

A comparison of intrathecal Dexmedetomidine and Buprenorphine as an adjuvants to isobaric spinal 0.75% Ropivacaine in patients undergoing elective lower limb surgery

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Abstract

Introduction: Ropivacaine is the single enantiomer specific local anaesthetic having reduced potential for cardiotoxicity and neurotoxicity. Its characteristics of slow onset, shorter duration of sensory analgesia and rapid motor recovery will necessitates for early analgesic intervention. Adding adjuvants to ropivacaine improves the efficacy of subarachnoid block. Drugs like dexmedetomidine, a highly selective alpha 2 adrenergic agonist and buprenorphine an opioid agonist and antagonist have been used as effective adjuvants.

Aim: To evaluate and compare whether the small dose of adjuvants buprenorphine and dexmedetomidine added to isobaric spinal ropivacaine prolongs the duration of sensory and motor block as well as the duration of postoperative analgesia. The adverse effects and hemodynamic variable were also studied.

Materials and Method: The study included 90 patients aged between 20-60 years belonging to either American Society of Anesthesiologists (ASA) Physical Status I/II scheduled for elective lower limb surgeries. The patients were randomly allotted to three groups. Group RS -received intrathecal 3ml of 0.75% ropivacaine with 0.5ml of normal saline. Group RB received 3ml of 0.75% ropivacaine with 60µg of buprenorphine. Group RD -received 3ml of 0.75% ropivacaine with 5µg of dexmedetomidine. The onset time to peak sensory level, onset of complete motor block (modified Bromage 3), duration of sensory and motor block, hemodynamic variables, and adverse effects if any were noted.

Results: There was no difference between groups regarding demographic data and duration of surgery. Duration of sensory and motor block was significantly prolonged with Dexmedetomidine when compared with buprenorphine or saline (P<0.001). Dexmedetomidine delayed the time for first analgesic requirement postoperatively (P<0.001). No significant side effects were observed. Hemodynamic parameters were stable.

Conclusion: Intrathecal dexmedetomidine as adjuvant to ropivacaine has shorter sensory onset time and is associated with prolonged duration of sensory and motor block and prolonged the time for first analgesic demand when compared with buprenorphine or plain ropivacaine with good hemodynamic stability and no significant side effects.

Keywords: Ropivacaine, Dexmedetomidine, Buprenorphine, Spinal anaesthesia, Post operative analgesia.

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Introduction

Intrathecal ropivacaine has gained popularity as an alternative to intrathecal bupivacaine hydrochloride because of its reduced risk of cardiotoxicity, neurotoxicity and good haemodynamic stability.^(1,2)

Ropivacaine has its own limitation of shorter duration of anaesthesia, which can be overcome by adding the adjuvants to local anaesthetics. The supplementation of local anaesthetics with adjuvants is in today's practice, to reduce the dose of local anaesthetic, minimize the side effects and prolong the duration of intra and post operative analgesia with good haemodynamic stability. Many studies using adjuvants like opioids and α_2 agonist to bupivacaine⁽³⁾ are available in the literature, whereas few studies have been done using these adjuvants with ropivacaine.⁽⁴⁾ Our purpose was to add low dose of dexmedetomidine and buprenorphine as adjuvants to ropivacaine intrathecally and compare the efficacy, post operative analgesia and hemodynamic stability.

Materials and Method

This prospective study was conducted after the approval of the Institutional Ethical Committee. Informed written consent was obtained from 90 patients aged 20-60 years of either sex belonging to American society of Anaesthesiologist physical status (ASA) I or II. Patients with bleeding disorders, on anticoagulant therapy, cardiac disease, heart blocks, β -blockers and α -antagonists were excluded from the study. All patients were examined and investigated a day prior to surgery. They were advised fasting for six hours and received diazepam 0.1 mg/kg orally as premedication on the night before surgery. The study solutions were prepared in a five ml syringe which would contain three ml of ropivacaine with 0.5 ml of saline or 0.5 ml of adjuvant drug. The anaesthesiologist who prepared the solution would then hand over the solution in a coded form to the attending anaesthesiologist blinded to the nature of drug given to him or her.

Patients were randomized by computer generated random number sequence technique into three groups: Group RS, Group RB and Group RD of 30 each.

Group RS: received 3cc of 0.75% isobaric ropivacaine with 0.5cc of saline.

Group RB: received 3cc of 0.75% isobaric ropivacaine with 60µg of buprenorphine

Group RD: received with 3cc of 0.75% isobaric ropivacaine with 5µg of dexmedetomidine.

