# A Prospective Single Blind Comparative Study of Levobupivacaine with Fentanyl and Levobupivacaine with Clonidine in Thoracic Epidural Block for Laparoscopic Cholecystectomy

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## ABSTRACT

**Introduction:** Regional anesthesia (RA) is gaining popularity for laparoscopic surgeries these days. Epidural anesthesia (EA) is being seen as a better alternative for Laparoscopic Cholecystectomy (LC) owing to it's lesser complication rate and making possible laparoscopic surgeries as day care surgeries. We conducted a clinical study comparing levobupivacaine with fentanyl and a combination of levobupivacaine with clonidine in thoracic EA for LC as sole anaesthetic.

**Material and Methods**: After taking approval from Institutional Ethical Committee, 80 adult patients of ASA grade I and II were selected and divided in two groups; group I levobupi-vacaine having 0.5% concentration in the dose of 2mg/kg with 1.5µg/kg fentanyl was administered and in group II levobupi-vacaine having 0.5% concentration in the dose of 2mg/kg with 1.5 µg/kg of clonidine was administered. Thoracic EA was given at the $T_{10}$-$T_{11}$ interspace to obtain a sensory block of $T_4$-$L_2$ dermatome which was judged every minute by pin prick method till complete sensory block was established.

**Result:** Onset of block was fast and duration of block was longer in group I patients. Also fall in blood pressure and heart rate was greater in group II patients.Also, shoulder pain was less in group I patients.Oxygen saturation($Spo_{2)}$ was comparable in both the groups and no respiratory distress was seen although respiratory rate was comparably higher in group II. More post-operative analgesia and vasopressor was required in group II patients.

**Conclusion:** Levobupivacaine with fentanyl provides better anaesthesia and haemodynamic stability than levobupivacaine with clonidine in thoracic EA for LC.


**Keywords:** Regional anesthesia, Epidural anesthesia, Laparoscopic Cholecystectomy, Levobupivacaine, Clonidine, Fentanyl

## INTRODUCTION

Since the advent of laparoscopic Surgery, laparoscopic cholecystectomy has been carried out in general anesthesia (GA) but regional anaesthesia like spinal and epidural have been used in recent times and are gaining popularity for LC.[1,2] Regional anaesthesia (RA) decreases morbidity, mortality, length of hospital stay and is less expensive in comparison to GA. Regional anaesthesia decreases intra operative blood loss and less blood transfusions is needed[3] and has advantage of decreased stress response as well as minimal complications for LC. Also, chances of teeth injury during intubation are also avoided with RA which are relatively common in patients having bucked teeth in GA.

Epidural anaesthesia also avoids chances of urinary retention as compared to spinal anesthesia leading to LC as a day care surgery. EA gives better cardiovascular stability than spinal anesthesia for LC and better titration of block level than spinal anesthesia, as with spinal anesthesia desired block level is difficult to achieve for LC. Cerebrospinal fluid volume varies in each patient so, level of anesthesia becomes unpredictable in every individual; Spinal anesthesia may cause high blockade which may extend over T4 level, required for LC, but cardiac depression may occur due to high blockade.[4]

During EA for LC patient is on spontaneous respiration and there is minimal weakness of respiratory muscles and patient can adjust their respiration and breathing intra-operatively.[5] EA may be advantageous in cardiac and respiratory disease patients, as EA results in gradual block and less muscle weakness.[6]

Also post-operative pain is better controlled with EA.[2] Some pre-requisites for EA these are - A relaxed and co-operative patient and Low intra-abdominal pressure.[7]

Local anaesthetic drugs presently used in RA are lignocaine, bupivacaine, ropivacaine and tetracaine. Levobupivacaine is a S(-) isomer of bupivacaine and has emerged as a better local anaesthetic drug then bupivacaine owing to it's greater cardiovascular stability and less neurotoxicity. Adjuvants like clonidine or fentanyl are increasingly being used along with levobupivacaine to improve block quality as well as to increase duration of block.[7]

Clonidine is an alpha2 agonist which causes presynaptic inhibition resulting in negative feedback mechanism and decrease dose requirement of levobupivacaine in EA.Clonidine also decreases blood pressure owing to it's central sympatholytic effect. Fentanyl is an opoid acting on mu-1 opoid receptors(widely distributed in CNS and other tissues) leading to supraspinal analgesia. Mu-receptors are located presynaptically in the peri-aqueductal grey region,and in the substantia gelatinosa of Rolando. We conducted a clinical study comparing lev-obupivacaine with fentanyl and a combination of in levobupivacaine with clonidine thoracic EA for LC as sole anaesthetic.

