Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; (Part - II) 6(1): 241-248
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.34

A Randomised Prospective Double Blinded Study of Intrathecal Levobupivacaine with Fentanyl Verses Clonidine for Infraumblical Surgeries

Greeshma N Murdeshwar[1], HG Manjunath[2], Somashekara SP[3]

[1]Assisstant Professor [2]Professor and Head [3]Post Graduate Student, Department of Anaesthesia, Mysore Medical College And Research Institute, Mysore, Karnataka 570001, India.

Abstract

Background and aims: Subarachnoid block can be performed with many local anaesthetic agents. Besides hyperbaric bupivacaine even isobaric levobupivacaine and ropivacaine can also be used with minimal cardiotoxicity. Adjuvants like opiods and alpha-2 agonist prolongs the duration of levobupivacaine action. The aim of the present study is to compare fentanyl and clonidine effect used as adjuvants to levobupivacaine with respect to onset of sensory and motor blockade; maximum level attained and the required for the same; duration of blockade and post operative analgesia. *Materials and Methods:* After ethical committee approval, 80 patients posted for infraumblical surgeries divided into two groups. Group LF received 15 mg of levobpivacaine with 25µg fentanyl whereas group LC received 15 mg of levobupivacaine with 30µg clonidine. The volume of solution was 3.5 ml in both groups. Hemodynamic, sensory and motor characteristics were monitored. *Results:* Onset of sensory and motor blockade as well as regression of both was faster with fentanyl than clonidine. There was slight fall in heart rate and mean arterial pressure in both the groups after intrathecal drugs but it was more with clonidine. Bradycardia and hypotension was noted more with clonidine than fentanyl which was easily manageable. Though the onset was delayed, sensory, motor and analgesic effect was prolonged with clonidine. *Conclusion*: Levobpiacaine can be safely used for spinal anaesthesia in infraumblical surgeries. Adding fentanyl causes early onset of action whereas clonidine has more prolonged action.

Keywords: Levobupivacaine; fentanyl; clonidine; spinal anaesthesia.

How to cite this article:

Greeshma N Murdeshwar, HG Manjunath, Somashekara SP. A Randomised Prospective Double Blinded Study of Intrathecal Levobupivacaine with Fentanyl Verses Clonidine for Infraumblical Surgeries. Indian J Anesth Analg. 2019;6(1):241-48.

Introduction

Spinal anaesthesia is the choice for infraumblical surgeries which includes lower abdominal, perineal and lower limb surgeries. It is a simple, cost effective technique having rapid onset of action with reliable sensory and motor blockade [1].

Levobupivacaine is a pure S-enantiomer of racemic bupivacaine (S-1nbutyl-2 piperidyl formo 2′6′ xylidide hydrochloride). It is a newer long acting local anaesthetic agent with minimal cardiovascular and central nervous system toxicity [2,3]. It is widely used in recent days for spinal anaesthesia and isobaric levobupivacaine alone has short lasting effect [4,5]. Addition of low dose adjuvants with local anaesthetic agents intrathecally improves the block quality and its duration [6]. The

Corresponding Author: HG Manjunath, Professor and Head, Department of Anaesthesia, Mysore Medical College and Research Institute, Mysore, Karnataka 570001, India.

E-mail: drhgmanjunathanes@gmail.com

Received on 16.11.2018, **Accepted on** 13.12.2018

adjuvants commonly used are opiods. Fentanyl has low risk of respiratory depression with rapid onset of action [7]. Intrathecal clonidine with alpha-2 agonistic activity is also an adjuvant potentiating the action of intrathecal drugs [8]. It reduces shivering and devoid of side effects associated with opiods like pruritis, nausea and vomiting, respiratory depression and urinary retention.

There are limited studies showing the difference in the effects of adjuvants like fentanyl verses clonidine with isobaric levobupivacaine for infraumblical surgeries. This triggered us to do the study to compare the potency of anaesthesia, hemodynamics and side effects between these two adjuvants in addition to isobaric levobupivacaine.

