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# COMPARATIVE CLINICAL STUDY OF EFFECT OF INTRAPERITONEAL INSTILLATION OF BUPIVACAINE PLUS DEXMEDETOMIDINE OR BUPIVACAINE PLUS CLONIDINE FOR POST OPERATIVE ANALGESIA IN CASES UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANAESTHESIA

Anaesthesiology

**Dr. P.S Malviya** MD, Professor, Department of anaesthesiology and critical care, Moti Lal Nehru medical college, Prayagraj, U.P. India.

**Dr. Dharmender K. Yadav** MD, Associate Professor Department of Anaesthesiology & Critical Care, Moti Lal Nehru Medical College, Prayagraj.

**Dr. Shobhit Singh** MD, Assistant Professor, Department of anaesthesiology and critical care, Moti Lal Nehru medical college, Prayagraj, U.P. India.

**Dr. Pooja Pawar*** Junior Resident, Department of anaesthesiology and critical care, Moti Lal Nehru medical college, Prayagraj, U.P. India. *Corresponding Author

## ABSTRACT

**Background-** Laparoscopic cholecystectomy has replaced open cholecystectomy as the treatment of choice, however multiple approaches has been studied to manage postoperative analgesia. **Material and method–** In present study, 108 patients of either sex, aged between 18 to 60 years belonging to ASA class I and II, scheduled for elective laparoscopic cholecystectomy surgeries. Group B (n = 36): - Received 40 ml of 0.25% bupivacaine, Group BC (n = 36): - Received 40ml of 0.5% Bupivacaine + Clonidine (1µg/kg), Group-BD (n = 36): Received 40 ml of 0.25% Bupivacaine + Dexmedetomidine (1 µg/kg).The intensity of pain recorded for all patients using Numerical Rating Scale (NRS) at 30 min ,1 ,2 ,4 ,6 and 24 h after surgery. The total analgesic requirement in the first 24 h was noted. **Results–** Numerical Rating Scale was significantly lower in clonidine as compared to Bupivacaine alone at 1 hr, 4 hrs, 6 hrs and 24 hrs post-operative interval. Time to first request (in minutes) for analgesia was shortest in group B (39.4±22.2) when compared to the other groups BC (50.4 ±39.5); BD (89±38.1). Total Fentanyl dose (in mcg) used was least in Dexmedetomidine (60.6±4.2) as compared to clonidine (62.8±4.4) and bupivacaine (77.5±21.6). **Conclusion-** The addition of alpha-2 agonists to bupivacaine reduces the post-operative opioid consumption, and dexmedetomidine proves to be a better alternative than clonidine due to its better efficacy in post-operative pain management.

## KEYWORDS

Laparoscopic cholecystectomy, Bupivacaine, dexmedetomidine, clonidine.

## INTRODUCTION-

Pain after Laparoscopic cholecystectomy is generally lesser than open cholecystectomy; however, patients often suffer from somatic pain (incisional site), visceral pain during coughing, respiration and mobilisation. This can lengthen hospital stay, increase morbidity, cost and delay in enhanced recovery after surgery (ERAS).

Opioid analgesic therapy has been served as the mainstay of treatment for acute postoperative pain. However, the recent rise in morbidity and mortality associated with opioid misuse has led to increasing demands for developing pain treatment strategies that placed more emphasis on using a multimodal approach.[1]

Bupivacaine is 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide. It is an amino-amide local anaesthetic drug belonging to the family of n-alkyl substitute pipecoloxylidide. Many studies have been conducted in providing post-op pain for lap cholecystectomy patients via intraperitoneal instillation alone and in combinations with different drugs[2]

Dexmedetomidine and Clonidine are selective α-adrenergic agonist. Dexmedetomidine has 8 times more specificity for α2 receptor makes it a more effective analgesic agent than clonidine.

The study has been undertaken to compare analgesic effect of two additives –Dexmedetomidine and clonidine given in combination with Bupivacaine (a local anaesthetic drug) given intraperitoneally and find out a better alternative.

## AIM AND OBJECTIVES

This study aims to compare the effect of intraperitoneal instillation of bupivacaine with alpha-2 agonists (dexmedetomidine and clonidine) for postoperative analgesia.

1.) To evaluate analgesic efficacy of combination of drugs (bupivacaine along with dexmedetomidine or clonidine) used for post-operative analgesia

2.) To compare onset and duration of combination of drugs (bupivacaine along with dexmedetomidine or clonidine) for post-operative analgesia.

3.) To study adverse effect, if any.

