Original Article

Perineural vs. intravenous dexmedetomidine as an adjunct to bupivacaine in ultrasound guided fascia iliaca compartment block for femur surgeries: A randomised control trial

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ABSTRACT

Background and Aims: Perineural and intravenous dexmedetomidine as a local anaesthetic adjunct has not been compared previously in fascia iliaca compartment block (FICB). The aim of this study was to compare the efficacy and side effect profile of dexmedetomidine as an adjunct to bupivacaine in single dose FICB for femur surgeries in two different routes i.e., perineural and intravenous route. **Methods:** Eighty American Society of Anesthesiologists physical status 1, 2 or 3 patients posted for femur surgeries were randomised to receive ultrasound guided FICB. Intravenous group(ID) received 40 mL of 0.25% bupivacaine with 2 mL of 0.9% saline for FICB along with 1 μg/kg dexmedetomidine intravenous infusion over 30 min as loading dose followed by 0.5 μg/kg/h as maintenance dose till the end of surgery. Perineural group (LD) received 40 mL of 0.25% bupivacaine with 2 mL of 1 μg/kg dexmedetomidine for FICB. M ean duration of postoperative analgesia and 24 h postoperative morphine consumption as primary and secondary outcome respectively, has been compared. **Results:** The duration of postoperative analgesia was 8 h 36 min ± 1 h 36 min and 10 h 42 min ± 1 h 36 min for the ID and LD groups, respectively (P = 0.001). A 24 h postoperative morphine consumption in Group ID was 19.7 ± 1.9 mg compared to 17.5 ± 2.2 mg in LD groups (P = 0.001). **Conclusion:** Perineural dexmedetomidine effectively prolongs the USG guided FICB analgesic duration and reduces the 24 h postoperative morphine consumption when compared to intravenous dexmedetomidine as a local anaesthetic adjuvant for femur surgeries.

Key words: Facia iliaca compartment block, intravenous dexmedetomidine, local anaesthetic adjuvant, perineural dexmeditomidine, sensory block

INTRODUCTION

Single injection fascia iliaca compartment block (FICB) along with general anaesthesia (GA) has shown promising results in both elective and emergency femur surgeries.[1] It reduces the surgical stress response by blunting the afferent nerve impulse carrying pain sensation and providing effective perioperative analgesia. This superiority of peripheral nerve block for the purpose of perioperative analgesia over intravenous (IV) analgesics has been proven well in terms of lesser perioperative opioid consumption, minimal requirement for inhalation anaesthetic agent, better intraoperative haemodynamic profile and faster recovery from GA.[2-5] However, single injection nerve blocks are limited by the duration of sensory blockade

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necessitating the use of local anaesthetic (LA) adjuvants.

Dexmedetomidine, an alpha 2 agonist, is used as a local anaesthetic adjuvant in both peripheral nerve blocks and neuraxial anaesthesia. Perineural dexmedetomidine when given with LAs for peripheral nerve block has shown to have prolonged duration of postoperative analgesia with other beneficial effects such as reducing the opioid consumption.[6] However, dexmedetomidine's effect as an adjuvant on prolonging the duration of action of LA when used through IV route is still in debate.[7-10] In addition, the efficacy of intravenous route when compared with perineural route is unknown. Hence, this study was conducted with the aim of comparing the clinical pharmacology in terms of efficacy and side effect profile of dexmedetomidine as an adjunct to bupivacaine in ultrasound guided single injection FICB for femur surgeries when used through two different routes.

METHODS

The scientific approval for the conduct of the study was obtained on 26th August 2014 from the Institute Post Graduate Research Monitoring Committee (PGRMC) with a Reg. No. of the proposal: PGRMC/ANAES/08/2014. The ethical approval for the study was obtained from Institute Ethics Committee (Human studies) with Reg. No. of ECR/342/Inst/PY/2013 on 6th January 2015. Written informed consent was obtained from all the study participants before enrolment into the study.

The trial was registered in clinical trial registry of India. The registration number is as follows: CTRI/2016/03/006757.

