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Efficacy of intrathecal α_2 agonists as adjuvants with low dose of levobupivacaine for lower limb surgeries in elderly patients

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Abstract

Introduction: Elderly orthopedic patients are frequently associated with systemic co morbidities like cardiac, pulmonary or endocrinal disorders. Regional anaesthesia has benefits over general anaesthesia in elderly. But the hypotension caused by regional anaesthesia is a limiting factor which can be overcome by using low dose of local anaesthetics. Low-dose local anaesthetics can limit the block level, but may not provide an adequate ansesthesia level and duration for surgery, requiring more analgesic consumption postoperatively. These shortcomes are overcome by adding intrathecal adjuvants with local anaesthetics. Among them α2 agonists are gaining popularity. Our aim was to compare the characteristics of spinal block, haemodynamic changes following administration of low dose of α2 agonist's intrathecally combined with low-dose levobupivacaine in elderly patients undergoing orthopaedic surgeries.

Material and Methods: In this prospective randomized double blind study, 90 patients of more than 65 years of age posted for lower limb surgeries were allotted into three groups. Group-LS received 1.5cc of 0.5% isobaric levobupivacaine with 0.5cc of normal saline, Group –LC received 1.5 cc of 0.5% isobaric levobupivacaine with 30µg of clonidine and Group-LD received 1.5 cc of 0.5% isobaric levobupivacaine with 5µg of dexmedetomidine. Onset of sensory and motor block, duration of sensory and motor block, haemodynamic parameters, sedation and side effects if any were evaluated.

Results: The onset of sensory and motor block were faster in dexmedetomidine group than clonidine or plain levobupivacaine group. Duration of the sensory and motor block were also prolonged in dexmedetomidine group when compared with clonidine or plain levobupivacaine group. Haemodynamic stability was maintained in all the three groups.

Conclusion: The addition of dexmedetomidine 5µg to7.5mg 0.5% isobaric levobupivacaine hastens the onset of sensory and motor block and also prolongs the duration of analgesia with good haemodynamic stability in elderly patients.

Keywords: Levobupivacaine, Clonidine, Dexmedetomidine, Spinal anaesthesia, Elderly patients.

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Introduction

Elderly patients are more vulnerable to the pharmacological effects of drugs because of their pathophysiological changes and associated co-morbid conditions. Low-dose local anaesthetics can limit the block level, there by providing haemodynamic stability.(1) Among the local anaesthetics, levobupivacaine a pure S (-) enantiomer of racemic bupivacaine, offers the advantage of lower cardiotoxicity and neurotoxicity,(2) and isobaric solutions prove less sensitive to positional changes.(3) However studies have shown that duration of analgesia with levobupivacaine to be shorter as compared to bupivacaine which will require early analgesic interventions postoperatively and levobupivacaine is also known to have shorter duration of motor block.(4) Adjuvants have been used along with local anaesthestics to prolong the duration of analgesia. Opioids are the time tested group of drugs used since many years for this purpose and have been proved in this regard.(5) Another group of drugs evolved recently are α_2 agonists like clonidine and dexmedetomidine which have variety of actions and are known to reduce anaesthetic requirements.(6) They provide pain relief by opioid independent mechanism. Various studies have reported the efficacy and safety of α_2 agonists with local anaesthetics in spinal anaesthesia.(7,8) Dexmedetomidine a newer selective adrenergic agonist, having a relatively high α_2/α_1 selectivity(1620:1) as compared to clonidine (220:1).(1) Very little data is available on the usage of low dose of levobupivacaine.(9,10) Our objective was to evaluate whether adding a small dose of adjuvant to smaller dose of levobupivacaine for spinal anaesthesia in elderly patients provides favourable operating conditions with good haemodynamic stability.