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The aim of this study was to establish the role of fentanyl and clonidine as an adjuvant to epidural levobupivacaine, to compare and study their beneficial clinical effects.

Objectives of this study were to compare and determine the onset of sensory analgesia and duration of post- operative analgesia in patients undergoing LC under thoracic EA with levobupivacaine having 0.5% concentration in the dose of 2mg/kg with 1.5µg/kg fentanyl and levobupivacaine having 0.5% concentration in the dose of 2mg/kg with 1.5µg/kg of clonidine, to study the hemodynamic responses of the drug during and after surgery, to detect any complication or side effects as a result of these drug, to study the need of intra-operative and post-operative analgesic drug (rescue analgesia) within 24hr after block.

## MATERIAL AND METHODS

After obtaining approval of ethical committee with research approval number IEC/31/2013 and written informed consent, 80 ASA physical status I and status II patients aged 18–60 years, of both sexes, scheduled for LC under EA were selected. Patients having chronic obstructive pulmonary disease, severe anemia, heart disease, morbid obesity, deranged liver function test, anticoagulant therapy, renal diseases and endocrine diseases were not included. Preanesthetic check up was done one day before surgery, investigation reports were seen and written informed consent was taken. Patient were to remain NPO 8 hours for solid food and 3 hours for clear fluid before surgery. Patient were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150mg. In OT a good IV line was established and patients were preloaded with 500ml RL and monitoring was done for ECG, HR, NIBP, SPO2, temperature, respiratory rate. Drug dosing was done according to the weight of the patient. Patients were asked to sit on the operation table with their elbows on their thighs. Flexion of the spine was done and midline approach was used for epidural anesthesia. Patients were positioned properly and all aseptic precautions were taken. Site of epidural was infiltrated with 2ml (2% lignocaine) containig adrenaline 1:200, 000 at T10-T11 intervertebral space. EA was administered using 18 G gauge Tuohy's needle (byL.O.R method). A test dose of 3ml (2% lignocaine) containing adrenaline 1:200, 000 was injected and there after patients in first group received 2mg/kg 0.5% L-bupavicaine along with 1.5 µgm/kg of fentanyl and patients in second group received 2mg/kg 0.5% L-bupavicaine along with 1.5 µgm/kg of clonidine. Patients were unaware of the anesthetic procedure. Onset of sensory block and it's level was assesed by pin prick method. The two groups were monitored intraoperatively for HR, non-invasive blood pressure and arterial $O_2$ saturation ($SpO_2$). 20% decrease from baseline SBP was considered as hypotension and was treated by fluids and vasopressors (mephentermine 6mg). Heart rate<50/min was considered bradycardia and patient was given 0.6 mg of atropine injection intravenously. Intraoperative nausea, vomiting, pruritus, sedation were noted and treated.

## STATISTICAL ANALYSIS

Data was analyzed with statistical package for social sciences (SPSS) software. Tests used were chi-square test and T-test (*P* value < 0.05 indicated a significant difference).

## RESULTS

Demographic data in both the groups were statistically similar. Mean heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP)s were statistically similar and in normal range between both the groups and were in normal ranges. Mean HR, SBP and DBP in both the groups were statistically similar at all times during the procedure (p>0.05) but at all times during the surgery mean HR, SBP and DBPs were significantly lower as compared to baseline (p<0.05) [Table 1and 2].

Mean time of onset of sensory block was 4.02±1.14 (Mean±SD) minutes in Group I and 8.82±2.74 (Mean±SD) minutes in Group II, indicating early achievement of block in Group I (p<0.05) [table-3]. Mean duration of sensory block was 6.5+0.78(Mean±SD) hours in Group I and 4.87±0.79 (Mean±SD) hours in Group II, thus showing a long lasting block in group I (p<0.05) [table 4].

Vasopressor requirement was significantly higher in Group II (62.5%) as compared to Group I (40%) (p<0.05). More keta-