This study is a prospective double blinded randomised control trial with two groups. The duration of the study was 16 months. The enrolment for the study began in March 2015, and the last study participant was enrolled in May 2016.

A total of 102 patients were assessed for eligibility; of those 22 were excluded (18 patients did not meet inclusion criteria, 2 patients declined to participate in the study and 2 patients had their surgery postponed). The CONSORT flow diagram [Figure 1] showing patient progress through various study phases has been depicted in figure. A total of 80 patients were randomised. Of whom only 78 patients underwent the trial and had their data analysed.

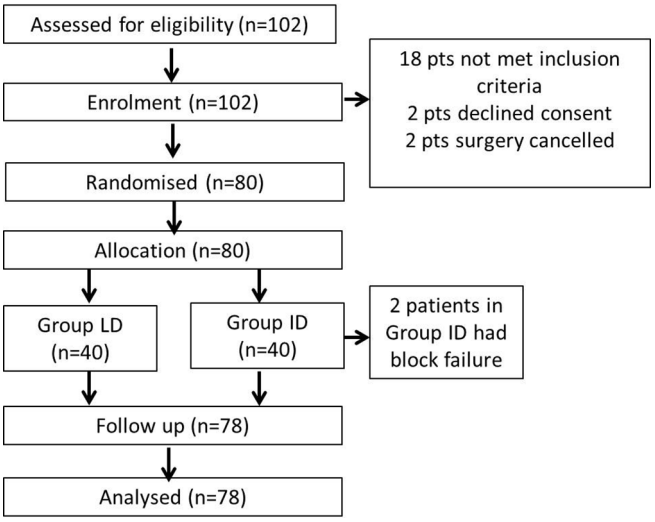

Figure 1: CONSORT diagram

Adult patients aged between 18 to 75 year with American society of Anesthesiologists' physical status grade (ASA) I to III scheduled for elective and emergency femur surgeries using standardised GA and postoperative analgesic regimens were recruited to participate in this prospective double blinded randomised controlled trial. Informed written consent was taken from all recruited patients. Eligible surgical procedures included femur interlocking nailing, cancellous screw fixation, and plating. Both the elective and emergency surgical patients who met inclusion criteria were interviewed, and they were provided with an information leaflet describing the study procedure. Exclusion criteria included patients with coagulation disorders, infection over injection site, post femoral bypass surgery and patients who are allergic to LAs and haemodynamic instability. Sampling techniques used in this study: Convenient sampling.

Consented study participants were randomised by using a computer generated random numbers in varying block sizes on a 1:1 ratio. Randomisation was performed using random allocation software 2.0. Allocation results were sealed in opaque envelopes. The research coordinator would hand over one envelope per patient to the anaesthesia care provider who performed the blockade in operation room. The research coordinator collecting the outcome measures were blinded to the allocation results. Study participants received the intervention according to their allocation group as follows: Group ID received 2 mL of 0.9% saline with 40 mL of 0.25% bupivacaine in FIC and 1 μg/kg IV dexmedetomidine loading dose over 30 min followed by 0.5 μg/kg/h maintenance dose

till the end of surgery. Group LD received perineural dexmedetomidine of 1μg/kg diluted to 2 mL with 0.9% saline added to 40 mL of 0.25% bupivacaine. Normal saline 0.9% infusion started at a fixed rate for loading and maintenance dose similar to Group ID for the purpose of blinding and continued till the end of the surgery.

All patients were explained about numerical rating scale (NRS) and how to operate patient controlled analgesia device. They were premedicated with oral famotidine 20 mg, metoclopramide 10 mg, diazepam 5 mg an hour before the surgical procedure. All ASA standards monitors i.e., non-invasive blood pressure, pulse oximeter, 5 lead electrocardiogram were applied and IV access secured. All patients received 100 μg/kg morphine intravenously before the block to prevent intubation response to tracheal intubation.

