Original Article

Effect of addition of dexmedetomidine to ropivacaine 0.2% for femoral nerve block in patients undergoing unilateral total knee replacement: A randomised double-blind study

Address for correspondence:
Dr. Sunny Rupal,
Department of Anesthesia and Intensive Care,
Max Super Specialty Hospital,
Mohali, Punjab, India.
E-mail: sunnyrupal@gmail.com

Bhawana Sharma, Sunny Rupal[1], Adarsh Chandra Swami[2], Sneh Lata[1]

Department of Anaesthesia, Maulana Azad Medical College, New Delhi, [1]Department of Anaesthesia and Intensive Care, Max Super Specialty Hospital, [2]Department of Anaesthesia and Intensive Care, Fortis Hospital, Mohali, Punjab, India

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.183392

Quick response code

ABSTRACT

Background and Aims: Total knee replacement (TKR) patients experience considerable post-operative pain. We evaluated whether addition of perineural dexmedetomidine to ropivacaine 0.2% in the femoral nerve block would enhance post-operative analgesia in patients undergoing unilateral TKR under spinal anaesthesia. **Methods:** Fifty patients were allocated randomly to two groups of 25 each. Group D received ropivacaine (0.2%) with dexmedetomidine (1.5 μg/kg), and Group C received ropivacaine (0.2%) with normal saline. Pain scores, time to the first request for analgesia and total consumption of ropivacaine in 48 h, along with haemodynamic parameters and sedation scores, were recorded. Quantitative data were compared using *t*-test, categorical data using Chi-square or Fisher's exact test and time variables using ANOVA. **Results:** The mean pain scores were significantly low till 2 h post-operatively in Group D. Time to the first demand for analgesia after initial loading dose was statistically prolonged in Group D, with mean duration of 346.8 ± 240 min, compared to 150 ± 115.2 min in Group C ($P = 0.001$). Total local anaesthetic consumption was also decreased over 24 and 48 h in Group D ($P = 0.001$). Haemodynamically, there was no significant variation in heart rate from their baseline mean values in either group ($P > 0.05$). However, the drop in systolic and mean blood pressure post-surgery was significant till 4 ($P = 0.002$) and 8 h ($P = 0.02$), respectively, in Group D. Group D patients were also significantly more sedated till 4 h post-operatively ($P < 0.005$). **Conclusion:** Adding dexmedetomidine to ropivacaine 0.2% in the femoral nerve block in patients undergoing unilateral TKR improves the quality and prolongs the duration of post-operative analgesia.

Key words: Dexmedetomidine, femoral nerve block, knee replacement, post-operative pain, ropivacaine

INTRODUCTION

Patients undergoing total knee replacement (TKR) experience considerable post-operative pain. It not only prolongs hospitalisation but also impairs early mobilisation and rehabilitation[1,2] and thus may worsen functional outcome.[3] Multimodal analgesia involves a combination of different analgesic agents and techniques to provide pain control after surgery. One of its objectives is to limit the perioperative use of opioids and their side effects.[4] In addition to parenteral drugs, continuous femoral analgesia is an important arm of multimodal analgesia for TKR, which has been proved to be superior to epidural

How to cite this article: Sharma B, Rupal S, Swami AC, Lata S. Effect of addition of dexmedetomidine to ropivacaine 0.2% for femoral nerve block in patients undergoing unilateral total knee replacement: A randomised double-blind study. Indian J Anaesth 2016; 60:403-8.

analgesia in terms of fewer side effects.[5] It also decreases the need for other intravenous non-steroidal anti-inflammatory drugs (NSAIDS) and opioids in patients undergoing TKR. To improve the quality of peripheral nerve blocks, many adjuvants to local anaesthetics have been investigated over the years.[6] One such agent is dexmedetomidine, and it is a α_2-agonist having an eight-fold greater affinity for α_2-adrenergic receptors (hypnotic and analgesic effects) than clonidine and much less α_1-effects.[6,7] Dexmedetomidine has been approved by the Food and Drug Administration for intravenous sedation in the Intensive Care Unit, and its off-label uses are intrathecal, epidural and perineural administration. Drug Controller of India does not approve its off-label uses as yet, but its perineural use is backed by consistently growing evidence of favourable outcomes.[8-10] Our study was approved by the Ethical Committee of our institute. In our study, we hypothesised that addition of dexmedetomidine 1.5 μg/kg to 0.2% ropivacaine in the femoral nerve block would intensify and prolong analgesia in patients undergoing TKR. Hence, through our study, we aimed to find the analgesic effect of perineural dexmedetomidine and its side effects if any.