| Time Interval | Group 1 | | | Group 2 | | | Statistical Significance | |
|---|---|---|---|---|---|---|---|---|
| | No. | Mean | SD | No. | Mean | SD | 't' | 'p' |
| Baseline | 40 | 128.9 | 19.48 | 40 | 132.07 | 17.01 | 0.775 | .4405 |
| 5 min | 40 | 118.8 | 15.4 | 40 | 114.75 | 6.74 | 1.302 | .1270 |
| 10 min | 40 | 115.8 | 19.97 | 40 | 113.27 | 10.57 | 0.078 | .9421 |
| 15 min | 40 | 115.35 | 17.26 | 40 | 112.67 | 6.89 | 1.184 | .2123 |
| 20 min | 40 | 114.72 | 18.19 | 40 | 110.45 | 13.84 | 0.346 | .8642 |
| 25 min | 40 | 114.67 | 23.33 | 40 | 109.97 | 9.71 | 0.905 | .3680 |
| 30 min | 40 | 113.8 | 14.48 | 40 | 109.50 | 8.48 | 0.911 | .3650 |
| 35 min | 35 | 113.2 | 16.84 | 36 | 109.32 | 9.44 | 1.1623 | .1127 |
| 40 min | 35 | 112.4 | 15.01 | 34 | 109.25 | 7.01 | 1.161 | .2536 |
| 45 min | 32 | 111.6 | 17.58 | 22 | 108.57 | 12.78 | 1.670 | .1008 |
| 50 min | 25 | 110.14 | 17.01 | 16 | 108.38 | 8.88 | 0.389 | .7174 |
| 55 min | 22 | 107.89 | 14.6 | 14 | 108.13 | 7.90 | 0.819 | .4186 |
| 60 min | 20 | 107.86 | 12.6 | 12 | 106.77 | 15.26 | 0.303 | .7640 |
| 65 min | 4 | 106.85 | 18.52 | 2 | 104.85 | 6.78 | 1.063 | .3479 |
| 70 min | 5 | 104.5 | 14.24 | 2 | 103.00 | 1.41 | 1.877 | .9117 |
| Mean Systolic blood pressure in group 1 was 128.9 ± 19.48 (Mean+SD) at base line and it was 132.07 ± 11.13 (Mean+SD) in group 2. There was decrease in mean Systolic blood pressure during different time period but there was no statistically significant difference in Systolic blood pressure of both the groups was observed at any of the above time periods. | | | | | | | | |

**Table-1:** Intergroup Comparison of Systolic Blood Pressure (mm Hg) at different time intervals

mine was needed in Group II (35%) patients as compared to Group I (20%) ($p<0.05$). Atropine was required more in Group II (10%) while nil in Group I ($p<0.05$).

Muscle relaxation was adequate. No patient complained of vomiting, headache and pruritis postoperatively. Also, Group I had significantly lower rescue analgesic need as compared to Group II ($p<0.05$).

## DISCUSSION

Regional anaesthesia owing to it's various advantages is becoming very popular for laparoscopic surgeries like better intra-operative analgesia[1,2], better post-operative pain control, less side effects as compared to GA during intra-operative period and reversal[3], less chances of teeth injury, cost effective, ventillation is maitained as patient is on spontaneous ventillation, less intra-operative blood loss and no marked increase in $EtCO_2$.[4,5]

For this purpose a single blinded prospective randomized controlled study was carried out in which a total of 80 patients belonging to ASA grade 1 or 2 undergoing LC procedure were divided randomly in two groups. 40 patients in Group I received EA with levobupivacaine having 0.5% concentration in the dose of 2mg/kg with 1.5 µg/kg fentanyl while another 40 in Group II received levobupivacaine having 0.5% concentration in the dose of 2mg/kg with 1.5 µg/kg clonidine

Pre-requisites for RA in LC are low intra-abdominal pressure and Sensory block of T4-L2.[6,7]

Epidural anaesthesia combined with postoperative epidural analgesia has shown less incidences of postoperative pain and vomiting in patients undergoing open cholecystectomy.[2]

Bupivacaine is used in thoracic epidural block for LC.[7] Levobupivacaine is more safe with equivalent efficacy. α2 agonists like clonidine, dexmedetomidine and opioids like fentanyl increases the analgesic efficacy of spinal and EA, by increasing the pharmacokinetics of the main drug used and helps to achieve block early and maintain it over longer time.[7-11]

So, we evaluated fentanyl and clonidine as adjuvant to levobupivacaine in thoracic EA for LC.