Material and Methods

After approval of Institutional Ethical Committee, 90 patients of age 65 years and above of either sex belonging to American society of Anaesthesiologist physical status(ASA) I/II were selected for this prospective randomized double blind study in a medical college in India for a period of eight months. From these patients Informed written consent was taken. Patients with bleeding disorders, on anticoagulant therapy, cardiac disease, heart blocks, dysarrythmias, altered liver function, hypersensitivity to local anaesthetics or dexmedetomidine/clonidine, and on 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 0.1mg/kg as premedication on previous night. The study solutions were prepared in a five ml syringe which would contain 1.5 ml of levobupivacaine with 0.5 ml of normal saline or 0.5 ml of adjuvant drugs. 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. The anaesthesia administrator, outcome assessors, and the patient were blinded to the allocation. On arrival to the operation theater all patients were connected to pulse oximeter, electrocardiogram and noninvasive blood pressure monitoring and the patients were preloaded with 500ml of Ringers lactate solution via an 18 gauge i.v. cannula in the dorsum of the hand. Patients were randomized by computer generated random number sequence and sealed envelope technique into three groups: Group-LS, Group- LC and Group- LD of 30 each.

Group LS: received 1.5cc of 0.5% isobaric levobupivacaine with 0.5cc of normal saline.

Group LC: received 1.5cc of 0.5% isobaric levobupivacaine with 30µg of clonidine (150 µg clonidine ampoule, diluted to 2.5cc with normal saline, in that 0.5 cc taken)

Group LD: received with 1.5cc of 0.5% isobaric levobupivacaine with 5µg of dexmedetomidine.(50µg dexmedetomidine ampoule, diluted to 5cc with normal saline, in that 0.5cc taken)

Under strict aseptic precautions subarachnoid block was performed by 25G Quincke Babcock spinal needle in the L3-L4 interspace in lateral position. The loaded drug was injected over 10-15 seconds following free flow of cerebrospinal fluid (CSF). Zero time is taken as the time at which injection was completed and all parameters were measured from this point. Patients were put in supine position after the block and data were recorded.

Primary objectives were onset of sensory block to L1 dermatomal level, onset of complete motor block, duration of two segments regression from maximum block height, sensory regression to S_1 dermatome, duration of complete motor recovery and haemodynamic parameters and secondary objectives were to see for side effects if any.

Time to reach L1 level block and highest level of sensory block were tested by pin prick method using 25G hypodermic needle in midclavicular line bilaterally every five minutes for 20 minutes after the injection. The duration of sensory block was measured every ten minutes to know the time of two segment regression and regression to S_1 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. Patients were removed from the study if block failed and general anaethesia was required. Basal haemodynamic parameters were recorded just before giving spinal anaesthesia and further readings are made at every five minute interval for one and half hour. Post operatively haemodynamics were monitored every 15 minutes for one hour and once in half an hour for another one hour. Hypotention 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.

The level of sedation was evaluated intraoperatively and post operatively every 15 minutes using Ramsey level of sedation scale.

1. Patient anxious, agitated, or restless;
2. Patient cooperative, oriented, and tranquil alert;
3. Patient responds to commands;
4. Asleep, but with brisk response to light glabellar tap or loud auditory stimulus;
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus.
6. Asleep, no response.

The incidence of any adverse effects such as hypotension, bradycardia, shivering, nausea, vomiting, respiratory depression and ECG changes were noted.

Post-operatively the two segment sensory block regression, regression to S1 dermatomal level, and motor block recovery to modified Bromage score of zero were assessed for every ten minutes.

Statistical analysis: Sample size estimation was based on an α= 0.05 and a power of 80%, 23 patients were required per group to detect a 20-minute difference in the mean time. We decided to include 30 patients per group to allow for possible drop-out. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). 5% level of significance was considered.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Tukey test (Post-hoc ANOVA) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

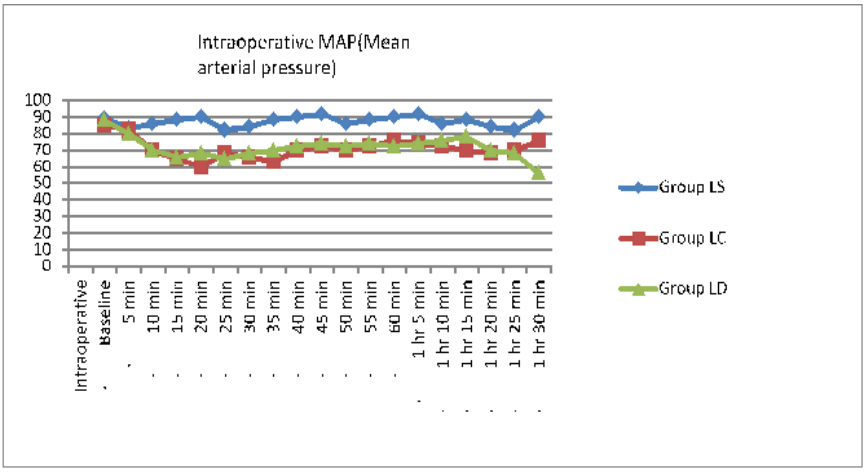
Results

The demographic data in all the three groups were comparable in terms of age, gender, weight, height and

duration of surgery (Table 1). There was no dropout of patients in the study.