METHODS

After taking the Institutional Ethics Committee approval and informed consent, a total of fifty adult patients undergoing unilateral TKR under spinal anaesthesia of either sex, aged 30–80 years, weight 50–90 kg, body mass index (BMI) 25–40 kg/m^2 of the American Society of Anesthesiologists physical status I and II, were selected. Patients with coagulopathy, local infection, pre-existing neuropathy, hypersensitivity to local anaesthetic, opioids, NSAIDS or dexmedetomidine were excluded from the study. Primary anaesthetic technique in all patients was spinal anaesthesia. Aseptically, using 27 gauge Quincke cutting needle, 15 mg of bupivacaine 0.5% (hyperbaric) along with fentanyl 25 μg was given intrathecally. The femoral nerve block with perineural catheter (Contiplex D™ continuous nerve block set) was placed at the completion of surgery. Nerve was located sonologically with a 5–10 MHz linear probe (SonoSite™, Bothell, WA, USA) and block assisted by nerve stimulator with quadriceps twitch at < 0.6 mA, 2 Hz being considered an adequate response. No response was elicited at current < 0.4 mA. Visual catheter confirmation was done with the injection of lignocaine 2% with adrenaline 3 ml (to rule out inadvertent, intravascular catheterisation) under real-time ultrasound control. Post-operatively, patients were randomly divided into two Groups, C and D using 'slip in envelope' technique, to receive study drug. At first complaint of pain, or when spinal anaesthesia segment receded to L1, the attending anaesthesiologist administered a bolus dose of ropivacaine (0.2%) 20 ml with normal saline (2 ml) in Group C and patients in Group D received 20 ml of 0.2% ropivacaine with 1.5 μg/kg dexmedetomidine, with total volume made to 22 ml with normal saline. Infusion of ropivacaine 0.2% was commenced at 6 ml/h in both the groups. Injection diclofenac 75 mg intravenous, 12 hourly and injection paracetamol 1 g intravenous, 6 hourly were given to all patients as per our departmental protocol of multimodal analgesia regimen. After this initial loading dose, at next complaint of pain at rest (Numerical Rating Pain Score [NRPS] ≥4), first demand bolus of ropivacaine 0.2% 6 ml was given through femoral catheter by post-anaesthesia care unit anaesthesiologist and infusion increased by 2 ml/h. NRPS and time to first demand of analgesia with bolus (duration) were taken as primary outcome variables. Both anaesthesiologists were unaware of the type of study drug used. If within 30 min patient's pain was not adequately controlled, another bolus of 6 ml of ropivacaine 0.2% was given and infusion rate increased further by 2 ml/h. Maximum infusion rate was kept within 12 ml/h in both groups. If pain was still not controlled (NRPS ≥ 4), injection tramadol 2 mg/kg intravenous was given as rescue analgesic. Demand boluses of ropivacaine 0.2% or rescue intravenous analgesic (tramadol) were given as per requirement keeping in mind their maximum dose (tramadol 400 mg and ropivacaine 700 mg in 24 h). Records were made of secondary outcome variables such as frequency of demand boluses, total consumption of local anaesthetic in 24 and 48 h and number of patients requiring rescue analgesic. Patients were monitored for 48 h and recordings of NRPS (0 being no pain and 10 being very severe pain) and modified Ramsay sedation scores (1 - awake, 2 - drowsy but verbally arousable, 3 - drowsy but arousable only to physical stimulus, 4 - unarousable) were made every ½ h for the first 2 h, then 4 hourly for 12 h post-operatively and every 6 hourly thereafter up to 48 h. After 48 h, ropivacaine infusion was stopped and femoral catheters were removed.