Hemodynamic parameters were similar at baseline and intraoperatively in both the groups. Hemodynamic parameters were lower or similar to the baseline levels intraoperatively in individual groups [table 1and Table 2]. There was 20-30%

| Time Interval | Group 1 | | | Group 2 | | | Statistical Significance | |
|---|---|---|---|---|---|---|---|---|
| | No. | Mean | SD | No. | Mean | SD | 't' | 'p' |
| Baseline | 40 | 80.05 | 10.08 | 40 | 79.30 | 11.13 | 0.3159 | .7529 |
| 5 min | 40 | 73.85 | 12.73 | 40 | 72.52 | 6.89 | 1.532 | .1270 |
| 10 min | 40 | 72.97 | 12.84 | 40 | 72.00 | 8.48 | 0.092 | .9151 |
| 15 min | 40 | 72.56 | 10.97 | 40 | 71.95 | 7.90 | 1.147 | .2492 |
| 20 min | 40 | 72.11 | 11.45 | 40 | 71.02 | 13.84 | 0.252 | .8231 |
| 25 min | 40 | 72.02 | 11.86 | 40 | 70.52 | 9.71 | 0.806 | .3880 |
| 30 min | 40 | 71.45 | 13.98 | 40 | 69.90 | 9.44 | 0.962 | .3858 |
| 35 min | 35 | 71.2 | 14.01 | 36 | 69.12 | 7.01 | 1.1623 | .1127 |
| 40 min | 35 | 70.9 | 10.25 | 34 | 68.90 | 10.57 | 1.181 | .2432 |
| 45 min | 32 | 70.8 | 5.02 | 22 | 68.50 | 8.88 | 1.913 | .0653 |
| 50 min | 25 | 69.6 | 10.78 | 16 | 66.91 | 6.74 | 0.389 | .7174 |
| 55 min | 22 | 69.05 | 12.31 | 14 | 65.70 | 15.26 | 1.924 | .0841 |
| 60 min | 20 | 68.13 | 8.24 | 12 | 65.47 | 12.78 | 1.813 | .8753 |
| 65 min | 4 | 65.02 | 13.96 | 2 | 65.07 | 6.78 | 0.489 | .6174 |
| 70 min | 5 | 65.0 | 8.28 | 2 | 63.00 | 1.47 | 1.934 | .9042 |
| Mean diastolic blood pressure in group 1 was 80.05 ± 10.08(Mean+SD) at base line and it was 79.30 ± 11.13(Mean+SD) in group 2. There was decrease in mean diastolic blood pressure during different time period but there was no statistically significant difference in diastolic blood pressure of both the groups was observed at any of the above time periods. | | | | | | | | |

**Table-2:** Intergroup Comparison of Diastolic Blood Pressure (mm Hg) at different time intervals

| S. No. | Time to achieve sensory block T4-L2 (minutes) | Group 1 | Group 2 |
|---|---|---|---|
| 1 | Number of patients | 40 | 40 |
| 2 | Minimum | 2 | 5 |
| 3 | Maximum | 8 | 15 |
| 4 | Median | 4 | 10 |
| 5 | Mean | 4.02 | 8.82 |
| 6 | S.D. | 1.14 | 2.74 |
| 7 | Statistical Significance | P=.0000 highly statistically significant | |
| Sensory block was achieved in 4.02±1.14 (Mean+SD) minutes by Group 1 patients while by Group 2 patients it was achieved in 8.82±2.74(Mean+SD) minutes. Sensory block onset was achieved much early in group 1 (p=.0000). | | | |

**Table-3:** Intergroup Comparison of Time to achieve sensory block (min)

| S. No. | Duration of sensory blockT4-L2 (hours) | Group 1 | Group 2 |
|---|---|---|---|
| | Number of patients | 40 | 40 |
| 1 | Minimum | 4.30 | 3.5 |
| 2 | Maximum | 8.0 | 7 |
| 3 | Median | 6.5 | 4.75 |
| 4 | Mean | 6.5 | 4.87 |
| 5 | S.D. | 0.78 | 0.79 |
| 6 | Statistical Significance | P=.0000 highly statistically significant | |
| It was found that duration of sensory block in Group 1 was found to be 6.5±0.78(Mean+SD) hours which was higher, 4.87±0.79 (Mean+SD) hours in Group 2. Duration of sensory block was more in group 1 and analgesia lasted for a longer duration in Group 1 patients (p=0.0000). | | | |

**Table-4:** Intergroup Comparison of Duration of sensory block (hours)

decline in the hemodynamic parameters as compared to baseline in individual groups. Gupta et al. in their study with ropivacaine and fentanyl for thoracic EA for LC and Agrawal et al in their study with bupivacaine or a mixture of bupivacaine and clonidine for thoracic EA for LC also found similar hypotensive effect of these drugs.[7-8]

Levobupivacaine do not have any cardiovascular side effects and is also safe, hypotension in both the groups was due to sympathetic cutdown. Low blood pressure helps to minimize stress response intraoperatively. But, significant hypotension were observed in both the groups. Clonidine causes hypotension up to eight hours. Clonidine and related alpha2 adrenergic receptor agonists lower arterial pressure primarily by an action within the central nervous system.[12-13]

Clonidine gets quickly redistributed on neuraxial injection producing central and peripheral effects. Hypotension with smaller doses due to central sympatholysis and peripheral vasoconstriction at higher doses. Hypotension developed by clonidine when given in low thoracic or lumbar region is similar to when given intravenously.[12-13] Mid or upper thoracic administration of epidural clonidine leads to greater hypotension[14]; Which is due to thoracic sympatholysis.