NRS score at rest and at movements were noted. Ultrasound guided (USG) FICB was performed under aseptic precautions by a trained anaesthesia care provider with adequate experience of USG guided FICBs. Under aseptic precautions and after skin infiltration given with 2 mL of 2% lignocaine, a high frequency linear array transducer with frequency ranging from 15 to 16 MHz Sonosite™ probe protected by a sterile drape was placed in parallel to the inguinal crease to visualise the femoral vein, artery and nerve in that order. Fascia iliaca was then identified as a thick hyperechoic structure just above the femoral nerve. This is confirmed by moving the probe laterally to trace the fascia till anterior superior iliac spine. From above downward the sonoanatomy is as follows: Skin, subcutaneous tissue, fascia lata, sartorius muscle, fascia iliaca and iliacus muscle. An 8 cm 18-gauge Tuohy needle was then inserted in plane with ultrasound probe at a point 1 cm below the point of junction of lateral 1/3 and medial 2/3 approach far away lateral from all vital structures. After confirmation of negative aspiration for blood, 42 mL of study solution was administered with visual confirmation of the spread of the drug in fascia iliaca compartment.

All study participants were assessed for sensory blockade in the corresponding dermatome which belongs to femoral and lateral femoral cutaneous nerve of thigh. This was assessed by loss of sensation to standard pinprick at 5 min and then every minute till 20 min. Block success was defined as complete loss of sensation to pin prick in anterolateral and medial aspect of the thigh. After sensory assessment, all patients were given GA using standard hospital protocol and monitored with ASA monitoring. GA was administered using 5 mg/kg Sodium thiopentone and 0.5 mg/kg atracurium intravenously (IV) followed by tracheal intubation using appropriate size endotracheal tube. GA was maintained with sevoflurane, oxygen and nitrous oxide 1:1 mixture titrated to a MAC level of 0.8 to 1. All patients were ventilated with a tidal volume of 6 mL/kg at rate titrated to $EtCO_2$ between 30 to 40 mm Hg.

During skin incision, heart rate and blood pressure were noted. Throughout the surgical procedure, heart rate, systolic and diastolic blood pressure was recorded every 15 min. Intravenous morphine bolus of 0.05 mg/kg as supplementary medication was given when the heart rate and blood pressure crossed 20% above the baseline value.

At the end of surgery, patients were extubated after reversal of neuromuscular blockade using neostigmine 50 μg/kg IV and glycopyrrolate 10 μg/kg IV. During this time Ramsay sedation score (RSS) was assessed for sedation at the time of extubation from 1 to 6.

Post extubation, all patients were shifted to post anaesthesia care unit. NRS score at this time was noted for assessment of pain. Standard monitoring was applied which included non-invasive blood pressure, electrocardiogram, pulse oximeter and intravenous patient controlled analgesia (PCA) was commenced as soon as the patient responded meaningfully to verbal commands. It was commenced with morphine of 1 mg bolus with lockout time interval of 10 min with 4 h limit of 6 mg without baseline infusion. This was continued for 24 h post operatively. Throughout these 24 h, heart rate and blood pressure were recorded every 15 m for first 2 h and then hourly interval. NRS was recorded every 4th hour starting from 1st hour of postoperative period both at rest and movement of operated limb sideways not against gravity. Nausea and vomiting were recorded using categorical scoring system from 0 to 1, 0 meaning none, 1 meaning nausea and vomiting. Intravenous metoclopramide of 10 mg bolus was offered once the score reached 1.

Time to first analgesic request was defined as time taken by the patient to activate first demand dose of PCA morphine from the time of extubation. This time period is taken as the duration of postoperative analgesia offered by the FICB. Number of used PCA

boluses of morphine at 0 to 4 h, 4 to 8 h, 8 to 12 h, 12 to 16 h, 16 to 20 h and 20 to 24 h was noted and the total consumption of morphine in 24 h was calculated. Intravenous paracetamol of 1 g as rescue medication over 5 min was given to ensure NRS below 4 at movement. Data were collected using data collection proforma during intraoperative and post-operative period.