All quantitative variables such as height, weight, BMI, systolic and mean blood pressures were expressed with standard deviation (SD). Normality of data was checked

by measures Kolmogorov–Smirnov tests of normality. For normally distributed data, means of quantitative variables (local anaesthetic doses, haemodynamic parameters) of two groups were compared using Student's *t*-test. For skewed data (pain and sedation scores), Mann–Whitney test was applied. Quantitative or categorical variables are described as frequencies and proportions. Proportions were compared using Chi-square or Fisher's exact test whichever is applicable for two. For time-related variables (time to first demand bolus), repeated-measure ANOVA was applied. All statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Study sample size was estimated based on the pilot study ($n = 10$) for mean time to first demand bolus of 150 min in dexmedetomidine group and 90 min in control group. With SD of 1.2, our sample size came out to be 22 per group at a power of 80% and confidence interval of 95%. For possible dropouts, it was decided to include 25 patients per group.

RESULTS

Fifty patients were enroled and all completed the study. The demographic data in both the groups were statistically insignificant [Table 1]. Pain scores were significantly less in Group D compared to Group C at 1 h, 1.5 h and 2 h, post-operatively, $P = 0.013$, 0.001 and 0.027, respectively [Figure 1]. Time to the first demand ropivacaine bolus was significantly prolonged in Group D, 346.8 ± 240 min as compared to Group C, 150 ± 115.2 min ($P = 0.001$).

Total local anaesthetic consumption was significantly reduced by adding dexmedetomidine up to 24 h, 432.32 ± 71.86 mg as compared to Group C, 546.24 ± 79.10 mg ($P < 0.002$) and in 48 h, 989.20 ± 147.24 mg as compared to 1109.20 ± 102.71 mg in Group C ($P < 0.001$) [Table 2]. The total consumption of rescue analgesic, tramadol was comparable in both the groups over 24 and 48 h, $P = 0.185$.

Haemodynamically, there was no significant variation in heart rate in either group as compared to the baseline values [Figure 2]. The drop in systolic blood pressure was significantly greater at 1 h, 1.5 h, 2 h and 4 h post-operatively in dexmedetomidine group as compared to control group ($P < 0.05$). Similarly, in dexmedetomidine group, mean blood pressure (but not diastolic pressures) also showed significant decrease at 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 8 h, $P < 0.05$ [Figure 3].

The difference in the sedation scores in both groups was statistically significant till 4 h post-operatively, with $P = 0.000$ at 2 h and $P = 0.005$ at 4 h in

Table 1: Demographic data values shown as mean±standard deviation

Variables	Group C (*n*=25)	Group D (*n*=25)
Age (year)	64.68±7.93	65.72±8.97
Height (cm)	158.84±22.04	158.60±7.46
Weight (kg)	73.04±11.00	68.68±12.23
Gender (female/male)	11/14	17/8
ASA Grade (I/II)	9/16	8/17
Duration of surgery (min)	151.2±31.8	141.6±29.4

Table: 2 Comparison of demand bolus, local anaesthetic (ropivacaine) and rescue analgesic (tramadol) consumption values shown as mean±standard deviation

Parameters	Group C (*n*=25)	Group D (*n*=25)	*P*
Time to first demand bolus (min)	150±115.2	346.8±240	0.001
Total number of demand bolus	4.24±1.48	2.84±1.54	0.002
LA consumption in 24 h (mg)	546.24±79.10	474.32±71.86	0.002
LA consumption in 48 h (mg)	1109.20±02.71	989.04±141.27	0.001
RA consumption in 24 h (mg)	116.67±38.34	100.00±0.00	0.185
RA consumption in 48 h	116.67±38.34	100.00±0.00	0.185

P>0.05 NS. LA – Local anaesthetic (ropivacaine); RA – Rescue analgesic (tramadol); NS – Not significant

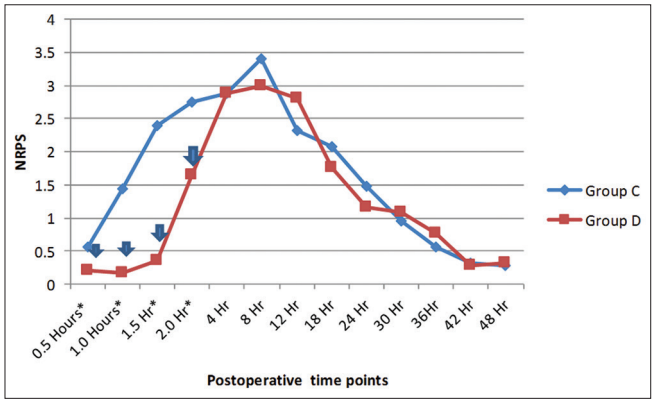

Figure 1: Mean Numerical Rating Score of pain (±SD) (*$P < 0.05$ till 2 h)

