

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

V. Bhavani^{1,*}, I Joseph Raajesh²

¹Assistant Professor, ²Professor & Head, Dept. of Anaesthesiology, Indra Gandhi Medical College & Research Institute, Puducherry

***Corresponding Author:**

Email: bhavanivaidyanathan@gmail.com

Abstract

Patients presenting with uterovaginal prolapse for vaginal hysterectomies will usually be in the age group of above 50years. Effective and prolonged post-operative analgesia will be of paramount importance in this group of patients as it is not uncommon to find associated comorbidities such as hypertension, diabetic mellitus and ischaemic heart diseases in these population.

Pain free postoperative period is mandatory in all post-surgical patients. Effective postoperative analgesia not only improves the patient comfort it also reduces the risk of deep vein thrombosis by early ambulation. Historically opioids are the mainstay of drugs used to treat postoperative pain. Drugs such as morphine and fentanyl are used either as additives to local anaesthetics intrathecally or through intravenous route. Although they are effective analgesics, the side effects such as respiratory depression, nausea and vomiting will produce additional discomfort to patients

In this study we compared isobaric Levobupivacaine and isobaric Levobupivacaine with clonidine against hyperbaric Bupivacaine in patients undergoing vaginal hysterectomy. Levobupivacaine is the pure S enantiomer of racemic bupivacaine but it is less toxic to cardio vascular system and central nervous system. Intrathecal clonidine has been extensively evaluated as an alternate to neuraxial opioid for control of pain and it had been proven as a potent analgesic. Though its efficacy with hyperbaric bupivacaine has been confirmed by many trials only very few studies are available which assessed its efficacy with levobupivacaine.

This is a prospective randomized control study, which was carried out in ninety patients who received subarachnoid block for vaginal hysterectomy. Ninety patients were divided into three groups namely Group B, Group LB and Group LC with thirty in each group. Control group (Group B) received 15 mg of hyperbaric bupivacaine plus 0.2ml of 0.9% normal saline, Group LB received 15 mg of isobaric levobupivacaine plus 0.2ml of 0.9% normal saline and Group LC received isobaric Levobupivacaine 15mg along with clonidine 30 micrograms. Onset and duration of sensory and motor blockade were the parameters studied along with perioperative hemodynamic changes.

Keywords: Bupivacaine, Levobupivacaine, Clonidine, Bupivacaine, Spinal anaesthesia

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.innovativepublication.com |
|  | DOI: 10.5958/2394-4994.2016.00031.7 |

Introduction

Subarachnoid block(SAB) is by far the most common type of anaesthetic technique employed for patients undergoing vaginal hysterectomies. Though use of intrathecal hyperbaric bupivacaine in SAB has been extensively studied, either, with or without additives for lower abdominal surgeries, only few studies are available involving isobaric levobupivacaine. Levobupivacaine is being routinely used in obstetric anaesthesia but there are only very limited few studies comparing hyperbaric bupivacaine, with levobupivacaine and clonidine as additive in non-obstetric surgeries. Levobupivacaine is a relatively new long acting local anaesthetic, with pharmacological

activity very similar to that of racemic bupivacaine⁽¹⁾ but minimal cardio and neurotoxicity than the racemic bupivacaine.⁽²⁾ Levobupivacaine can be used for all indications where in the anaesthesiologist needs a long acting local anaesthetic with effective anaesthesia and analgesia for a wide range of clinical indications. and can be considered as a useful alternative to bupivacaine^{(3),(4)}.

Clonidine is an alpha -2 adrenergic agonist which potentiates the action of local anaesthetics when used intrathecally and improves the quality of analgesia^{(5),(6)}. Though the additive effect of clonidine with hyperbaric bupivacaine has been well appreciated, only very few studies are available which looked in to the effectiveness on post-operative analgesia when added with levobupivacaine. This study is aimed to assess the effectiveness of intrathecal levobupivacaine alone as well as with clonidine in providing better peri operative conditions when compared with hyperbaric bupivacaine.

Materials and Methods

This is a prospective, randomized, double-blind study undertaken after getting the approval from Institute

Ethics Committee. All patients belonging to ASA physical status I and II were included for the study and the exclusion criteria were patients belonging to ASA physical status III and above as well as patients who are not willing for regional anaesthesia.