Table 1: Demographic data

	Group LS (n =30)	Group LC (n=30)	Group LD (n =30)	P value
Age(years)	70.97±5.54	72.87±7.29	69.87±4.08	0.493
Sex (M:F)	15:15	15:15	15:15	1.000
Weight(kilograms)	55.80±7.40	58.70±6.74	58.43±9.49	0.372
Height(cms)	157±1.3	156±1.7	162±1.5	0.665
Duration of surgery(mins)	96.68±25.21	99.44±38.11	94.67±36.10	0.07



Group LD had demonstrated a shorter onset of sensory block (time to reach L1), a longer time to reach regression of 2 sensory dermatomal level from maximum height attained and longer time to reach sensory regresssion to S1 dermatome when compared to Group-LC and Group-LS. The maximum sensory height of subarachnoid block is shown in Table 2.

Table 2: Max sensory height in three groups of patients studied

Max sensory height	Group LS		Group LC		Group LD	
	No	%	No	%	No	%
T10	6	20.0	7	23.33	11	36.66
T12	12	40.0	17	56.66	15	50
L1	12	40.0	6	20	4	13.33
Total	30	100.0	30	100.0	30	100.0

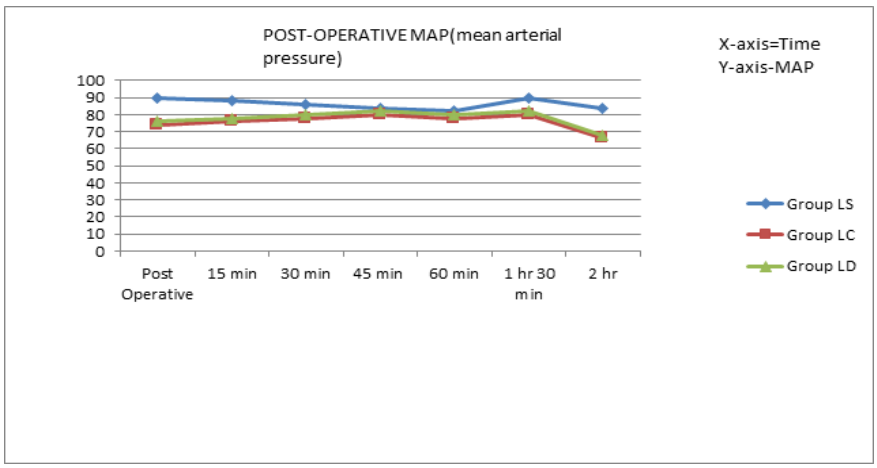
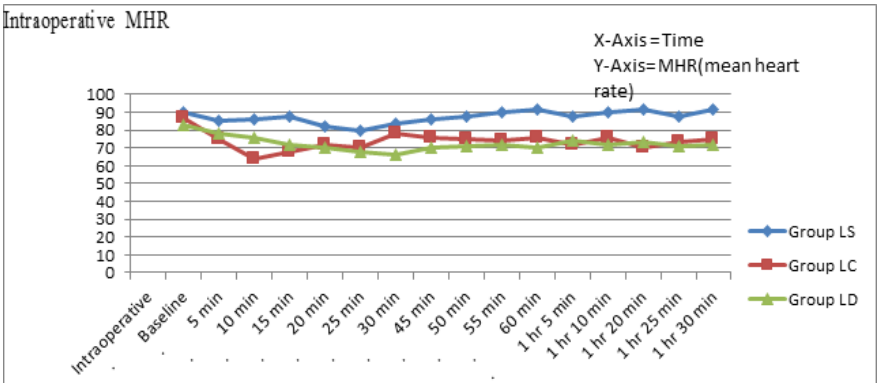