The primary objective of the study was to compare onset of sensory and motor blockade; maximum level attained and time required for the same; total duration of sensory and motor blockade and two segment sensory regressions time; postoperative analgesic requirement and hemodynamic effects. The secondary objective was to assess for any side effects like shivering, pruritus, nausea and vomiting, respiratory depression and sedation.

Materials and Methods

It is a prospective, randomised and double blinded study. After institutional ethical and scientific committee approval, 80 patients scheduled for the elective infra umbilical surgeries at our hospital were selected. Informed written consent was taken from the patients after the procedure was explained to them. Inclusion criteria were adult patients of either sex, aged between 18-55 years belonging to ASA class I or II with height between 154 to 174 centimetres. Exclusion criteria were patients belonging to ASA class III, IV, V and with Body Mass Index > 30 kg/m^2; or with absolute contraindications for spinal anaesthesia like raised intracranial pressure, severe hypovolumia, bleeding diathesis, local infection and history of allergy to any of the drugs.

The data were collected in a presetperforma meeting the objectives of this study. They were made aware of visual analogue score (VAS) scoring system required post operatively for pain assessment. They were randomly divided using sealed opaque envelope technique into 2 groups of 40 patients each. Group LF and Group LC. Group LF received 15 mg of 0.5% isobaric levobupivacaine with 25 µg of fentanyl whereas group LC received 15 mg of 0.5% isobaric levobupivacaine with 30 µg clonidine.

After preoperative assessment patients were kept fasting overnight. Patients were premedicated on the night before surgery with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg. On morning of surgery intravenous (IV) line obtained with 18 guage cannula and preloaded with ringer lactate 10 ml/kg half an hour before anaesthesia. The monitoring was done using multiparameter monitor having pulse oximetry, electrocardiograph (ECG) and non invasive blood pressure (NIBP). Baseline pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiography (ECG) and arterial oxygen saturation (SpO_2) were noted. Patients were placed in lateral decubitus position with operative side downwards. Under aseptic precautions subarachnoid block was performed at level of L3-L4 through a midline approach using 25G Quincke's spinal needle. In both the groups the volume was kept constant up to 3.5ml by adding saline. Study drug was loaded by the senior anaesthesiologist who was not involved in the study. All spinal blockades was performed by the another anaesthesiologist, who was also the observer. Thus both patient and observer were blinded for the study. During injection operating table was kept flat. Patient was turned to supine posture immediately. Sensory blockade was tested using pinprick method with a blunt tipped 27G hypodermic needle at midclavicular line every 30 seconds for first 2 minutes, every minute for next 5 minutes and every 5 minutes for next 15 minutes and every 10 minutes for next 30 minutes and every 15 minutes till the end of surgery and there after every 30 minutes until sensory block is resolved. Quality of motor blockade was assessed by modified Bromage scale (MBS): 0 – patient is able to move the hip, knee and ankle; 1- patient is unable to move the hip but is able to move the knee and ankle; 2 – patient is unable to move the hip and knee but is able to move the ankle; 3- patient is unable to move the hip, knee and ankle and 4- patient is unable to move toes.

The following time were noted from the point of drug injection:

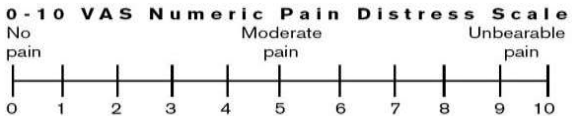
1. Onset of sensory blockade when the sensory loss was up to the T8 dermatome. Surgery was allowed to start when this level was attained. Onset of motor blockade which was the time taken for MBS to be one.
2. Maximum level of sensory and motor blockade attained and time taken for it.
3. Duration of sensory blockade which was time taken for sensory regression to L1 and

duration of motor blockade which was the time taken for MBS to be 1.