After obtaining informed consent, ninety patients scheduled for vaginal hysterectomy were recruited into the study over a period of two years

The patients were then randomly assigned into three groups namely Group B, Group LB and Group LC using opaque sealed envelope technique. Patients in Group B received 15 mg of hyperbaric bupivacaine plus 0.2ml saline and Group LB received isobaric levobupivacaine 15mg plus 0.2ml saline and group LC received isobaric levobupivacaine 15mg plus Clonidine 30 micrograms intra thecally. Thus all patients received the final volume of 3.2 ml intrathecally.

All patients were started on 18G IV cannula and preloaded with 10ml/kg of Ringer Lactate and were briefed about the methods used for sensory and motor assessments and also about ten point visual analogue scale (VAS). On arrival in the operating room, routine physiological monitoring were applied, including electrocardiogram (ECG), non-invasive blood pressure(NIBP), heart rate (HR), and pulse oximetry(SpO₂) and base line parameters were noted. The study drug was prepared by an Anaesthesiologist who was not a part of the study thus making the anaesthesiologist who administered the drugs and assessed the block was blinded to the combination used. With the patient in lateral position, SAB was achieved at L3-L4 using 25 gauge spinal needle (Becton Dickinson India Pvt Ltd., Quincke type) and immediately the patient was resumed to supine position

During the procedure HR, NIBP, ECG, and SpO₂ were monitored initially every minute for first 5 minutes after the block, then every 5th minute for next 15 minutes, and every tenth minute for next one hour and every 15 minutes till the end of the procedure. Sensory levels were checked bilaterally along the mid clavicular line by pinprick test every minute until desired level of T8 was obtained. Motor block was assessed based on modified Bromage scale as follows.

0. no paralysis, able to flex hips/knees/ankles;
1. able to move knees, unable to raise extended legs
2. able to flex ankles, unable to flex knees;
3. Unable to move any part of the lower limb.

Motor blockade was assessed every minute until Bromage score 3 was achieved.

Surgery was started once the level of sensory block had reached T8.

The onset of adequate sensory block was defined as the achievement of a sensory block level of T8 dermatome. The onset time of motor block was defined as the interval between intrathecal administration and to a Bromage score of 3.

In the postanesthesia care unit, the patients were assessed for the following parameters.

Status of sensory and motor blockade were monitored every 30 min till the complete recovery of both. Status of pain, based on a visual analog scale (VAS) ranging from 0 (no pain) to 10 (maximal pain). All tests (i.e., sensory/motor block and VAS) were performed by a staff not involved in the study.

Duration of sensory block was defined as the interval between intrathecal administrations of the study drug to the point of the VAS score of three.

Duration of motor block was defined as the interval from intrathecal administration to the point in which the Bromage score was back to zero.

Hemodynamic alterations like hypotension and bradycardia or any other post-operative events were also noted and treated accordingly.

Hypotension was defined as a decrease in the systolic blood pressure of more than 30% from the baseline or less than 90 mmHg. It was treated with infusion of 100ml of ringer lactate solution and/or i.v. boluses of mephentermine 5mg. Bradycardia was defined as a heart rate of less than 50 beats per minute and was treated with i.v. injection of atropine 0.6mg.

Sample size: Assuming an alpha level of 0.05 and a power of 0.80, a minimum of 30 patients in each group were required to detect a mean difference in MAP of 15mmHg between groups.

Statistical analysis: Statistical analysis was performed using the Software SPSS version 17. Data were analysed using one way ANOVA and Bonferroni test was used for "post hoc" comparisons. Categorical variables were analyzed using Chi-square test. A p value less than or equal to 5% was considered as significant. Continuous variables were presented as mean+/-SD or as median (range); categorical data were presented as number (%).

Results

The study & control groups did not differ significantly with respect to any demographic variables as depicted in Table 1.