Table 3: Comparison of study variables in three groups of patients studied

Variables	Group LS	Group LC	Group LD	P value
Time of onset of sensory block in minutes(L 1)	2.48±0.44	1.99±0.38	1.03±0.39	0.000
Time to reach highest level of sensory block in minutes	13.37±3.18	12.42±1.72	11.42±2.61	0.016
Time to obtain complete motor blockade[Bromage 3]in minutes	14.53±3.86	13.70±2.85	13.38±3.33	0.398
Time to two segment regression of sensory block in minutes	85.13±9.97	113.00±8.20	127.67±10.03	0.000
Time to sensory regression to S1 dermatome in minutes	218.8±12.74	324.27±11.05	350.40±18.54	0.000
Time to motor block regression to Bromage 0	197.47±14.74	283.37±15.37	331.87±19.52	0.000

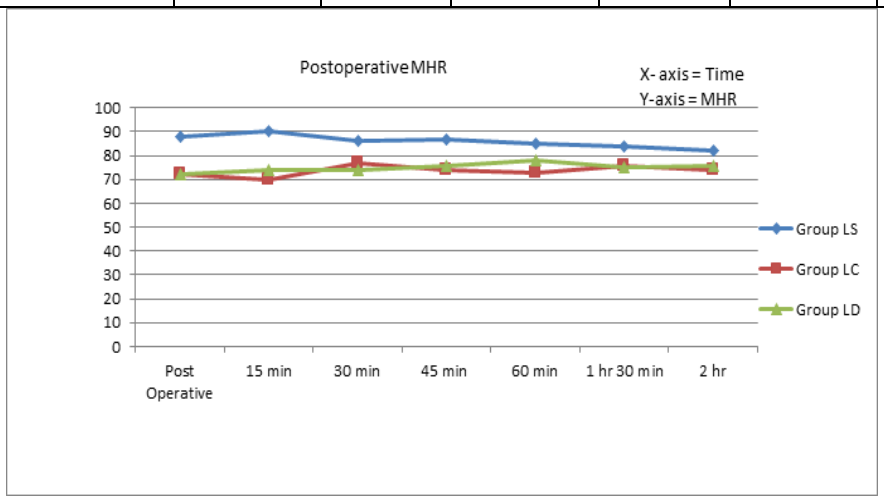


Onset of sensory and motor block was faster in Group-LD compared to Group- LS and Group-LC (Table 3 & 4). Duration of sensory motor block was significant between groups (P<0.001). Dexmedetomidine (Group LD) had a significantly prolonged duration of sensory and motor block when compared with clonidine(Group LC)(Table 3 & 4).

Table 4: Pair-wise comparison of study variables in three groups of patients studied

Variables	Group LS-Group LC		Group LS-Group LD		Group LC-Group LD	
	Difference	P value	Difference	P value	Difference	P value
Time of onset of sensory block in minutes(L1)	0.493	<0.001**	1.450	<0.001**	0.957	<0.001**
Time to reach highest level of sensory block in minutes	0.950	0.330	1.950	0.012*	1.000	0.330
Time to obtain complete motor blockade[Bromage3]in minutes	0.833	0.606	1.150	0.387	0.317	0.606
Time to two segment regression of sensory block in minutes	-27.867	<0.001**	-42.533	<0.001**	-14.667	<0.001**
Time to sensory regression to S1 dermatome in minutes	-105.467	<0.001**	-131.600	<0.001**	-26.133	<0.001**
Time to motor block	-85.900	<0.001**	-134.400	<0.001**	-48.500	<0.001**

regression to Bromage 0						



Ramsay sedation score was shown in (Table 5)
Incidence of hypotension, bradycardia, nausea and vomiting were comparable between three groups(Table 6).