The sample size was calculated using Open Epi software to estimate the difference in the duration of analgesia between two groups. Assuming 95% confidence interval and 80% power, the mean duration of analgesia in group intravenous dexmedetomidine (IVD) is 222.8 ± 123.4 min and in group saline is 138.4 ± 21.62 min.[9] Expecting a 10% failure rate in the FICB, sample size were estimated to be 40 in each of the groups.

The primary outcome was the duration of analgesia which is defined as the time taken for the first analgesic requirement in the post-operative period. Secondary outcomes were cumulative 24 h postoperative total morphine consumption, intraoperative supplementary morphine used, intraoperative haemodynamic changes in terms of heart rate and systolic blood pressure at baseline, surgical incision, at 1st, 2nd, 3rd, 4th and 5th hour and at the end of surgery, RSS at the time of extubation, postoperative NRS score (0 meaning no pain to 10 meaning severe pain experienced in their life time) at rest and at movement at 1, 4, 8, 12, 16, 20, 24 h in the post-operative period, incidence of side effects such as nausea, vomiting and desaturation and proportion of patients requiring paracetamol as rescue analgesic.

The SPSS for windows statistical package (version 20, IBM, USA) was used for calculations. We performed our analysis under the assumptions that the two groups are independent, the source population of our data is normally distributed and variances within each group are equal.

We presented our continuous data such as age, height, weight of the patients, intraoperative and 24 h postoperative morphine consumption, intraoperative parameters as mean ± SD; non-parametric data such as NRS at rest and movement was presented as mean ranks, and categorical data such as gender, ASA classification, RSS, incidence of side effects and requirement of rescue paracetamol as numbers and percentages. Independent *t* test, repeated measures ANOVA were used in analysing the continuous data. The Chi-square or Fisher exact test was used in analysing the categorical data. Mann-Whitney U test was used in analysing non-parametric data. Friedman test was used in analysing non-parametric variables that appeared at repeated intervals. To reject the null hypothesis, *P* value of less than 0.05 was considered as significant.

RESULTS

Patient demographic characteristics such as age, height, weight and duration of surgery showed no statistical difference between the groups [Table 1]. Other demographic characters such as gender and ASA classification showed no statistical difference between the groups, $P = 0.648$ and $P = 0.822$ respectively.

The duration of postoperative analgesia was 8.6 ± 1.6 h and 10.7 ± 1.6 h for the ID and LD groups, respectively ($P = 0.001$). A 24 h postoperative morphine consumption in Group ID was 19.7 ± 1.9mg compared to 17.5 ± 2.2 mg in LD groups ($P = 0.001$). There was no statistically significant difference in the supplementary intraoperative morphine consumption for Group ID (4.32 ± 3.6 mg) and Group LD (3.28 ± 2.7 mg), $P = 0.160$ [Table 2].

There was no statistical significance between the effect of perineural dexmedetomidine and intravenous dexmedetomidine on heart rate and SBP between the groups at different time intervals, i.e., at surgical incision, 1st, 2nd, 3rd, 4th, 5th hour and at the end of the surgery, $P = 0.325$ and $P = 0.243$, respectively.

Table 1: Demographic parameters

Parameters	Mean±SD		*P*
	ID (*n*=38)	LD (*n*=40)	
Age (yrs)	47.11±17.56	50.68±21.66	0.203
Height (cm)	156.47±8.65	159.40±10.35	0.277
Weight (kg)	59±6.37	59.05±6.78	0.705
Duration of surgery (H)	6.26±0.92	6.3±1.17	0.409

Table 2: Duration of postoperative analgesia, intraoperative supplementary morphine and 24 h postoperative morphine consumption

Outcome	Mean±SD		*P*
	ID (*n*=38)	LD (*n*=40)	
Postoperative analgesia (H)	8.6±1.6	10.7±1.6	0.001
24 h Postoperative morphine (mg)	19.7±1.9	17.5±2.2	0.001
Intraoperative supplementary morphine (mg)	4.32±3.6	3.28±2.77	0.160

Patients in Group LD had RSS of 2 (50%) and RSS of 3 (37.5%) when compared to Group ID had RSS of 2 (21.1%) and RSS of 3 (26.3%). Similarly, patients in Group LD had RSS of 4 (2.5%) and RSS of 5 (10%) when compared to Group ID had RSS 4 (31.6%) and RSS of 5 (21.1%) which is statistically significant ($P = 0.001$).