Table 1: Demographic parameters in all three groups

| Demographic Variables | Group B | Group LB | Group LC |
|-----------------------|----------|-----------|-----------|
| Age | 53 ±1.92 | 53 ±2.24 | 54 ±2.56 |
| Weight | 51 ±3.36 | 52 ±4.1 | 51 ±3.9 |
| Height | 156 ±3.5 | 156 ±3.34 | 158 ±4.21 |
| *ASA I/II | 25/5 | 24/6 | 26/4 |

*American society of Anesthesiologists (ASA)

Sensory onset time, (5.8±1.09 min) duration of motor blockade were lowest in bupivacaine (B) compared to levobupivacaine (LB) and Levobupivacaine clonidine (LC) groups. Motor onset time was much delayed in LC (7.48±2.20min) group compared to group B (5.8±1.09 min) and LB (6.67±1.47mins) groups. However duration of analgesia (288±18 min) was found to be prolonged in LC group(288±18 min) compared to group B (167.5±12.25) and group LB(225.1±16.19). Duration of motor blockade was found to be least in group B (150±11.414) and highest in group LC (190±17.38).

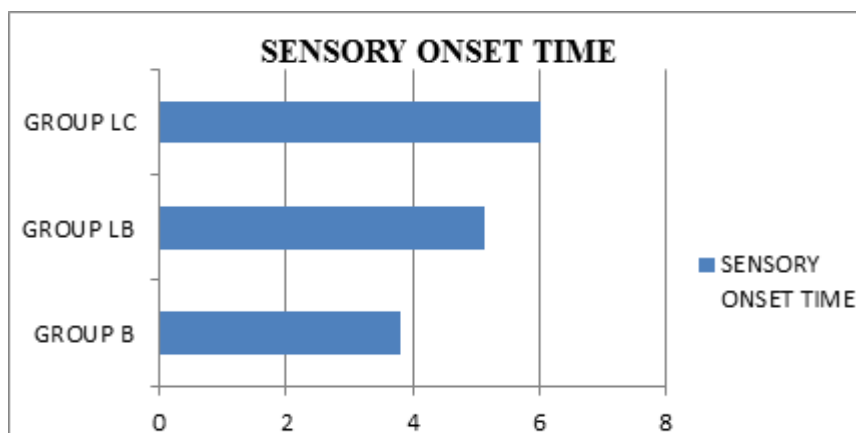
Table 2: Study variables studied in all three groups

| Variables | Group B | Group LB | Group LC |
|---------------------------|----------------|---------------|---------------|
| Sensory onset time | 3.80±0.877 | 5.13±1.008 | 6.03 ±1.923 |
| Motor onset time | 5.80±1.095 | 6.67±1.47 | 7.48±2.20 |
| Duration of sensory block | 167.50±12.252 | 225.10±16.198 | 288.87±18.651 |
| Duration of motor block | 150.27±11.414) | 178.83±13,752 | 190.97±17.38 |

Hypotension was noted almost in all three groups.(60-70%) shivering was more group B (27%)compared to LB and LC. Bradycardia was noted in 27% of group LC whereas only (10%) in group B and (3%) in LC. Hypotesion was less in group LB compared to group B and group LC(20%).

Table 3: Comparison of side-effects in all the 3 groups

| Side effects | Group B | Group LB | Group LC |
|-------------------|---------|----------|----------|
| Bradycardia | 3(10%) | 1(3%) | 8(27%) |
| Hypotension | 21(70%) | 18(60%) | 20(66%) |
| Nausea & vomiting | 4(13%) | 2(6%) | 3(10%) |
| shivering | 8(27%) | 3(10%) | 1(3%) |