4. Two segments sensory regression time which is the duration between highest sensory level attained to two segment regression.
5. Total duration of analgesia was upto the period where patient had VAS of 4. Haemodynamics were monitored via PR, SBP, DBP, MAP, ECG and oxygenation monitored via SpO_2. If MAP decreases more than 30% of basal it was considered hypotension managed with IV ephedrine 6 mg bolus doseand fluid bolus at the rate of 2-3 ml/kg/hour. Heart rate decreasing to less than 50 was considered as bradycardia and it was treated with IV atropine 0.6 mg. If patient complained of pain regional was converted to general anaesthesia and they were excluded from the study. Total duration of surgery and side effects like nausea and vomiting, shivering, pruritus were also noted. Sedation was assessed using Ramsay's sedation score (RSS) every half an hourly after spinal anaesthesia. RSS is as follows: 1) anxious, agitated or restless; 2) co-operative, oriented and tranquil; 3) responds to commands; 4) asleep but has a brisk response to light glabellar tap or loud auditory stimulus; 5) asleep but has a sluggish response to light glabellar tap or loud auditory stimulus; 6) asleep no response.

Post operatively patient shifted to post anaesthesia care unit (PACU). Here hemodynamic, sensory and motor level and pain assessment via VAS (0-10) was done. Rescue analgesic IV diclofenac 75 mg was given if VAS score was 4 or above.

Statistical analysis was done using SPSS 19 version. Data are presented as mean and standard deviation. p value of < 0.05 was considered as significant and < 0.001 highly significant. Paired and unpaired t-test and analysis of variance was used for statistical calculations. Numerical variables were compared using chi-square test for nonparametric data and Student-t test for parametric data.



Results

Both LF and LC groups were comparable with respect to their demographic characteristics; duration of surgery and mean of baseline HR and BP as shown in Table 1 and type of surgeries as shown in Table 2.

Sensory onset time was significantly faster with fentanyl than clonidine. Average maximum sensory level attained in both the groups was 6.3 in group LF and 5.35 in group LC. Time to attend this level was statistically significantly shorter with fentanyl than clonidine. TSSR and SRL1 were also statistically significantly faster with fentanyl. This means the regression of spinal effect with fentanyl as additive was faster than clonidine as additive. Onset of motor blockade and time

Table 1: Demographic; surgical characteristics and mean of baseline heart rate and mean arterial pressure

Sl. No	Characters	Group LF	Group LC	p Value
1.	Age	37.37±10.65	36.15±10.8	0.611
2.	Sex (M:f)	31:9 (77.5% : 22.5%)	34:6 (85% :15%)	0.390
3.	American Society of Anesthesia Grade (I:ii)	22:18 (55% : 45%)	25:15 (62.5% : 37.5%)	0.496
4.	Body Mass I Ndex	22.66±1.53	22.91±1.22	0,423
5.	Duration of Surgery (Min)	134.37±33.28	126.05±28.88	0.236
6.	Mean Baseline Heart Rate	75.67±12.71	78.72±10.51	0.2
7.	Mean Baseline Of Mean Arterial Pressure	100.58±10.02	99.15±8.66	0.5

Table 2: Type of surgeries

Sl. No	Type of Surgeries	Group LF	Group LC	p Value
1.	Lower Abdomen	13	15	0.639
2.	Orthopedic Surgery	17	14	0.491
3.	Genital Surgeries	7	6	0.761
4.	Varicose Veins	3	5	0.711

Table 3: Sensory and motor characteristics in both the groups.