NRS at rest and movement showed statistically significant difference within groups during the post-operative period. However, it was found that the NRS at rest especially at 12, 16, 20, 24 h following surgery were significantly less ($P < 0.05$) for Group LD than for Group ID [Figure 2]. The NRS at movement especially at 4, 8, 12, 16, 20, 24 h were significantly less ($P < 0.05$) for Group LD than for Group ID [Figure 3]. A 24 h cumulative postoperative morphine consumption has been shown in Figure 4.

It was found that proportion of patients who had nausea and vomiting as a side effect of morphine ($P = 0.483$) and rescue paracetamol used ($P = 0.483$) during post-operative period in the first 24 h were similar between the Groups LD and ID.

DISCUSSION

This study demonstrates that dexmedetomidine when applied perineurally is an effective LA adjuvant with the ability to prolong the duration of FICB analgesia by 2 h 6 min and to reduce the total cumulative postoperative analgesic consumption at 24 h following surgery by 2.2 mg when compared to intravenous dexmedetomidine as an adjuvant to bupivacaine in FICB for femur surgeries.

Our study demonstrates perineural dexmedetomidine favours better emergence from GA in terms of desirable RSS when compared to the intravenous dexmedetomidine group.

Previous studies which tried to find the efficacy of perineural and intravenous dexmedetomidine as a LA adjuvant have shown varying results. Marhofer D *et al.*[11] conducted a prospective observational study in healthy volunteers. They examined the effect of low dose (20 μg) perineural and intravenous dexmedetomidine on the duration of sensory blockade after ulnar nerve block. The duration of sensory blockade was higher (555 ± 118 vs 395 ± 40 min) in perineural dexmedetomidine group when compared to systemic dexmedetomidine. Although the results were similar to our study, this study was done on ulnar nerve in healthy volunteers who did not undergo any surgery, and therefore, this finding cannot be readily generalised to duration of analgesia following FICB neither to any routine regional anaesthesia practice for surgical procedures.

