guided femoral nerve block and extends the duration of analgesia in patients undergoing arthroscopic ACL surgery in a dose dependent manner. Although the best analgesic profile is achieved with the 75μg dose level, this dose should be cautiously used due to the risk of hypotension.

Kewords:(ACL- dexmedetomidine - pharmacodynamic – bupivacaine)

Anatomy of the femoral nerve and Innervation of the knee joint

The femoral nerve is the largest branch of the lumbar plexus. It arises from the second, third, and fourth lumbar nerves [(1)].

Course:

The nerve descends through the fibers of the psoas muscle, emerging from the psoas at the lower part of its border, and passes down between the psoas and the iliacus. Eventually, the femoral nerve passes underneath the inguinal ligament into the thigh, where it assumes a more flattened shape. As the femoral nerve passes underneath the inguinal ligament, it is positioned immediately lateral and slightly deeper to the femoral artery (Figure 1) [(2)]. At the femoral crease the nerve is covered by the fascia iliaca and is separated from the femoral artery and vein by a portion of the psoas muscle and the ligamentum ileopectineum. This physical separation of the femoral nerve from the vascular fascia explains the lack of the spread of a "blind paravascular" injection of local anesthetics toward the femoral nerve [(1)].

Figure 1: Anatomical relations of the femoral nerve [(2)]
FN: Femoral nerve FA: Femoral artery FV: Femoral vein

Motor branches

1) Anterior division branches:
    - Sartorius
    - Pectineus
2) Posterior division branches:
    - Rectus femoris
    - Vastus medialis
    - Vastus lateralis
    - Vastus intermedius [3].

Sensory branches

1) Anterior division branches:
    - Provides sensation to antero-medial aspect of the thigh, consists of 2 branches
        - Medial cutaneous nerve of thigh.
        - Intermediate cutaneous nerve.
2) Posterior division:
    - Saphenous nerve provides sensation to anteromedial aspect of lower leg.
    - Infra-patellar branches to the knee pierces the sartorius muscle and fascia lata medial to the knee, and provides cutaneous innervation to the skin anteriorly over the patella [3].

Sono-anatomy of the femoral nerve

Distal to the inguinal ligament, the femoral nerve lies lateral to the femoral artery, deep to the fascia iliaca, on the anterior aspect of the iliopsoas muscle (Figure 2**)** [4]. It is often found within a triangular hyperechoic region. The nerve may also appear as a

biconvex or oval hyperechoic structure [5,6]. The artery is easily located due to its pulsation and/or flow by Doppler (Figure 3) [4].

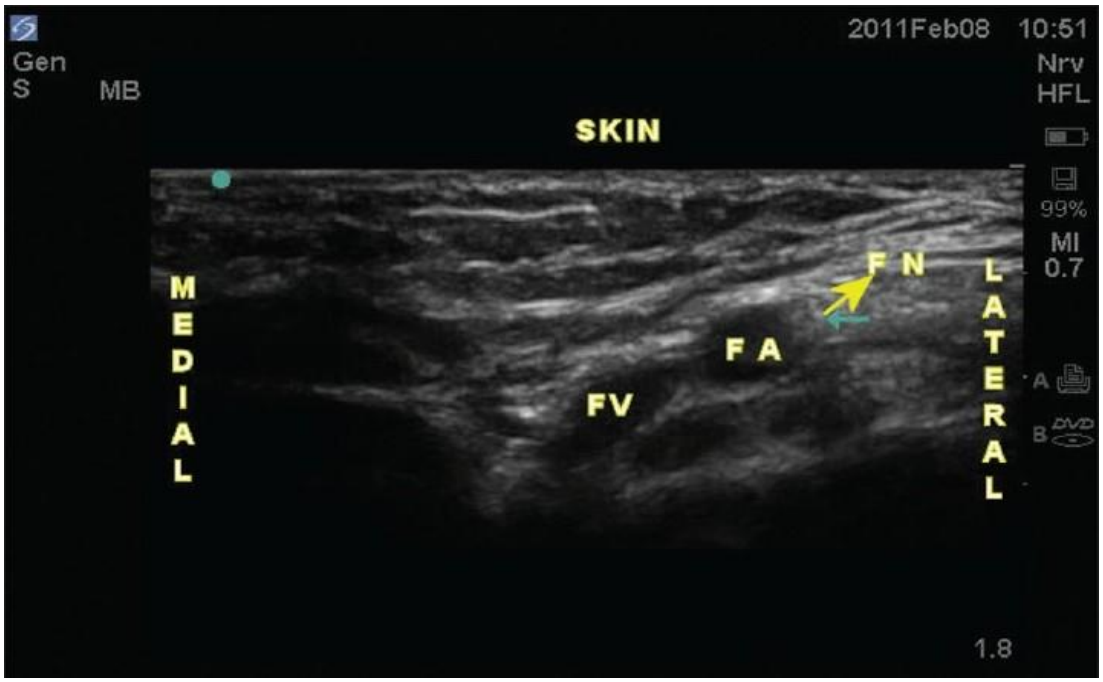

Figure 2: Ultrasound scan of the left femoral nerve (short axis) at the level of inguinal crease (lateral to femoral artery, deep to fascia lata, superficial to iliopsoas muscle). [4] FN: Femoral nerve FA: Femoral artery FV: Femoral vein