Sl. No	Characters	Group LF	Group LC	P Value
1.	Time of onset of sensory blockade -TOSB in seconds (minutes)	155.62 ±18.26 (2.59 min)	184.75±21.89 (3.07 min)	<0.005
2.	Maximum level of sensory blockade – MLSB	6.3±1.62	5.35±1.51	0.1662
3.	Time taken for maximum level of sensory blockade - TMLSB(min)	4.73±1.09	6.96±1.15	<0.005
4.	Two segment sensory regression-TSSR(min)	94.75±11.23	107.00±11.39	<0.005
5.	Sensory regression to L1-SRL1(min)	303.25±31.91	324.12±25.84	0.002
6.	Time of onset of motor blockade-TOMB(seconds)	198.62±23.12 (3.31 min)	245.00±36.37 (4.08)	<0.005
7.	Maximum level of motor blockade –MLMB	3.17	3.25	0.598
8.	Time taken for maximum level of motor blockade -TMLMB(min)	6.66±1.21	7.62±1.43	0.0354
9.	Total duration of motor blockade - TDMB(min)	287.12±20.7	298.25±21.03	<0.005

Table 4: Complications and postoperative analgesia in both groups.

Sl. No	Complications	Group LF	Group LC	P- Value
1.	Bradycardia	2 (5%)	5 (12.5%)	0.235
2.	Hypotension	3 (7.5%)	5 (12.5%)	0.456
3.	Nausea	1 (2.5%)	0	0.314
4.	Vomiting	2 (5%)	0	0.152
5.	Pruritis	3 (7.5%)	0	0.077
6.	Shivering	0	0	-
7.	No of Patients with Ramsay Sedation Score >2 at 90 Minutes	2 (5%)	8 (20%)	<0.005
8.	Postoperative Analgesia Duration (Minutes)	318.00±78.21	393.37±81.91	<0.005

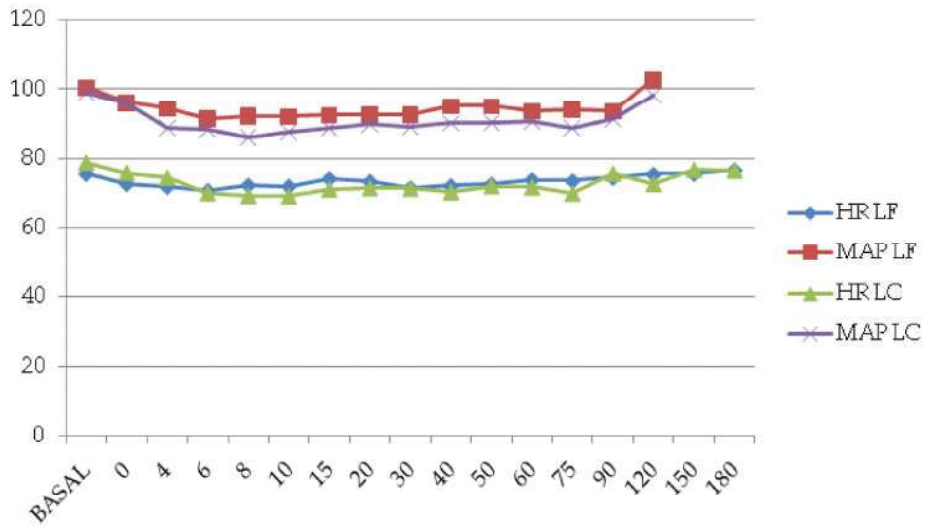


Fig. 1: Variation in HR and MAP after intrathecal block in both the groups.

taken for maximum motor blockade were earlier with fentanyl than clonidine. Average maximum motor blockade was around B3 in both the groups. Duration of motor blockade was lower in both the groups than sensory blockade (which is SRL1) but it was prolonged with clonidine than fentanyl as shown in Table 3.

There was fall in HR and MAP in both the groups after spinal anaesthesia. But there was statistically significant fall in HR and MAP with LC group than LF group during the first 15-30 minutes which was eventually managed as shown in figure-1. Bradycardia and hypotension was more with clonidine than fentanyl. One patient had nausea, two patients had vomiting and three patients had pruritus with fentanyl. Patients in clonidine group were more sedated than fentanyl after about 90 minutes after intrathecal drug injection administration.

Postoperative analgesia was statistically significantly longer with clonidine than fentanyl as shown in Table 4.