Table 5: Ramsay sedation score

Score	1	2	3	4	5	6
Group LS(no of patients)	4	26	-	-	-	-
Group LC(no of patients)	-	26	4	-	-	-
Group LD(no of patients)	-	23	7	-	-	-

Table 6: Adverse events in three groups of patients studied

Adverse events	Group LS (n=30)		Group LC (n=30)		Group LD (n=30)		P value
	No	%	No	%	No	%	
Hypotension	1	3.3	1	3.3	1	3.3	1.000
Bradycardia	2	6.7	2	6.7	1	3.3	1.000
Nausea	1	3.3	2	6.7	1	3.3	1.000
Vomiting	1	3.3	1	3.3	0	0.0	1.000

Discussion

The primary end-point of this study was 5 μg of intrathecal dexmedetomidine caused rapid onset of sensory block to L1 dermatomal level, with prolonged two segments regression from maximum block height, and prolonged sensory regression to S_1 dermatome, compared to the clonidine and saline groups for low-dose levobupivacaine spinal anesthesia Intrathecal dexmedetomidine also prolonged duration of complete motor block. Our study was in accordance with other studies.[1,11]

In the present study we have included elderly patients with fracture of lower limb. These elderly patients are more prone for intra and postoperative adverse events particularly ischemia, anaemia which may lead to secondary complications like myocardial infarction,chronic renal failure or death.[12] This has made us to select more cardiostable drug for spinal anaesthesia. Studies done by Nirmala et al[13] and Monica et al[10] had showed isobaric levobupivacaine to have delayed onset of sensory as well as motor block and also shorter duration of analgesia compared to bupivacaine. Additives have proved beyond doubt in prolonging the duration with superior quality of anaesthesia and post-operative analgesia with relatively small doses of individual drugs with less requirement of post-operative analgesia.

In our study, levobupivacaine 7.5mg was used intrathecally for lower limb surgeries as an alternative to bupivacaine. Dexmedetomidine and clonidine has been used effectively in many studies as adjuvants to hyperbaric bupivacaine,[14] ropivacaine[15] and levobupivacaine.[11] Our study has focused on the comparison between α_2 agonists dexmedetomidine and clonidine as intrathecal adjuvants to low dose of isobaric 0.5% levobupivacaine. In the present study, we selected a intrathecal dose of dexmedetomidine of 5 µg and clonidine of 30µg. Studies done by Halder et al[16] using various doses of dexmedetomidine had showed incidence of bradycardia to be less with 5 µg compared to 10 µg. Reports of varying doses of clonidine with bupivacaine have suggested, 1mcg/kg of clonidine

increases the duration of block by two-fold compared to plain isobaric bupivacaine and is not associated with haemodynamic or respiratory alterations. Increasing dosage to 2 mcg/kg increased incidence of side effects with a similar duration of block.[17]

Local anaesthetics and α_2 adrenergic agonist dexmedetomidine both have different mechanism of action. While the action of local anaesthetics is by blocking sodium channels, α_2 adrenergic agonists act by binding to presynaptic C fibres and to postsynaptic dorsal horn neurons. This reduces the release of C fibre transmitters and causes hyperpolarisation of post synaptic dorsal horn neurons.[1] This additive or synergistic effect explains the prolongation of sensory block when α adrenergic agonist is added to spinal anaesthesia. 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. Prolonged duration of analgesia seen with dexmedetomidine compared to clonidine is attributed to dexmedetomidine being eight to ten times more selective to α_2-adrenoreceptor especially for α_{2A} and α_{2B} subtype of this receptor.[18]

Greater vasoconstrictive action is seen at all concentrations of levobupivacaine compared to bupivacaine. This explains the lower incidence of haemodynamic effects with levobupivacaine.[19] Haemodynamic stability was seen in all the three groups. In plain levobupivacaine group, the low dose of the drug did not cause much sympathetic blockade and addition of low dose of adjuvants did not show any significant haemodynamic variability. According to our investigations we concluded that clonidine 30µg or dexmedetomidine 5µg did not add to the hypotension caused due to sympathetic block by levobupivacaine. None of the patients in the levobupivacaine had a sedation score of more than 2. In dexmedetomidine and clonidine group patients had a sedation score of either 2 or 3 which correlates with other studies demonstrating that low dose of intrathecal dexmedetomidine or clonidine will not produce the sedation.

Side effects like shivering, nausea/vomiting were not significant, may be because of small dose of adjuvants used.

Conclusion

We conclude, 7.5mg of 0.5% isobaric levobupivacaine with low dose adjuvants, dexmedetomidine and clonidine in elderly patients shortens the onset of sensory and motor block and prolongs the duration of sensory and motor block with good haemodynamic stability and shows no significant side effects. However intrathecal dexmedetomidine has significantly longer duration of spinal anaesthesia when compared to clonidine.