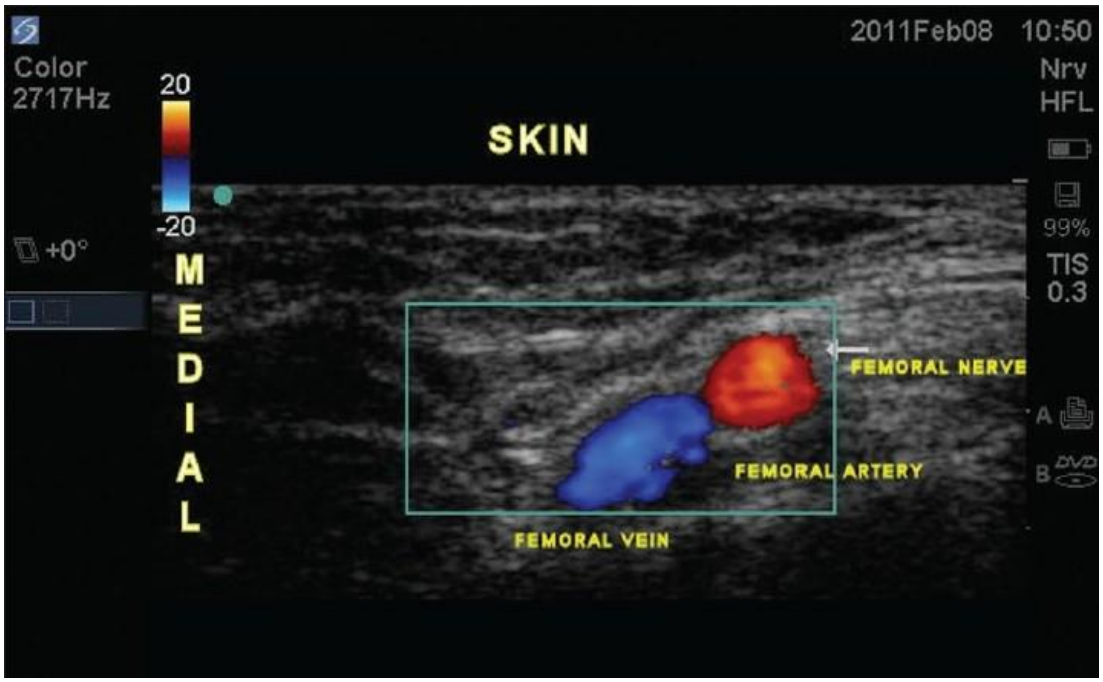

Figure 3: Identification of the femoral artery by Doppler flow. [4]

Innervation of the knee Joint

(I) **Femoral nerve** via the branch to vastus medialis (anterior aspect of the joint capsule).

(II) **Sciatic nerve** via genicular branches of both tibial and common peroneal components (posterior aspect of the joint capsule and all of the intra-articular structures).

(III) **Obturator nerve** by a branch from its posterior division that accompanies the femoral artery through adductor magnus into the popliteal fossa [(7)].

Cutaneous innervation of the anterior aspect of the knee is supplied by the femoral nerve. The obturator nerve supplies the skin on the medial aspect of the knee in less than 40% of people [(7)].

Pharmacology of dexmedetomidine

Alpha 2-adrenoceptor agonists are being increasingly used in anesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery; but also cause sedation and analgesia. They are also used as an adjuvant during regional anesthesia. Dexmedetomidine is the most recent agent in this group approved by the FDA in 1999 for sedation and analgesia in humans [(8)].

Alpha-2 receptors:

Found in the peripheral and central nervous systems, platelets, and many other organs including the liver, pancreas, kidney, and eye [(9)]. Stimulation of Alpha-2 receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation and analgesia. The responses from other organs include: decreased salivation, decreased secretion, decreased bowel motility, inhibition of renin release, increased glomerular filtration, increased secretion of sodium and water in the kidney, decreased intraocular pressure and decreased insulin release from the pancreas [(9)].

Mechanism of action:

Dexmedetomidine has selective alpha 2-adrenoceptor agonist effect especially for the 2A subtype of this receptor. Dexmedetomidine is much more effective sedative and analgesic agent than clonidine [(8)].

Pharmacokinetics:

Dexmedetomidine undergoes almost complete hydroxylation through direct glucuronidation and cytochrome P450 metabolism in the liver. Metabolites are

excreted in the urine (about 95%) and in the feces (4%). It is unknown whether they possess intrinsic activity. The elimination half-life is approximately 2 hours. It may be necessary to decrease the dose in patients with hepatic failure, since they will have lower rates of metabolism of the active drug. Dexmedetomidine metabolites might accumulate in patients with renal failure with unknown consequences [8]. The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl, ketorolac, theophylline, digoxin and lidocaine [8].

Pharmacodynamics:

The majority of patients receiving dexmedetomidine are effectively sedated yet easily arousable, a unique feature not observed with other sedatives [10].

Dexmedetomidine does not appear to have any direct effects on the heart [11]. A biphasic cardiovascular response has been described after the loading dose [8,12,13]. The bolus of 1 μg/kg dexmedetomidine initially results in a transient increase of the blood pressure and a reflex fall in heart rate, especially in younger patients [14]. Stimulation of alpha B-2-adrenoceptor in vascular smooth muscle seems to be responsible for the initial rise in the blood pressure, which can be attenuated by a slow infusion [15]. However, even at slower infusion rates, the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7%, with a decrease in heart rate between 16% and 18% [14]. The initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of the central sympathetic outflow [15]. The pre-synaptic alpha 2-adrenoceptors are also stimulated decreasing the norepinephrine release resulting in fall in blood pressure and heart rate [13]. These effects may also be observed in the postoperative period, and can be easily