Discussion

There are many adjuvants available along with levobupivacaine agents to increase its potency. Fentanyl used in our study facilitates the afferent sensory blockade by stimulating μ1 and μ2 receptors in the spinal cord [9]. On the other hand clonidine prolongs the blockade by activation of post-synaptic α2 receptor in substantia gelatinosa of spinal cord [10].

In Glaser et al. study, who compared isobaric levobpivacaine 3.5 ml with isobaric bupivacaine 3.5 ml in hip replacement surgeries, onset of sensory blockade, was 11±6 minutes [11]. Compared to this the onset time of sensory blockade was shorter in our study. Though the volume of the intrathecal drug was similar as in our study, the adjuvants we used caused the shorter onset time of sensory blockade in our study. In Agarwal A P et al. sensory onset time was 2.62±0.95 minutes and motor onset time was 3.53±0.17 with intrathecal 3 ml levobupivacaine and 25 μg fentanyl in lower abdomen and lower limb surgeries [12]. In Bhavani V et al. sensory onset time was 6.03±1.923 minutes and motor onset time was 7.48±2.2 minutes with intrathecal 3 ml levobupivacaine and 30 μg clonidine in vaginal hysterectomy patients [13]. In our study sensory onset time was 155.62 seconds (2.59 minutes) and the motor onset time was 198.62 seconds (3.31 minutes) with isobaric levobupivacaine 3.5 ml combined with 25 μg fentanyl whereas sensory onset time was 184.75 seconds (3.07 minutes) and the motor onset time was 245.00 seconds (4.08 minutes)with isobaric levobupivacaine 3.5 ml combined with 30 μg clonidine in our study The dosage of intrathecal drug used in Agarwal AP et al. and Bhavani V et al. study were similar to our study and the sensory onset and motor onset time in both these studies are consistent to our study. In our study sensory onset and motor onset were statistically significantly faster with the adjuvant fentanyl than clonidine.

Glaser et al. also had highest sensory level at T8 level [11]. In our study the maximum sensory level attained with isobaric levobupivacaine was at an average of 6.3 when combined with fentanyl and 5.35 when combined with clonidine. In Filiz Karaca et al. and Nesrin Bozdogan et al. study the effect of isobaric levobupivacaine with fentanyl was observed in patients undergoing caesarean section [14,15]. Both the studies had highest sensory level of T4 level with levobupivacaine. The gravid uterus and raised abdominal pressure might have caused higher sensory level in the above studies. Camorcia M et al. who compared relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine reported intermediate motor blocking effects of levobupivacaine in his study [16]. In our study the average maximum motor block was MBS-B3 which correlates with the above study asthe complete motor blockade of MBS-B4 was hardly achieved with either of the group which signifies that adjuvant might have no much effect on levobupivacaine to enhance the motor blockade.

Agarwal archana et al. compared the effect of intrathecal fentanyl 15 μg with clonidine 30 μg on 2.5 ml of 0.5% isobaric levobupivacaine in the patients undergoing lower limb surgery [17]. Time to attend the peak sensory effect was 9.67±1.18 minutes with fentanyl and it was 9.70±1.32 minutes with clonidine. Though not statistically significant it was relatively lower with fentanyl. In our study, the time to attend maximum sensory blockade was 4.73 minutes with fentanyl and 6.96 minutes with clonidine. It was statistically significantly lower with fentanyl might be because of higher dose of fentanyl of 25 μg which we used. The delayed onset of maximum sensory effect with clonidine than fentanyl is also consistent with other studies where these two adjuvants were compared with different local anaesthetic agents like: Chabbra Anita R et al. assessed the effect of 60 μg clonidine verses 25 μg fentanylcombined with intrathecal 3 ml of isobaric 0.5% ropivacaine in lower limb surgeries. Here time to attend peak sensory level

was 6.86±3.73 minutes with fentanyl and 8.61±7.18 minutes with clonidine [18]. Sharan Radhe et al. compared the effect of 30 μg of clonidine verses 25 μg of fentanyl with 2.5 ml of 0.75% ropivacaine in lower abdomen surgeries. Here time to attend peak sensory level was 9.64±1.67 minutes with fentanyl and 9.68±1.78 minutes with clonidine [19]. Bajwa et al. compared 50 μg clonidine verses 25 μg fentanyl with 2.5 ml 0.5% hyperbaric bupivacaine in lower abdomen surgeries. Time for peak sensory onset was 7.34±0.96 minutes with fentanyl and 7.56±1.78 with clonidine [6]. The alteration in the values is because of different doses of adjuvants and the difference in local anaesthetic agents used.