**Fig. 1: Sensory onset time in all three groups in minutes**

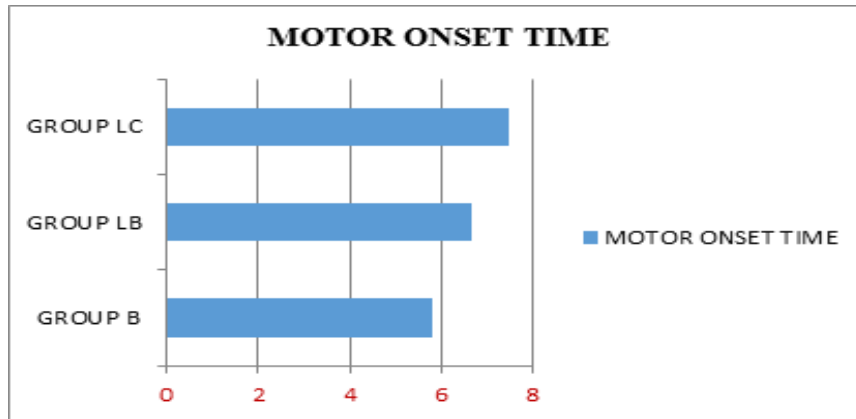


Fig. 2: Motor onset time in all three groups in minutes

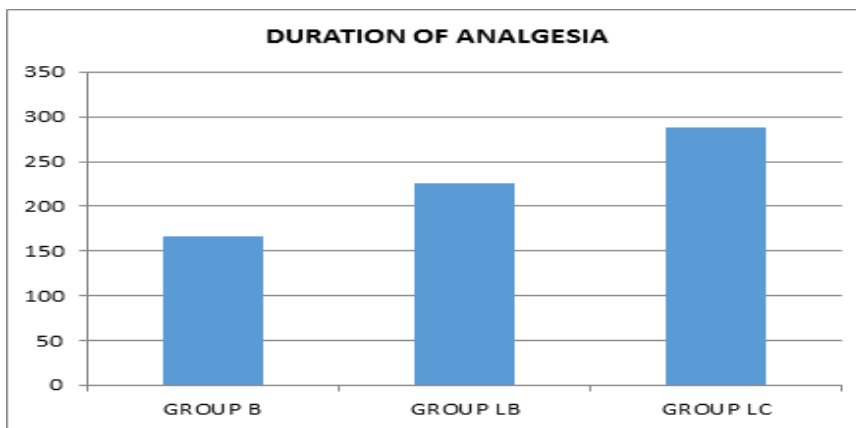


Fig. 3: Duration of Analgesia in all three groups in minutes

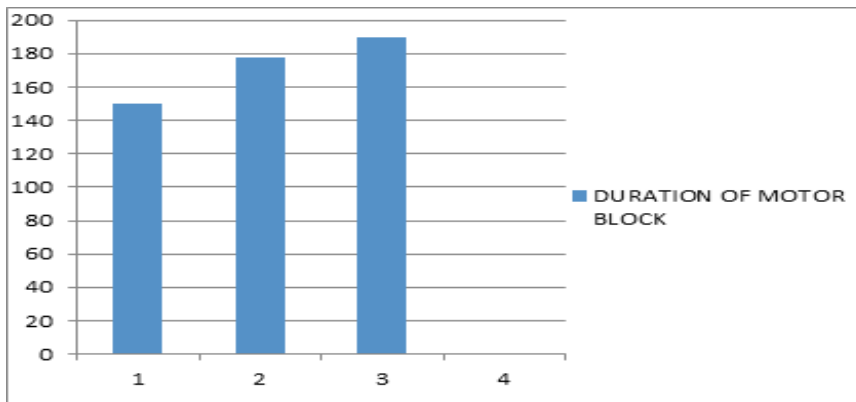


Fig. 4: Duration of motor blockade in all three groups in minutes

Mean SBP in mmHg

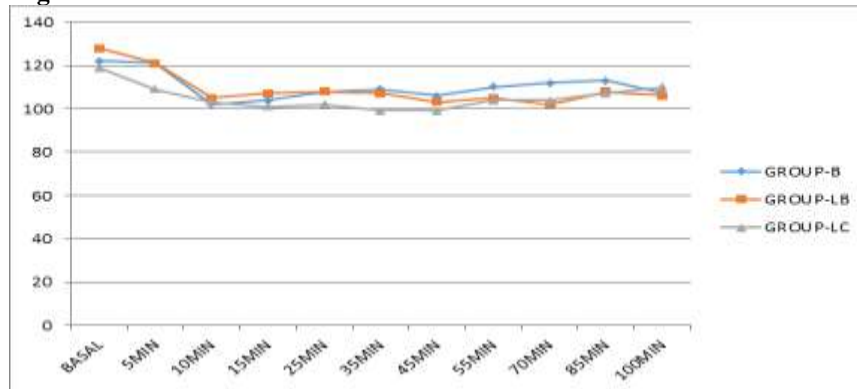


Fig. 5: Mean systolic blood pressure in control and study groups

Mean DBP in mmHg

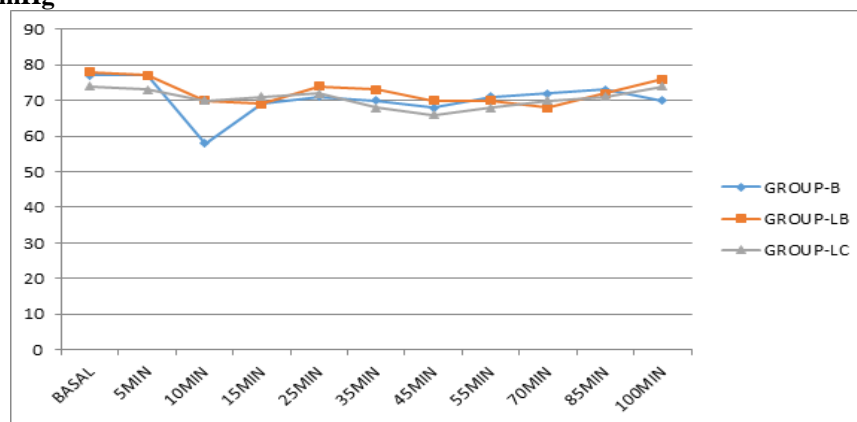