Under strict aseptic precautions subarachnoid block was performed by 25G Quincke Babcock spinal needle in the L3-L4 interspace in lateral decubitus position. The loaded drug was injected over 10-15 seconds following free flow of Cerebrospinal Fluid (CSF). The time at which injection was completed was considered zero time of the study and all measurements were recorded from this point. Following subarachnoid block, patients were made to lie supine and data were recorded by an independent third anaesthesiologist who was unaware of the group allocation.

Primary objectives were onset of sensory block to highest dermatomal level, onset of complete motor block, duration of two segment regression from maximum block height, duration of sensory block regression to S₂ dermatome and duration of complete motor recovery and the time for first rescue analgesic in the post operative period. Highest level of Sensory block was tested by pin prick method using 25G hypodermic needle in midclavicular line bilaterally every five mins for 20 mins after the injection. The level of sensory block was measured every ten minutes to know the time of two segment regression and regression to S₂ dermatome by pin prick. Motor block was assessed using Modified Bromage Scale (Bromage 0 – patient is able to move hip, knee and ankle; Bromage 1 – not able to move hip but able to move knee and ankle; Bromage 2 – not able to move hip and knee, but able to move ankle; Bromage – 3 not able to move hip, knee and ankle). The time taken to reach modified Bromage 3 was recorded as the time for complete motor block. Time taken to reach modified bromage 0, was taken as time for complete motor recovery. In cases with failure of subarachnoid block and conversion to general anaesthesia we planned to exclude such patients from the study. Secondary objectives include hemodynamic parameters and side effects.

Basal hemodynamic parameters were recorded just before giving spinal anaesthesia and further readings are

made at one minute, five minute, 10 minute, 15, 20, 30, 60, 90, 120 minutes after the administration of subarachnoid block. Hypotension was defined as fall in systolic blood pressure (SBP) by 30% from baseline and was treated with intravenous fluids and injection mephentermine in three mg aliquots. Bradycardia was defined as HR <50 beats per minute and treated with intravenous atropine 0.6 mg. Patients did not receive any additional analgesic in intraoperative period. The incidence of any adverse effects such as hypotension, bradycardia, shivering, nausea, and vomiting, respiratory depression and ECG changes were noted.

Post-operatively the two segment sensory block regression, regression to S₂ dermatomal level, and motor block recovery to modified Bromage score of zero was assessed for every ten minutes.

In the post operative period any patient showing VAS more than or equal to 3 was administered a supplemental dose of IV tramadol 50 mg.

Hemodynamic variables and oxygen saturation was recorded.

Statistical analysis: Based on the outcome variables such as duration of sensory and motor block and to detect an increase in the mean duration of sensory and motor block difference of 30mins between the groups, with 90% statistical power and 5% level of significance the sample size of 90 was considered adequate with 30 in each group.

Significant figures: P value ≤ 0.05 is significant and P value ≥ 0.05 is not significant. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Post-Hoc Tukey Test has been used to find the pair wise significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Results

The demographic data in all the three groups were comparable in terms of age, gender, weight height and duration of surgery (Table 1).

Table 1: Demographic data

	Group RS (n =30)	Group RB (n=30)	Group RD (n =30)	P value
Age(years)	47.40±9.68	43.50±	43.23±	0.326
Sex (M:F)	15:15	16:14	17:13	0.875
Weight(kilograms)	52.80±7.40	55.70±6.74	54.43±9.49	0.372
Height(cms)	156±1.3	158±1.7	160±1.5	0.665
Duration of surgery(mins)	92.68±25.21	95.44±38.11	92.67±36.10	0.07

Table 2: Maximum Sensory height attained

MAX Sensory HT	Group RS	Group RB	Group RD	Total
T10	10(33.3%)	0(0%)	2(6.7%)	12(13.3%)
T8	10(33.3%)	1(3.3%)	2(6.7%)	13(14.4%)
T6	6(20%)	13(43.3%)	10(33.3%)	29(32.2%)
T5	0(0%)	1(3.3%)	0(0%)	1(1.1%)
T4	4(13.3%)	15(50%)	16(53.3%)	35(38.9%)
Total	30(100%)	30(100%)	30(100%)	90(100%)