In Nesrin Bozdogan et al. study where isobaric levobupivacaine was given with fentanyl the TSSR was 96.48±24.46 minutes and in Kuikarni J et al. study with isobaric levobupivacaine combined with clonidine the TSSR was 157.83±3.49 minutes [15,20]. Both the above mentioned study were done on patients undergoing lower segment caesarean section. This shows the faster regression action of fentanyl than clonidine. The observation in these two studies is in accordance to our study where we noticed TSSR of 94.75±11.23 minutes in fentanyl whereas it was 107.00±11.39 minutes with clonidine as additive to isobaric levobupivacaine. The difference was highly significant statistically.

In our study total duration of sensory blockade was 303.25±31.91 minutes and motor blockade was 287.12±20.7 minutes in fentanyl group. Total duration of sensory blockade was 324.12±25.84 minutes and motor blockade was 298.25±21.03 minutes in clonidine group. In Agarwal et al. study total duration of sensory blockade was 241.57±1.87 minutes and motor blockade was 187.48±12.12 minutes with 15 mg isobaric levobupivacaine and 25 μg fentanyl [12]. In Bhavani V et al. study total duration of sensory blockade was 288.87±18.651 minutes and motor blockade was 190.97±17.38 minutes with 15 mg isobaric levobupivacaine and 30 μg clonidine [13]. This is in accordance to our study as the drug volume and quantity in the above two studies is resembling our study. This suggests that clonidine has longer sensory and motor blockade effect compared to fentanyl as an adjuvant to isobaric levobupivacaine.

Duration of postoperative analgesia was 249.59±10.40 minutes in Agarwal A P et al. study and 288±18.6 minutes in Bhavani V et al. study with fentanyl and clonidine respectively [12,13]. Clonidine have more tendency to prolong the analgesia. This is also in accordance with Singh Baljit Bajwa et al. and Chabbra Anita et al. study who used both these adjuvants with bupivacaine and ropivacaine respectively [6,18]. Even in Agarwal Archana et al. study where both these adjuvants were used with isobaric levobupivacaine there was prolonged postoperative analgesia with clonidine than fentanyl in lower limb surgeries. Likewise in our study postoperative analgesia duration was highly statistically significantly prolonged with clonidine. It was 318.00±78.21 minutes with fentanyl and 393.37±81.91 minutes with clonidine as adjuvant to isobaric levobupivacaine. From the above mentioned studies it can be derived that clonidine hashigher potency than fentanyl to prolong the analgesic duration.

There was fall in BP in both the groups; more in the group LC from baseline immediately after intrathecal drug administration. This is similar to Glaser et al. study, which used volume of 3.5 ml of levobupivacaine for hip surgeries [11]. Around 5% patients in group LF and 12.5% patients in group LC had hypotension and around 7.5% of patients in group LF and 12.5% of patients in group LC bradycardia which was managed. Though not statistically significant these haemodynamic changes were, more with clonidine may be because of presynaptic noradrenaline inhibition and its action on atrioventricular node after systemic absorption [21].