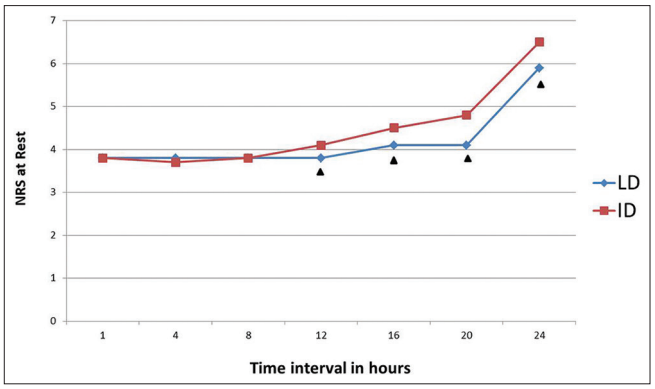

Figure 2: Postoperative NRS at rest for the first 24 h

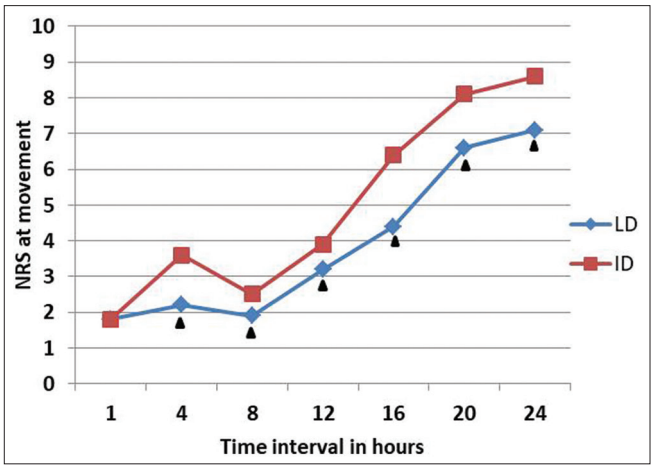

Figure 3: Postoperative NRS at movement for the first 24 h

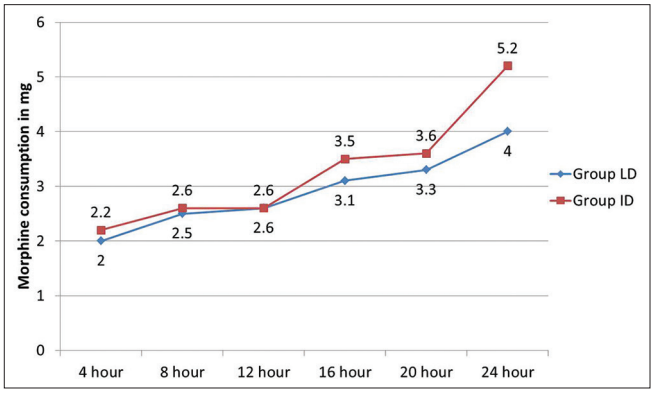

Figure 4: Cumulative 24 h morphine consumption

Abdallah FW *et al.*[12] had conducted a similar study in individuals undergoing upper limb orthopaedic procedures. Patients received interscalene brachial plexus blockade using either ropivacaine alone or

with ropivacaine-perineural dexmedetomidine or ropivacaine-intravenous dexmedetomidine. They used a dose of 0.5 μg/kg for both perineural as well as systemic dexmedetomidine as an adjuvant to 15 mL of 0.5% ropivacaine. This study showed results such that there are no differences in analgesic duration and total cumulative 24 h analgesic consumption between the perineural and systemic dexmedetomidine group. This is in contrast to our results that our study showed a statistically significant difference between the perineural dexmedetomidine and systemic dexmedetomidine as a LA adjuvant for peripheral nerve block. This gross difference in the findings may be owing to higher dose of perineural as well as intravenous dexmedetomidine used in our study. Therefore, the dose related prolongation of LA action warrants further evaluation.

The mechanism of action of dexmedetomidine as adjuvant to peripheral nerve block is unknown. Proposed mechanisms for perineural action include the drug's direct action over peripheral nerve, absorption into systemic circulation causing central effect, alpha 2a receptor mediated vasoconstriction and attenuation of inflammatory response.[6,13,14] Similarly, intravenous dexmedetomidine prolongs the LA duration through supraspinal analgesic effects by inhibition of norepinephrine release and its associated activity in descending medullo spinal norepinephrine pathway terminating the propagation of pain signal resulting in reduced awareness to pain signal. In addition, it suppresses neuronal firing in locus ceruleus leading to decreased histamine release leading to sedation. At spinal level, it acts by inhibition of glutamate and substance P. It also causes activation of potassium channels causing hyperpolarisation of interneurons.[6] The stress response caused by surgery is attenuated by post synaptic activation of alpha 2 receptor mediated sympatholysis.[6,15,16] In a recent metanalysis, Vorobeichik L *et al.*[17] concluded that 50–60 μg of perineural dexmedetomidine as an adjuvant to LA found to increase the risk of transient bradycardia and hypotension. In our study, the use of 1 μg/kg perineural dexmedetomidine was not associated with any such side effects.

There are a few limitations in our study. First, the duration of motor blockade which is most important in terms of early ambulation in day care surgeries was not measured. In our study, this was not a major limitation as all our patients with fracture femur in their immediate 24 h following surgery would be immobilised as these surgeries were not done as day care procedures. Second, patients are followed up only for the first 24 h postoperatively and overall outcome such as total number of hospital days, long term neurological adverse effects were not noted.

CONCLUSION

Perineural dexmedetomidine as an adjuvant to LA in USG guided FICB effectively prolonged analgesic duration and also reduced the 24 h postoperative morphine consumption when compared to intravenous dexmedetomidine in elective and emergency femur surgeries. The side effect profiles are comparable.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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