P=0.050*, Significant

Table 3: Comparison of study variables

	Group RS (n =30)	Group RB (n=30)	Group RD(n=30)	Total	P value
Time for max sensory Block(minutes)	9.57±2.51	8.93±1.74	7.73±2.20	8.74±2.28	0.006**
Time for Complete motor block(minutes)	5.20±0.92	5.27±1.17	5.50±1.43	5.32±1.19	0.595
Time for 2 segment regression(minutes)	74.23±14.34	100.73±12.57	138.57±12.48	104.51±29.56	<0.001**
Time for s2 regression (minutes)	238.77±9.68	324.87±19.35	430.27±16.55	331.30±80.27	<0.001**
Complete motor recovery(minutes)	147.13±7.53	267.83±48.31	323.83±27.39	246.27±80.75	<0.001**
Time for first rescue analgesic	230.67±10.22	336.76±15.75	460.45±20.75	342.66±15.56	<0.001**

Table 4: Comparison of study variables (Pair-wise comparison)

Pair wise comparison	Group RS-Group RB		Group RS-Group RD		Group RB-Group RD	
	Difference	P value	Difference	P value	difference	P value
Time for max sensory Block(minutes)	0.633	0.499	1.833	0.004**	1.200	0.088+
Complete motor block(minutes)	-0.067	0.975	-0.300	0.596	-0.233	0.731
Time for 2 segment regression(minutes)	-26.500	<0.001**	-64.333	<0.001**	-37.833+	<0.001**
Time for s2 regression(minutes)	-86.100	<0.001**	-191.500	<0.001**	-105.400	<0.001**
Complete motor recovery(minutes)	-120.700	<0.001**	-176.700	<0.001**	-56.000	<0.001**

Table 5: Side effects and intervention

Adverse effects	Group RS (n =30)	Group RB (n =30)	Group RD (n=30)	Total (n =90)	P value
Nausea/ vomiting	2(6.7%)	6(20%)	4(13.3%)	12(13.3%)	0.374
Shivering	4(13.3%)	4(13.3%)	6(20%)	14(15.6%)	0.815
Atropine required	3(10%)	4(13.3%)	5(16.7%)	12(13.3%)	0.925
Mephenteramine required	14(46.7%)	12(40%)	16(53.3%)	42(46.7%)	0.585

The maximum sensory height of subarachnoid block is shown in Table 2. Our study showed no statistical significance between group RB and group RD in the highest level of sensory block achieved, but the time to reach maximum height of sensory block was shorter with dexmedetomidine(7.73±2.20min) when compared to

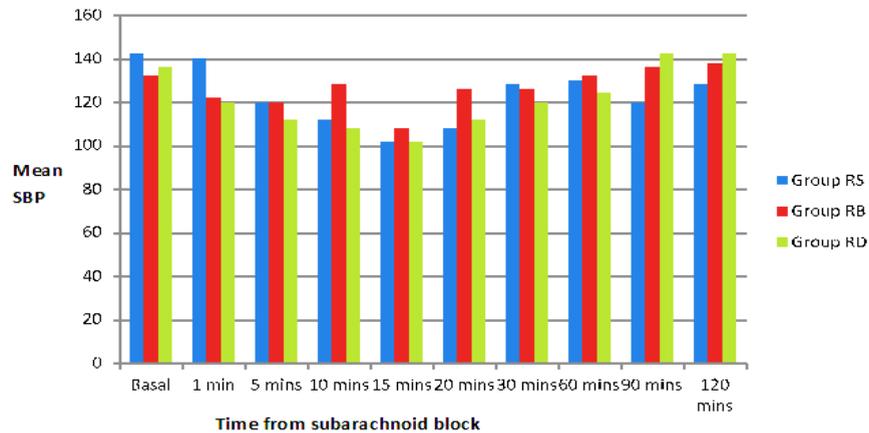
buprenorphine(8.93±1.74min)(P=.006). However onset of motor block was comparable among the groups (P=0.595).

Time for sensory regression by two segments from maximum height attained, and time for sensory regression toS₂ dermatome and time for complete motor