Patra et al. reported 46% of patients had pruritus with fentanyl [22]. Similarly other investigators have also reported pruritis with fentanyl. Erkan et al. reported pruritus in around 25% of transurethral resection of prostate patients anaesthesised with intrathecal levobupivacaine and clonidine [23]. Liu S et al. also noticed pruritus with intrathecal fentanyl in his study [24]. In our study 5% of patients developed pruritus. The effect of pruritus was transient and hardly needed treatment. In our study 20% of patients had sedation with clonidine and 5% of patients in fentanyl. None had respiratory depression or fall in saturation. This is due to the action at nucleus cerueleus where hyperpolarisation of excitatory neurons takes place [25]. In Kothari et al. study, where 45 μg clonidine was added to bupivacaine in ceasserean patients there was sedation in 35% to 45% patients [26]. One patient in the fentanyl group had nausea and two patients had vomiting. Incidence of nausea and vomiting were noticed with intrathecal fentanyl in the literature [27].

Conclusion

There are many studies stating that levobupivacaine can be safely used for spinal

anaesthesia in infraumblical surgeries. With the adjuvants adequate level can be attained for lower abdomen and lower limb surgeries. Adding 25 µg fentanyl causes early onset of action whereas 30 µg clonidine to 15 mg isobaric levobupivacaine has more prolonged action. But isobaric levobupivacaine with clonidine is better than levobupivacaine with fentanyl because with clonidine there is longer duration of sensory blockade and postoperative analgesia. But there were more chances of hypotension and bradycardia with clonidine than fentanyl as well as prolonged effect can delay ambulation which can be easily managed. The hemodynamic parameters should be vigilantly monitored with these adjuvants and should be more meticulous when clonidine used.

References

1. Covino BG. Rationale for spinal anesthesia. International Anaesthesiology Clinics. 1989;27:8-12.
2. Bardsley H, Gristwood R, Baker H, et al. A 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. Huang YF, Pryor ME, Mather LE, et al. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. AnesthAnalg. 1998;86:797–804.
4. Girgin NK, Gurbet A, Turker G, Bulut T, Demir S, Kilic N, et al. The combination of low-dose levobupivacaine and fentanyl for spinal anaesthesia in ambulatory inguinal herniorrhaphy. J Int Med Res. 2008;36:1287–92.
5. Akan B, Yagan O, Bilal B, Erdem D, Gogus N. Comparison of levobupivacaine alone and in combination with fentanyl and sufentanil in patients undergoing transurethral resection of the prostate. J Res Med Sci. 2013;18:378–82.
6. Bajwa Baljit Singh, Singh Arwinder Pal and Rekhi. Comparison of intrathecal clonidine and fentanyl in hyperbaric bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing lower abdominal surgeries. Saudi J Anaesth. 2017 Jan-Mar;11(1):37–40.
7. Selvaraju KN, Sharma SV. Comparison of forced expiratory spirometric flow changes following intrathecal bupivacaine and bupivacaine with fentanyl. South Afr J AnesthAnalg. 2008;14:33–7.
8. Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth. 1990;15:211–4.
9. Goel S, Bhardwaj N, Grover VK. Intrathecal fentanyl added to intrathecal bupivacaine for day case surgery: A randomized study. Eur J Anaesthesiol. 2003;20:294–7.
10. Shah BB, Joshi SS, Shidhaye RV, Lakhe JN. Comparison of different doses of Clonidine as an adjuvant to intrathecal Bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing caesarean section. Anaesth Pain and Intensive Care. 2012;16(3):266-272.
11. Christian Glaser, Peter Marhofer, Gabriela Zimpfer, Marie T. Heinz, Christian Sitzwohl, Stephan Kapral, and Ingrid Schindler. Levobupivacaine Versus Racemic Bupivacaine for Spinal AnesthesiaAnesthAnalg. 2002;94:194–8.
12. Agarwal A.P, Khan Mehvish, Agarwal Malti, Singh Rampal, Gopal Krishnan, Mitra Subhro. A comparision of intrathecal isobaric 0.5% levobupivacaine with fentanyl and isobaric 0.5% ropivacaine with fentanyl for lower abdomen and lower limb surgeries. A prospective randomized double blind controlled study. Annals of international medical and dental research. 2018;4(3):1-5.
13. Bhavani V, I Joseph Raajesh. Comparison of intrathecal isobaric levobupivacaine, levobupivacaine- clonidine, with hyperbaric bupivacaine as a control for quality of anaesthesia intraoperative hemodynamics and duration of post-operative pain relief in patients undergoing vaginal hysterectomy Indian Journal of Clinical Anaesthesia, 2016;3(2):148-54.
14. Filiz Karaca, Ezgi Erkılıç, Alev Akdıkan, Tülin Gümüş, Orhan Kanbak. Assessment of the effect of Intrathecal low dose levobupivacaine or bupivacaine combined with fentanyl in patients undergoing cesarean section. Journal of anesthesia & clinical research 2014;5(11):1-5.
15. Nesrin Bozdogan Ozyilkan, Aysu Kocum, Mesut Sener, Esra Caliskan, Ebru Tarim, Pinar Ergenoglu, Anis Aribogan. Comparision of intrathecal levobupivacaine combined with sufentanil, fentanyl or placebo for elective caesarean section: A prospective randomized double blind controlled study. Current therapeutic research. 2013;75:64-70.
16. Camorcia M, Capogna G, Berrita C, Columb MO. The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine. AnaesthAnalg. 2007;104(4):904–7.
17. Agarwa Archana, Lakhotia Rajiv, Longwani Somnath, Srivastava Sandeep, Kumar Srivastava Amit and Bogra Jaishri. A comparison of fentanyl and clonidine as adjuvants to intrathecal levobupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing for lower limb surgery. International Journal of Biomedical Research. 2018;09(02):76-80.
18. Chabbra Anita R, Jagtap Sheetal R, Dawoodi Sunny F. Comparison of clonidine versus fentanyl as an adjuvant to intrathecal ropivacaine for major