Fig. 6: Mean Diastolic blood pressure in control and study groups

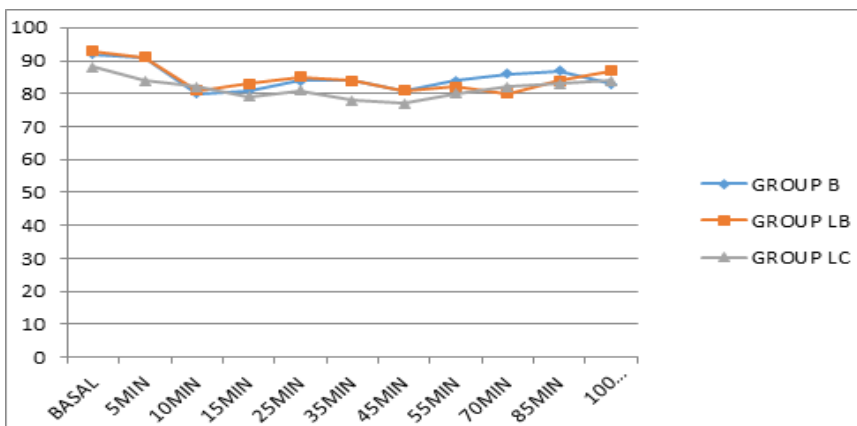


Fig. 7: Mean arterial pressure in control and study groups

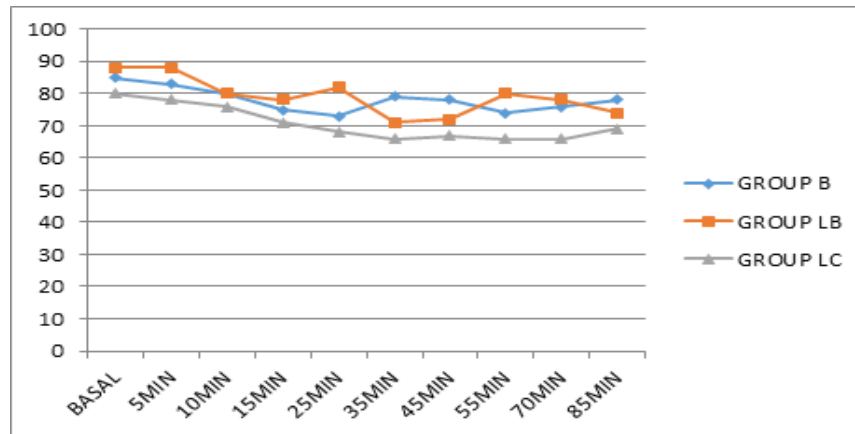


Fig. 8: Mean heart rate in control and study groups

Discussion

Hyperbaric bupivacaine has been the most commonly and routinely used intrathecal agent for variety of surgical indications including gynaecological surgeries. Unfavourable cardiac profile, short duration of sensory and motor blockade are few limitations associated with this drug.