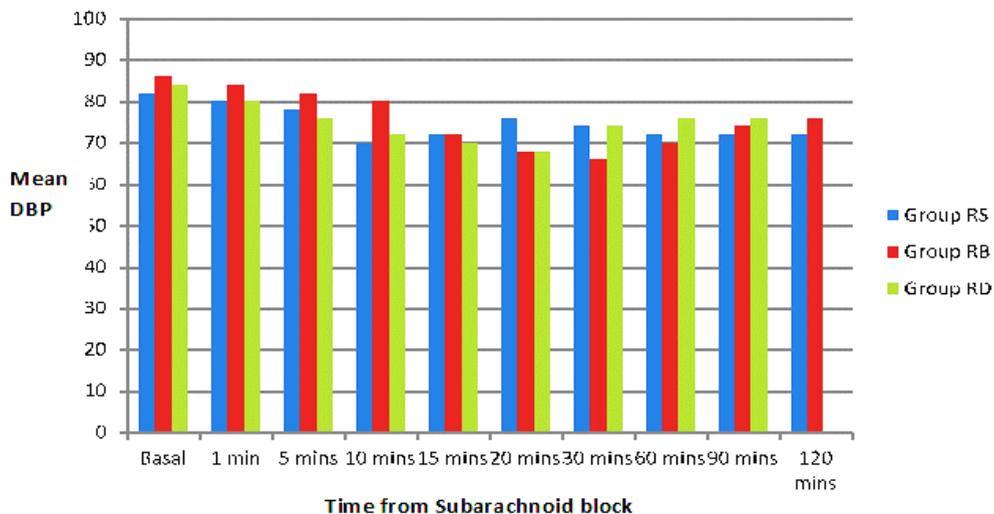
recovery was significantly prolonged in dexmedetomidine group (138.57 ± 12.48 , 430.27 ± 16.55 , 323.83 ± 27.39 mins respectively) when compared to buprenorphine group (100.73 ± 12.57 , 324.87 ± 19.35 , 267.83 ± 48.31 mins respectively) Saline group (74.23 ± 14.34 , 238.77 ± 9.68 , 147.13 ± 7.53 mins respectively) ($P < 0.001$) (Table 4). However dexmedetomidine had a significant longer duration of sensory and motor block when compared to buprenorphine.

Time for first analgesic requirement in post operative period was delayed in group RD (460.45 ± 20.75 min) compared to group RB (336.76 ± 15.75 min) and RS (230.67 ± 10.22 min) (Table 3). Incidence of hypotension, bradycardia, shivering, nausea and vomiting were comparable between three groups (Table 5). Patients who required atropine (3/4/5 patients in RS/RB/RD groups respectively) with $P = 0.925$ and mephentermine (14/12/16 patients in group RS/RB/RD respectively) with $P = 0.525$ was comparable.

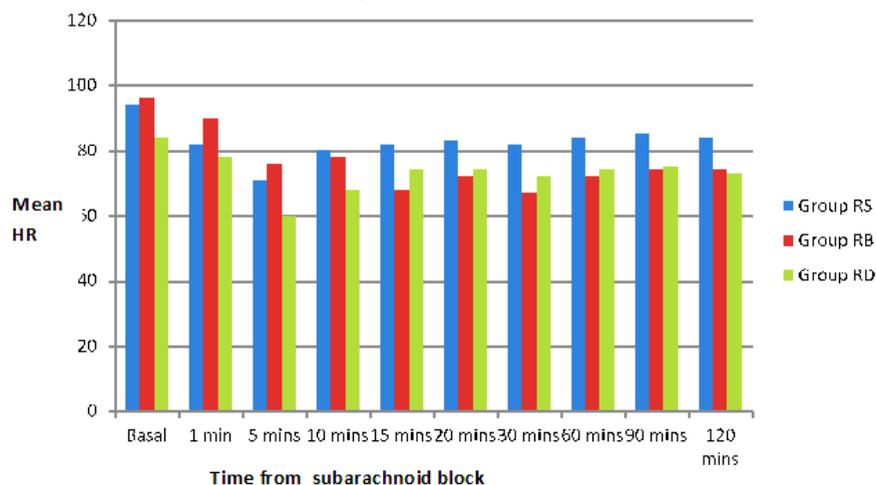
Graph 1: Mean systolic blood pressure



Graph 2: Mean diastolic blood pressure



Graph 3: Mean Heart rate



Discussion

Ropivacaine has a definite edge over bupivacaine by its reduced toxic potential in regional anesthetic techniques. This drug has also been extensively studied over last many years for its intrathecal use. When identical doses of isobaric ropivacaine and bupivacaine were compared, ropivacaine was found to have almost similar efficacy but shorter duration of sensory and motor block.⁽⁵⁾

Many studies have showed that Intrathecal opioid and dexmedetomidine as adjuvants to hyperbaric bupivacaine greatly enhanced the analgesic effects.^(6,7,8,9,10) whereas limited studies are available where these adjuvants are added to isobaric ropivacaine.^(11,12) Our study has focused on the comparison between opioid buprenorphine and newer α_2 agonist dexmedetomidine as intrathecal adjuvants to isobaric 0.75% ropivacaine.