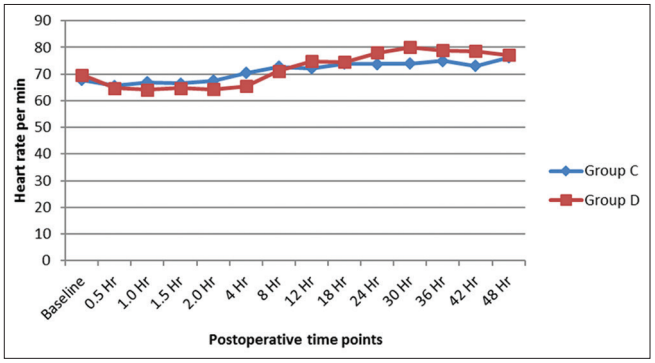

Figure 2: Comparison of mean heart rate between two groups

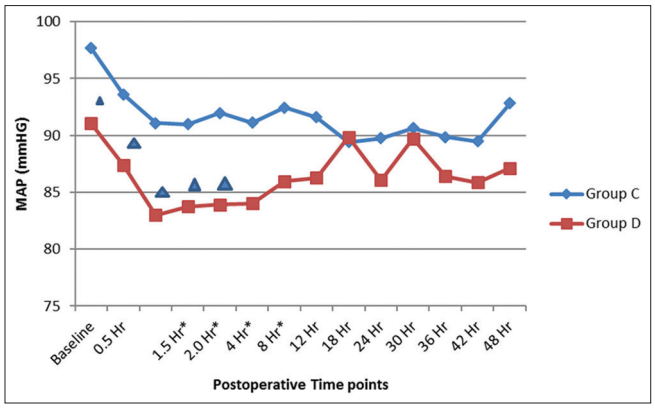

Figure 3: Comparison of mean arterial pressure in both groups (*▲ $P < 0.05$ till 8 h)

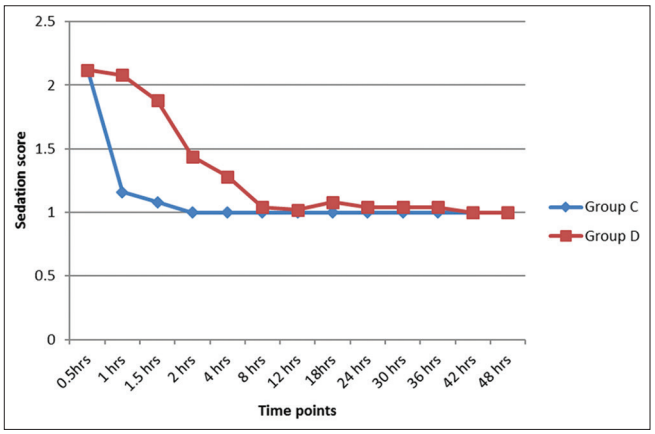

Figure 4: Comparison of (modified Ramsay) sedation scores

dexmedetomidine group [Figure 4]. After 4 h, the difference became statistically insignificant. None of the patients had respiratory depression.

DISCUSSION

The mechanism by which dexmedetomidine acts perineurally is not understood very well and is mainly extrapolated from studies on clonidine, both being α_2-adrenoreceptor blockers. α_2-adrenoreceptor blockers directly increase hyperpolarisation of action potential that follows a single compound action potential of the peripheral nerve.[8] Like clonidine, dexmedetomidine too enhances the degree of hyperpolarisation by blocking the Ih current (generated by low-grade stimulation and activation of Na^+/K^+ pump).[8] Other indirect actions of dexmedetomidine include central analgesia, vasodilatation and anti-inflammation properties.

So far, dexmedetomidine has been used in various peripheral nerve blocks at different sites, mainly of upper limb (axillary, supraclavicular brachial plexus, greater palatine nerve block, etc.). Further, there is no homogeneity in dexmedetomidine dose and type of local anaesthetic used. Doses have ranged from 1 μg/kg to 2 μg/kg,[9] up to 100 μg in conjunction with bupivacaine, levobupivacaine or ropivacaine in variable concentrations.[10] We decided to use a dose of 1.5 μg/kg.