Levobupivacaine, a pure S enantiomer of racemic bupivacaine has been shown to be less toxic to cardiovascular and central nervous systems with better hemodynamic properties^{(7),(8),(9),(10)}. Clonidine an alpha 2 adrenoceptor agonist, has been extensively used as an adjuvant to local anaesthetics.⁽¹¹⁾ The efficacy of clonidine in improving the post-operative analgesia has been well documented and contributed to spinal cord anti-nociception via post-junctional alpha 2 adrenoceptor mediated noradrenaline release in the dorsal horn. Absence of respiratory depression or addiction which are associated with opioids, further makes clonidine as an attractive adjuvant.

There are numerous studies using clonidine as an adjuvant to bupivacaine intrathecally to enhance its postoperative analgesia^{(12),(13)}. But its efficacy when used along with levobupivacaine has not been extensively studied so far.

In our present trial we had investigated the effects of isobaric levobupivacaine as well as the effect of clonidine when injected along with isobaric levobupivacaine intrathecally. The findings are compared against the control group who received the standard hyperbaric Bupivacaine.

The onset of sensory and motor blockade, are found to be faster in hyperbaric bupivacaine group than other two study groups and slowest in group LC. This sequence of onset time may be explained by the density of the solution used. The density of clonidine which has been used in our study is 0.9930. As the density of levobupivacaine is 1.00376, adding clonidine makes it much lighter than levobupivacaine alone and making it the least in density. This could be the reason for the delayed onset of sensory and motor blockade in levobupivacaine clonidine group.

However a study done by Opas Vanna MD in 2006 found no difference in onset time between isobaric levobupivacaine and hyperbaric bupivacaine in regard to both the onset time and duration of sensory blockade.⁽¹⁴⁾

In our study sensory and motor onset time was more in LB group than Bupivacaine group and this discrepancy in result might be due to differences in volume used. Our finding of delayed onset of sensory blockade in Group LC is in accordance with the study reported by E. Van Sommeren.⁽¹⁵⁾

Duration of sensory analgesia was found to be maximum in LC group (288 ± 18 min) ($p < .000$) and also statistically significant. Niemi, L in 1994 found that by adding clonidine in a dose of 3 mic/kg, increases the duration of analgesia in knee surgeries⁽¹⁶⁾. As in our study, he also reported that intra the cal bupivacaine induced analgesia was about 168 minutes. The mean duration of clonidine enhanced analgesia in his study was found by 217 minutes. But in our study we found that by adding clonidine, the duration of sensory analgesia can be further enhanced to 288 minutes.

Duration of motor blockade is shown to be enhanced when clonidine is added to local anaesthetics by earlier studies.^{(17),(18)} In our study motor blockade also has been found to be prolonged in levobupivacaine with clonidine group than other two groups. Duration of motor blockade by intra the cal bupivacaine was found by 152.7 ± 9.79 min by Atri J et al⁽¹⁹⁾ in infra umbilical surgeries. But in our study this duration was little prolonged by 26 minutes (178 minutes). This prolongation of motor blockade can be explained by the difference in dosing between two studies. Van sommeren in 2003 also reported that clonidine when added to levobupivacaine prolongs the duration of motor blockade⁽¹⁵⁾.

Hypotension and bradycardia are the most commonly reported adverse events after administering SAB with local anaesthetic agents. This incidence can be anticipated to be more when alpha 2 agonists like clonidine are added as adjuvants.

In our study, significant reduction in heart rate was found in group LC (levobupivacaine with clonidine)

which is statistically also significant ($p < 0.05$) than other groups. This change in heart rate was significant between 25th min until 70 min after injection. This is apparently due to effect of clonidine on presynaptic mediated inhibition of noradrenaline as well as direct action on atrioventricular node after systemic absorption⁽²⁰⁾. Though the maximum reduction in heart rate was seen in this group, the number of patients who required intervention were only eight. But group LB had better hemodynamic stability compared to group B and group LC.

Though there was fall in mean DBP in group B starting from 5th to 15th minute the reduction in mean arterial pressure was not statistically significant between the groups.