In the present study, intrathecal dose of dexmedetomidine five μg was selected based on the studies done by Shah A et al,⁽¹²⁾ which showed excellent hemodynamic stability and previous studies by Naithani U et al⁽¹¹⁾ had showed both sensory and motor block to be prolonged with five μg of dexmedetomidine. Buprenorphine 60 μg was used based on the study of Mahima Gupta et al⁽³⁾ which showed good hemodynamic stability and study done by Shaikh SI et al⁽¹³⁾ using low dose of intrathecal buprenorphine (1 μg Kg-1) provided good post-operative analgesia without any significant increase in side effects.

T₄ dermatomal level was reached by only four patients (13.3%) and T₆ dermatomal level by six patients (20%) in group RS. When intrathecal dexmedetomidine or buprenorphine was added as adjuvants to spinal anaesthesia $\geq 50\%$ of the patients achieved a higher sensory block of T₄. As we have not included lower abdominal surgeries in our study, we could not come to the conclusion if lower abdominal surgeries could be performed when adjuvants are added to ropivacaine.

Incidence of failures were frequent with intrathecal plain ropivacaine than with plain bupivacaine.⁽¹⁴⁾ Also previous studies using three μg or five μg of dexmedetomidine as adjuvants to isobaric ropivacaine had not shown much promise for abdominal surgeries, as one third cases required analgesic supplementation.⁽¹¹⁾

Studies have shown that dexmedetomidine hastens the onset of sensory and motor block.⁽¹⁵⁾ We also observed that mean time to reach T₄ dermatome was significantly less in group RD when compared with RS and RB groups. Onset of motor block was comparable among the three groups.

Duration of sensory and motor block was prolonged in both RD and RB group, when compared to RS group. Comparing dexmedetomidine group with buprenorphine group, the former showed a significant prolongation of sensory and motor duration (Table 4). Our study was in accordance to study done by Rajini Gupta et al⁽¹⁶⁾ where five μg of intrathecal dexmedetomidine added to ropivacaine prolonged sensory and motor block. We did not find any previous studies done using buprenorphine with ropivacaine. In our study we found significant delay in "first rescue analgesic demand" in dexmedetomidine group.

Local anaesthetics and α_2 adrenergic agonist dexmedetomidine both have different mechanism of action. while local anaesthetics act by blocking sodium channels, α_2 adrenergic agonists act by binding to presynaptic C fibers and to postsynaptic dorsal horn neurons. This reduces the release of C fibre transmitters and causes hyperpolarisation of post synaptic dorsal horn neurons.⁽¹⁷⁾ This additive or synergistic effect explains the prolongation of sensory block when dexmedetomidine is added to spinal anaesthesia.⁽¹⁸⁾ The prolongation of motor block of spinal anaesthesia may be due to binding of α_2 adrenoreceptor agonists to motor neuron in the dorsal horn.⁽¹⁹⁾ Intrathecal buprenorphine causes prolonged analgesia because of its high lipophilic

nature. It remains attached to spinal opioid receptors for long duration thus prolonging the duration of block.⁽²⁰⁾

Hemodynamic stability was seen in all the three groups. Mepentermine was received by 16 patients in group RD, 12 patients in RB group and 14 patients in RS group. Intrathecal local anaesthetics block the sympathetic outflow and reduce the blood pressure and heart rate.⁽²¹⁾ Addition of low dose of adjuvants did not show any statistical difference in the number of patients treated for hypotension or bradycardia. Shah et al⁽¹²⁾ in their study using dexmedetomidine five µg with ropivacaine had shown excellent hemodynamic stability. Contrary to this, some studies have shown higher incidence of hypotension with 5µg of dexmedetomidine.⁽¹¹⁾ According to our investigations we concluded that buprenorphine 60µg or dexmedetomidine five µg did not add to the hypotension caused due to sympathetic block by ropivacaine. Larger study could be carried out in future. Side effects like shivering, nausea/vomiting were not significant, may be because of small dose of adjuvants used.

Our study had some limitations, we conducted study on healthy patients and hence the effect of these adjuvants on patients with uncontrolled co-morbid conditions could not be investigated. We have found good hemodynamic stability in plain ropivacaine and with adjuvants, for which we would have included ASA III /IV patients.