We found that perineural dexmedetomidine significantly improved the quality and duration of post-operative analgesia. Since there was continuous infusion of ropivacaine for 48 h in both the groups, duration of analgesia could not be measured. Hence, it was indirectly interpreted from the time to first demand of bolus. These effects automatically led to decreased overall local anaesthetic consumption. Although rescue analgesic, tramadol consumption also decreased in dexmedetomidine group, it failed to achieve any significance ($P = 0.185$). Various researchers in the past sought to determine the effect of addition of dexmedetomidine to local anaesthetic agents in the peripheral nerve blocks for reducing post-operative pain and consumption of local anaesthetics and other analgesics. Its beneficial effects and side effects have been variable (as discussed below), probably due to the difference in the methodology, patient population, dexmedetomidine dosages, types of surgery and post-operative pain management regimens.

Similar to our results, various studies showed favourable outcomes on onset, duration and quality of peripheral nerve blocks when dexmedetomidine is added to local anaesthetics. One such study demonstrated that on adding dexmedetomidine to bupivacaine for greater palatine nerve block in thirty children scheduled for cleft palate repair, and pain scores were significantly low till 24 h in the group that received bupivacaine with dexmedetomidine, $P < 0.05$. In addition, the time to the first request for analgesia was longer in this group (mean 22 h) as compared to plain bupivacaine (mean 14.2 h).[11] In another randomised double blind study on axillary brachial plexus block for elective forearm and hand surgery, it was observed that in the group that received combination of ropivacaine and dexmedetomidine,the sensory and motor block onset times were shorter (9.03 ± 1.15 min and 9.50 ± 1.04 min, respectively), as compared to the ropivacaine only group (10.46 ± 1.30 min, 11.10 ± 1.24 min respectively) . Also duration of sensory block was significantly prolonged in combination group, (1008.69 ± 164.04 min versus 887.14 ± 260.82 min) as compared to levobupivacaine

group ($P < 0.05$).[12] Our positive results are also supported by two other clinical trials conducted on patients for upper limb surgery under supraclavicular brachial plexus block. The first study demonstrated significant increase in duration of analgesia when dexmedetomidine 100 μg was added to ropivacaine and also decreased sensory and motor block onset times, $P < 0.05$.[12] In the second study of 60 patients, the group of patients receiving dexmedetomidine with bupivacaine needed rescue analgesic at 456 ± 97 min as compared to the group getting clonidine with bupivacaine at 289 ± 62 min ($P = 0.001$).[13]

Tramadol consumption was comparable in both of our groups ($P < 0.185$). Other studies found significantly decreased consumption of rescue analgesics such as diclofenac and morphine.[14,15] This is probably because we used additional analgesics, paracetamol and diclofenac as part of multimodal analgesia regime.

Haemodynamically, dexmedetomidine group showed significant fall in systolic (up to 8 h) and mean blood pressures (till 4 h) post-operatively without much effect on heart rate. Initial 2 h of fall was associated with parallel decrease in NRPS scores and enhanced analgesia. Low sympathetic state of patient in the first 2 h can explain low pressures. Subsequently, the haemodynamic changes may be reflective of the systemic absorption from site of drug administration and thus, beyond 2 h, reduced NRPS scores failed to achieve any statistical significance. Previous studies on dexmedetomidine, when used perineurally in various peripheral nerve blocks, have shown variable results. Esmaoglu *et al*., in a study with addition of dexmedetomidine to levobupivacaine in axillary brachial plexus block, observed significant fall in systolic blood ($P < 0.01$), diastolic blood pressures ($P < 0.05$) and heart rate ($P < 0.05$) at 2 h in group receiving dexmedetomidine as compared to the control group.[12] In a comparative study between dexmedetomidine and clonidine, there was significant drop in pulse rate (not < 60 bpm), systolic and diastolic pressures in dexmedetomidine group up to 2 h post-drug administration in the supraclavicular block as compared to the group that received clonidine.[13,15] We infer that these haemodynamic effects are possibly due to systemic absorption of dexmedetomidine and are also dose dependent as no significant haemodynamic variations have been seen in clinical trials where its dose is <1 μg/kg or <100 μg.[11,16]