lower limb surgeries: A randomized double-blind prospective stud. 2013;27(3):170-174.

19. Sharan Radhe, Verma Rajan, Dhawan Akshay, and Kumar Jugal. Comparison of clonidine and fentanyl as adjuvant to ropivacaine in spinal anesthesia in lower abdominal surgeries. Anesth Essays Res. 2016 Sep-Dec;10(3):526–31.
20. Kulkarni Jyoti, Lodha Veena, Patil Tushar and Misal Ullhas Comparison of Levobupivacaine and Clonidine with Bupivacaine and Clonidine in Spinal Anaesthesia for Lower Segment Caesarean. Journal of Dental and Medical Science. 2016 August;15(8): 92-97.
21. Anatassiou E, Karmiri E, Kolotoura A, Apostolaki S, Andreotti V, Chapsa Ch. Low dose intrathecal clonidine to levobupivacaine spinal anaesthesia for total knee arthroplasty. Regional anaesthesia and pain medicine 2003.
22. Patra P, Kapoor MC, Nair TG. Spinal anesthesia with low dose bupivacaine and fentanyl for endoscopic urological surgeries. J Anaesthesiol Clin Pharmacol 2005;21:147-54.
23. Erkan Yavuz Akcaboy, Zeynep Nur Akcaboy,and Nermin Gogus. Low dose levobupivacaine 0.5% with fentanyl in spinal anaesthesia for transurethral resection of prostate surgery J Res Med Sci. 2011 Jan;16(1):68–73.
24. Liu S, Chiu AA, Carpenter RL, Mulroy MF, Allen HW, Neal JM, et al. Fentanyl prolongs lidocaine spinal anaesthesia without prolonging recovery. AnesthAnalg. 1995;80(4):730–4.
25. Chandra Richa, Nanda Harjeet singh, Kumar Abhishek. Comparison of intrathecal Levobupivacaine versus Bupivacaine with Clonidine as adjuvant. International Journal of scientific study. 2014 Oct;2:(7).
26. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth. 2011;5:31–5.
27. Alain Borgeat, Georgios Kkatodramis, Carlo A Schenker. Post operative nausea and vomiting in regional anaethesia: a review. Anaesthesiology. 2003;98:530-47.