Intraoperative sedation should have been studied, where in many studies had shown varied degree of sedation with dexmedetomidine 5µg and buprenorphine 60µg.^(3,22)

Conclusion

We conclude, adding adjuvants dexmedetomidine and buprenorphine to isobaric ropivacaine 0.75%, prolonged the duration of sensory and motor block, maintaining good hemodynamic stability and showing no significant side effects. However intrathecal dexmedetomidine five µg significantly prolonged the duration of spinal anaesthesia and post operative analgesia thus prolonging the time for first rescue analgesic demand when compared to buprenorphine.

References

1. Simpson D, Curran MP, Oldfield V, Keating GM. Ropivacaine: A review of its use in regional anaesthesia and acute pain management. *Drugs*. 2005;65:2675-717.
2. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. *Indian J Anaesth*. 2011;55:347-51.
3. Gupta M, Shailaja S, Hegde KS. Comparison of intrathecal dexmedetomidine with buprenorphine as adjuvant to bupivacaine in spinal anaesthesia. *J Clin Diagn Res*. 2014;8:114-17.
4. Maharani B, Prakash MS, Kalaiah P, Elango NC. Dexmedetomidine and Buprenorphine as adjuvant to spinal anaesthesia. *Int J Cur Res Rev*. 2013;05:97-103.
5. McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: Comparison of plain ropivacaine 5mg ml(-1) with bupivacaine 5mg ml(-1) for major orthopaedic surgery. *Br J Anaesth*. 2002;89:702-6.
6. Kallio H, SnallEv, Suvanto S.J, Tuomas C.A, Linonen M.K, Pokk JP et al. Spinal hyperbaric ropivacaine-fentanyl for day surgery. *Reg Anesth pain Med*. 2005;30:48-54.
7. Gujar S, Jagtap P, Swapnil, Tejas, Kruti. Adjuvants to spinal anaesthesia- what is better, comparison between intrathecal clonidine with intrathecal buprenorphine. *Sch. J. App. Med Sci* 2014;2:1274-77.
8. Al Ghanem SM, Massad IM, AL Mustafa MM, AL-Zaben KR, Qudaisat IY, Qatawneh AM, et al. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. *American J of Applied sciences*. 2009;6:882-87.
9. Kanazi GE, Aouad MT, Jabbour-Khoury SI et al. Effect of low dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* 2006;50:222-7.
10. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. *J Anaesthesiol Clin Pharmacol*. 2011;27:339-43.
11. Naithani U, Meena MS, Gupta S, Meena K, Swain L, Pradeep DS. Dose dependent effect of intrathecal dexmedetomidine on isobaric ropivacaine in spinal anaesthesia for abdominal hysterectomy: Effect on block characteristics and hemodynamics. *J Anaesthesiol Clin Pharmacol*. 2015 ;31:72-79.
12. Shah A, Patel I, Gandhi R. Haemodynamic effects of intrathecal dexmedetomidine added to ropivacaine intraoperatively and for postoperative analgesia. *Int J Basic Clin Pharmacol*. 2013;2:26-29.
13. Shaikh SI, Kiran M. Intrathecal Buprenorphine for Post-operative Analgesia: A Prospective Randomised Double Blind Study. *J Anaesth Clin Pharmacol*. 2010;26:35-38.
14. Gautier P, De Kock M, Huberty L, Demir T, Izydorczak M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for caesarean section. *Br J Anaesth*. 2003;91:684-9.
15. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulphate used as adjuvants to Bupivacaine. *J Anaesthesiol Clin Pharmacol*. 2011;27:495-9.
16. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. *Indian J Anaesth*. 2011; 55: 347-51.
17. Eisanach JC, De Kock M, Klimschaw. α₂ adrenergic agonists for regional anaesthesia. *Anesthesiology* 1996;85:655-74.
18. Salgado PF, Sabbag AT, Silva PC et al. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anaesthesia. *Rev Assoc Med Brass* 2008;54:110-5.
19. Harada Y, Nishioka K, Kitahato LM, Kishikawa K, Collins JG. Visceral anti-nociceptive effects of spinal clonidine combined with morphine, [D-Pen sup 2, D-Pen SUP 5 enkephalin] or U50,488H. *Anesthesiology*. 1995;83:344-52.
20. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *British. J. Anaesth* 1985;57:192-6.
21. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anaesthesia: comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. *Acta Anaesthesiol Belg*. 2008;59:65-71.
22. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R. A Comparison of intrathecal dexmedetomidine, clonidine and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind study. *J Anaesthesiol Clin Pharmacol*. 2013;29:496-502.