α_2-agonists produce sedation centrally by activating α_2-adrenoceptor in locus coeruleus and by inhibiting substance *P* release in the nociceptive pathway at the level of the dorsal root neurons. Majority of studies show no significant effect of perineural dexmedetomidine on sedation.[11,12,13,15] However, contrastingly, our patients were significantly more sedated till 4 h post-operatively. This effect could probably be due to site-specific absorption properties and also as highlighted earlier, we used higher dose than other studies. Hence, sedation too seems dose dependent. The main limitation of our study was that we assessed only analgesia-enhancing actions of dexmedetomidine, but no objective assessments of motor and sensory block onset times and duration were made. We also cannot comment on its effect on the onset time of block because we placed femoral catheters in post-operative period under residual analgesic effect of spinal anaesthesia. Further dose-quantifying studies are needed to explain the hemodynamic changes associated with the administration of dexmedetomidine in the peripheral nerve block, the side effects and safe, optimal dose of dexmedetomidine.

CONCLUSION

Dexmedetomidine, when added as an adjuvant to ropivacaine in the femoral nerve block in adult patients undergoing unilateral TKR under spinal anaesthesia, prolongs the duration and enhances the quality of analgesia without reduction in rescue analgesic consumption. These effects are associated with significant haemodynamic changes and sedation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Puolakka PA, Rorarius MG, Roviola M, Puolakka TJ, Nordhausen K, Lindgren L. Persistent pain following knee arthroplasty. Eur J Anaesthesiol 2010;27:455-60.
2. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-73.
3. Bergeron SG, Kardash KJ, Huk OL, Zukor DJ, Antoniou J. Functional outcome of femoral versus obturator nerve block after total knee arthroplasty. Clin Orthop Relat Res 2009;467:1458-62.
4. Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: Role of multimodal analgesia. Anesthesiol Clin 2010;28:217-24.

5. Paul JE, Arya A, Hurlburt L, Cheng J, Thabane L, Tidy A, *et al.* Femoral nerve block improves analgesia outcomes after total knee arthroplasty: A meta-analysis of randomized controlled trials. Anesthesiology 2010;113:1144-62.
6. Brummett CM, Wagner DS. The use of alpha two agonists in peripheral nerve blocks. Semin Anaesth Perioper Med Pain 2008;25:84-92.
7. El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth 2009;103:268-74.
8. Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. Anesthesiology 2011;115:836-43.
9. Anand VG, Kannan M, Thavamani A, Bridgit MJ. Effects of dexmedetomidine added to caudal ropivacaine in paediatric lower abdominal surgeries. Indian J Anaesth 2011;55:340-6.
10. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: A systematic review and meta-analysis. Br J Anaesth 2013;110:915-25.
11. Obayah GM, Refaie A, Aboushanab O, Ibraheem N, Abdelazees M. Addition of dexmedetomidine to bupivacaine for greater palatine nerve block prolongs postoperative analgesia after cleft palate repair. Eur J Anaesthesiol 2010;27:280-4.
12. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg 2010;111:1548-51.
13. Swami SS, Keniya VM, Ladi SD, Rao R. Comparison of dexmedetomidine and clonidine (α_2-agonist drugs) as an adjuvant to local anaesthesia in supraclavicular brachial plexus block: A randomised double-blind prospective study. Indian J Anaesth 2012;56:243-9.
14. Das A, Majumdar S, Halder S, Chattopadhyay S, Pal S, Kundu R, *et al.* Effect of dexmedetomidine as adjuvant in ropivacaine-induced supraclavicular brachial plexus block: A prospective, double-blinded and randomized controlled study. Saudi J Anaesth 2014;8 Suppl 1:S72-7.
15. Ammar AS, Mahmoud KM. Ultrasound-guided single injection infraclavicular brachial plexus block using bupivacaine alone or combined with dexmedetomidine for pain control in upper limb surgery: A prospective randomized controlled trial. Saudi J Anaesth 2012;6:109-14.
16. Gandhi R, Shah A, Patel I. Use of dexmedetomidine along with bupivacaine for brachial plexus block. Natl J Med Res 2012;2:67-9.