Shivering was found to be least in group LC (1%) than other groups. This property of clonidine suppressing the perioperative shivering has been well supported by previous studies but the underlying mechanism of action remains unknown.⁽²¹⁾

Conclusion

Of all the three groups isobaric levobupivacaine was found to be having better hemodynamic stability. Though the onset time of sensory and motor blockade were delayed while adding clonidine to levobupivacaine, the prolonged duration of sensory analgesia and safer pharmacological profile without any untoward adverse events makes this combination a good alternate for hyperbaric bupivacaine in gynaecological surgeries where prolonged pain relief is warranted.

References

1. The I. Manuel Galindo Arias, MD, Professor of Anesthesiology Fundacion Univarsitaria San Martin, Bogota:23–5.
2. Foster RH, Markham a. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs*. 2000;59(3):551–79.
3. Sanford M, Keating GM. A Review of its Use in Regional Anaesthesia and Pain Management. 2010;70(6):761–91.
4. Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine Versus Racemic Bupivacaine for Spinal Anesthesia. 2002;194–8.
5. Bhure A, Kalita N, Ingley P, Gadkari CP. Comparative study of intrathecal hyperbaric Bupivacaine with Clonidine, Fentanyl and Midazolam for quality of anaesthesia and duration of post-operative pain relief in patients undergoing elective caesarean section Abstract: Introduction :2012;5(1).
6. Bazin M, Bonnin M, Storme B, Bolandard F, Vernis L, Lavergne B. Addition of clonidine to a continuous patient-controlled epidural infusion of low-concentration levobupivacaine plus sufentanil in primiparous women during labour. 2011;769–79.
7. Sanford M, Keating GM. Levobupivacaine: a review of its use in regional anaesthesia and pain management. *Drugs* [Internet]. 2010;70(6):761–91. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20394458>.
8. Herrera R, De Andrés J, Estañ L, Olivas FJM, Martínez-Mir I, Steinfeldt T, et al. Hemodynamic impact of isobaric levobupivacaine versus hyperbaric bupivacaine for

- subarachnoid anesthesia in patients aged 65 and older undergoing hip surgery. *BMC Anesthesiol*. 2014;14:1–11.
9. Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *Anesth Analg*. 1998;86(4):797–804.
10. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46(3):245–9.
11. Tryba M, Gehling M. Clonidine—a potent analgesic adjuvant. *Curr Opin Anaesthesiol*. 2002;15(5):511–7.
12. Grandhe RP, Wig J YL. Evaluation of Bupivacaine-Clonidine Combination for Unilateral Spinal Anesthesia in Lower Limb Orthopedic Surgery. *J Anaesth Clin Pharmacol*. 2008;24(2):155–8.
13. van Tuijl I, van Klei W a, van der Werff DBM, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: a randomized controlled trial. *Br J Anaesth* [Internet]. 2006;97(3):365–70. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16861258>.
14. Vanna O. Levobupivacaine and Bupivacaine in Spinal Anesthesia for Transurethral Endoscopic Surgery. 2006;89(8):1133–9.
15. E VS, Hoffmann V, Vercauteren M. Clonidine postpones discharge when added to spinal levobupivacaine for day-case arthroscopy. 2003;(1):2003.
16. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. *Acta Anaesthesiol Scand* [Internet]. 1994;38(7):724–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7839785>.
17. Polaiiah KPMD, D TVGRM. The Effects of Clonidine with Bupivacaine in Spinal Anaesthesia to Lower Limb Orthopaedic Surgery Cases: A Retrospective Cohort Study. 2015;14(3):31–4.
18. Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. 2006;932–7.
19. Attri JP, Kaur G, Kaur S, Kaur R, Mohan B, Kashyap K. Comparison of levobupivacaine and levobupivacaine with fentanyl in infraumbilical surgeries under spinal anaesthesia [Internet]. *Anesthesia, Essays and Researches*. 2015. p. 178–84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4563977/>.
20. Baker A, Klimscha W, Eisenach JC, Li X-H, Wildling E, Menth-Chiari WA, et al. Intrathecal clonidine for postoperative analgesia in elderly patients: the influence of baricity on hemodynamic and analgesic effects. *Anesth Analg*. 2004;99(1):128–34.
21. Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI. Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. *Anesthesiology*. 1993;79:470–4.