20% decrease from baseline SBP was considered hypotension and was treated by crystalloid fluids and vasopressors (mephentermine 6mg). Heart rate<50/min was considered bradycardia and patient was given 0.6 mg of atropine injection intravenously for it. In group 1, sixteen patients required mephentermine while in group 2, twenty five patients required mephentermine, although both fentanyl and clonidine cause hypotension but hypotension was more pronounced in clonidine group as fentanyl only causes minor reduction in blood pressure. Gupta et al. in their study with ropivacaine and fentanyl for thoracic EA also observed need for vasopressors to treat transient hypotension in their study.[8] Fentanyl causes hypotension due to a reduction in systemic vascular resistance through centrally mediated reduction in sympathetic tone while clonidine causes more pronounced fall in blood pressure and heart rate due to central sympatholytic activity.[7] Also two patients in clonidine group required atropine for treatment of bradycardia.

Sensory block was achieved in 4.02±1.14(Mean±SD) minutes and lasted for 6.5+0.78 (Mean±SD) hours in Group I [table 3- 4] although Gupta et al in their study with ropivacaine and fentanyl for thoracic EA for LC found sensory block level achievement in 15 minutes as they used ropivacaine instead of levobupivacaine.[8]

Sensory block was achieved in 8.82±2.74(Mean±SD) minutes and lasted for 4.87±0.79(Mean±SD) hours in Group 2 [table 3-4] Pandey et al in their study also found that maximum number of patients received sensory block upto $T_4$ level at 10 minutes.[15]

In present study, Group I had significantly lower rescue analgesic need as compared to Group 2, thus showing that levobupivacaine in combination with fentanyl provided a better analgesic effect as compared to levobupivacaine in combination with clonidine. Fair sedation and muscle relaxation was present. Shoulder pain due to diaphragmatic irritation by carbon dioxide used in creating pneumoperitoneum is not fully relieved by EA alone as T4 to L2 blockade is required.[7] Thoracic EA for LC is a satisfactory alternative technique in selected cases. Addition of clonidine (1.5µg/kg) to bupivacaine produces better qualitative anesthetic conditions. It prevents hemodynamic perturbations produced by pneumoperitoneum and also decreases the incidence of shoulder pain.[7,11] No increase in HR and BP was observed after creation of pneumoperitoneum in both the groups. Agrawal et al also found this in their study.[7]

Ketamine 20mg was used for alleviating shoulder pain in eight patients in group 1 and fourteen patients in group 2. Gupta et al. and Agrawal et al in their study on thoracic EA for LC also found similar results.Shoulder pain is related to the level of IAP.[6-8,11,16] The thoracic EA with 0.75% ropivacaine and fentanyl for elective LC has decreased the changes in hemodynamic parameters along with preserving proper ventillation during pneumoperitoneum.[8]

Respiratory rate in group 1 was slightly lesser this may be due to dose dependent respiratory depression produced by fentanyl whereas respiratory rate was slightly higher in group 2 also observed by Agrawal et al which may be due to hypercapnia.[7]

No patient complained of vomiting, headache and pruritis postoperatively. Also, Gupta et al. in their found that none of the patient complained of headache, pruritis and retention of urine postoperatively.[8]

## CONCLUSION

Thoracic EA for LC is a satisfactory alternative technique in selected cases. Addition of anaesthetic adjuvant drugs like fentanyl or clonidine to levobupivacaine produces better and longer block. These drugs also provide better hemodynamic stability decreasing alterations by pneumoperitoneum and chances of shoulder pain.

Levobupivacaine and fentanyl combination in EA for LC provides faster and longer block than with levobupivacaine and clonidine group. As less vasopressors, atropine and post-operative analgesics were required in fentanyl group. Also, better hemodynamic stability during pneumoperitoneum and less incidence of shoulder pain was found in fentanyl group. Thus we recommend the addition of fentanyl as an adjuvant to levobupivacaine in thoracic EA for LC.

We should further study clonidine in lesser doses for better patient safety and decreased vasopressor and atropine use.

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