References

1. Ji Eun Kim, Na Young Kim, Hye Sun Lee, and Hae Keum Kil, Effects of Intrathecal Dexmedetomidine on Low-Dose Bupivacaine Spinal Anesthesia in Elderly Patients Undergoing Transurethral Prostatectomy *Biol. Pharm. Bull.* 36(6):959–965 (2013).
2. Bardsley H, Gristwood R, Baker H et al. Comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol.1998;46:245-9.
3. Goyal A, Shankaranarayan P, Ganapathi P.A randomized clinical study comparing spinal anesthesia with isobaric levobupivacaine with fentanyl and hyperbaric bupivacaine with fentyl in elective cesarean sections. Anesth Essays Res. 2015;9(1):57-62.
4. Gautier P, De Kock M, Huberty L et al. Comparison of the effects of intratecal ropivacaine levobupivacaine and bupivacaine for caesarean section. B. Jr. Anaesth.2003;91(5)684-9.
5. Akan B, Yagan O, Bilal B et al. Comparison of levobupivacaine alone and in combination with fentanyl and sufentail in patients undergoing transurethral resection of the prostate. J Res Med Sci.2013;18(5)378-82.
6. Khan Z P, Ferguson CN, Jones RM. α2 and imidazoline receptor agonists: Their pharmacology and therapeutic role. Anaesthesia. 1999;54:146-65.
7. Basani AS, Ahmed HA. Dexmedetomidine as supplement to low dose Levobupivacaine spinal anesthesia for knee arthroscopy. Eguptia J anesthesia 2014;30(2):149-53.
8. Kanazi GE, Aouad MT, Jabbour-Khoury SI et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesth Scand 2006;50:222-7.
9. Girgin NK, Guebet A, Turker G et al. The combination of low-dose levobupivacaine and fentanyl for spinal anaesthesia in ambulatory inguinal herniorrhaphy. J Int Med Res.2008;36(6):1287-92.
10. Vellosillo MR, Garcia Medina JJ, Pinazo-Duran MD, Cotaina AA. Doses and effects of levobupivacaine and bupivacaine forspinal anaesthesia. Br. J. Anaesth. 2014;113(3):521-522.
11. Kanvee V, Rina G, Shruti S et al. A Comparative Evaluation of Dexmedetomidine and Clonidine as an Adjunct with Intrathecal Inj. Levobupivacaine in Spinal Anaesthesia. J Res Med in Sci 2015;3(1) Res Med Den Sci 2015;3(1):12-6.
12. Rosa Herrera R, De Andrés J, Estan L et al, Hemodynamic impact of isobaric levobupivacaine versus hyperbaric bupivacaine for subarachnoid anesthesia in patients aged 65 and older undergoing hip surgery. BMC Anesthesiology. 2014;14:97.
13. Dr Nirmala BC, Dr Sabarpathy S, Dr Vijayan M, Dr Mitesh F. Comparative study of isobaric bupivacaine and isobaric levobupivacaine in spinal anaesthesia. International Journal of Current Research. 2015:7(6):16955-58.
14. Sarma J, Narayana PS, Shivakumar MC. A comparative study of intrathecal clonidine and dexmedetomidine on characteristics of bupivacaine spinal block for lower limb surgeries. Anesth Essays Res.2015;9(2):192-207.
15. Srivastava S, Yadav U, Verma R et al. A comparative clinical study of intrathecal ropivacaine and ropivacaine – clonidine combination for lower limb orthopaedic surgeries. Int J Pharm Sci Res. 2016;7(3):1292-97.
16. Halder S, Das A, Mandal D et al. Effect of different doses of dexmedetomidine as adjuvant in bupivacaine induced subarachnoid block for traumatized lower limb orthopaedic surgery: A prospective double blinded and

randomixes controlled study. J clin Diagn Res.2014;8(11)GC01-6.
17. Rochette A, Raux O, Troncin R, Dadure C et al. Clonidine prolongs spinal anesthesia in newborns: A prospective dose-ranging study. Anesth Analg 2004;98:56-9.
18. Feld JM, Hoffman WE, Stechert MM et al. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth 2006;18:24-8.
19. Burke D, Mackenzie M, Newton D: A comparison of vasoactivity between levobupivacaine and bupivacaine. Br J Anaesth. 1998,81:631-63.