## MATERIALS AND METHODS

The study entitled as **"a comparative clinical study of effect of intraperitoneal instillation of bupivacaine plus dexmedetomidine or bupivacaine plus clonidine for post operative analgesia in cases undergoing laparoscopic cholecystectomy under general anaesthesia"** was carried out in Swaroop Rani Nehru Hospital, attached to Moti Lal Nehru Medical College, Prayagraj over a period of one year [October 2021 to September 2022] after approval from the Institutional Ethical Committee and obtaining written and informed consent from all the patients.

108 patients posted for elective laparoscopic cholecystectomy surgery were included in the study. The study population was blinded and randomly divided into 3 groups with 36 patients in each group (n=36) using shuffled, closed, opaque envelope method.

All the patients were explained about Numerical Rating Scale (NRS) to indicate their pain perception by identifying zero/0 as no pain and ten/10 as worst imaginable pain during pre-anaesthetic check-up and re-explained on the day of surgery.

Study drugs were made to an equal volume of 40 ml by adding Bupivacaine (20ml of 0.5%) and mixing it with 20ml of normal saline and dexmedetomidine or clonidine according to the group. During laparoscopy, intra-abdominal pressure was maintained between 12- and 14-mm Hg. Towards the end of skin closure and before removal of the trocar, 20 mL of the study drug was instilled intraperitoneally at the gall bladder and 20 mL in the margins of skin incision by the operating surgeon.

In the recovery room, heart rate, pulse oximetry, level of consciousness and signs and symptoms of adverse effects were monitored. The intensity of pain was recorded for all patients using NRS at 30min, 1, 2, 4, 6, and 24 hours after surgery. The total analgesic requirement in the first 24 hours was noted. Patients with NRS of score >3, patients were prescribed paracetamol 15 mg/kg intravenously. Injection fentanyl(1µg/kg) was given intravenously as rescue analgesia to the patients complaining pain within 6 hours of giving paracetamol. The incidence of adverse effects such as nausea, vomiting, pruritus, bradycardia (HR <60 beats/minute), hypotension (20% reduction in the baseline blood pressure), and rhythm disturbances on electrocardiography (ECG) was noted.

**Statistical analysis:**
Quantitative data was analysed with one-way analysis of variance (ANOVA) (for normally distributed data) along with significance between the pairs. Descriptive variables were presented as frequency, percentage, or a number and was compared by Chi-square test. P value < 0.05 was considered as significant.

ANOVA was used to compare the effectiveness of drugs for all the groups while independent t-test was used to compare the same measure in pair-wise manner. The independence and association of qualitative variable was checked by using Chi-square test. The test of significance was based on p-value.

## OBSERVATION AND RESULTS:

**Table 1- Demographic figure of the groups and significance.**

| | | Group B | Group BC | Group BD | p-value | Statistical Result |
|---|---|---|---|---|---|---|
| Gender | F | 21 (58.3%) | 17 (47.2%) | 23 (63.9%) | 0.3483 (Chi-square test) | Not significant |
| | M | 15(41.7 %) | 19(52.8 %) | 13(36.1 %) | | |
| ASA Grade | I | 22(61.1 %) | 26(72.2 %) | 23(63.9 %) | 0.586 (Chi-square test) | Not significant |
| | II | 14(38.9 %) | 10(27.8 %) | 13(36.1 %) | | |
| Mean±SD Age (in year) | | 41±10.8 | 42.9±10.7 | 41.3±11.8 | 0.735 (ANOVA) | Not significant |
| Mean±SD Height (in cm) | | 157.5±7.6 | 160.7±6.8 | 159.9±5.6 | 0.09 (ANOVA) | Not significant |
| Mean±SD Weight (in Kg) | | 64.6±8.5 | 65.5±6.4 | 64.1±7 | 0.115 (ANOVA) | Not Significant |
| Mean±SD BMI | | 26±2.6 | 25.3±1.3 | 25±1.9 | 0.712 (ANOVA) | Not Significant |

**Table 2- Mean±SD of Numerical Rating Scale (NRS) for pain assessment of patients in post-operative period**

| Time | Group B | Group BC | Group BD | p-value (ANOVA) & statistical significance |
|---|---|---|---|---|
| 30 min | 3.1±1.3 | 2.6±1.1 | 1.2±0.4 | 0.00000000005438 (Significant) |
| 1 hour | 3.2±1 | 1.6±0.8 | 1.6±0.6 | 0.00000000000004 (Significant) |
| 2 hours | 2.4±1.1 | 2±1.1 | 1.5±0.8 | 0.00296042445550 (Significant) |
| 4 hours | 2.4±1.1 | 1.3±0.7 | 1.3±0.7 | 0.00000004470643 (Significant) |
| 6 hours | 2.6±1.1 | 1.2±0.6 | 1.1±0.2 | 0.00000000000001 (Significant) |
| 24 hours | 1.6±0.8 | 1.1±0.2 | 1 | 0.00000018261482 (Significant) |

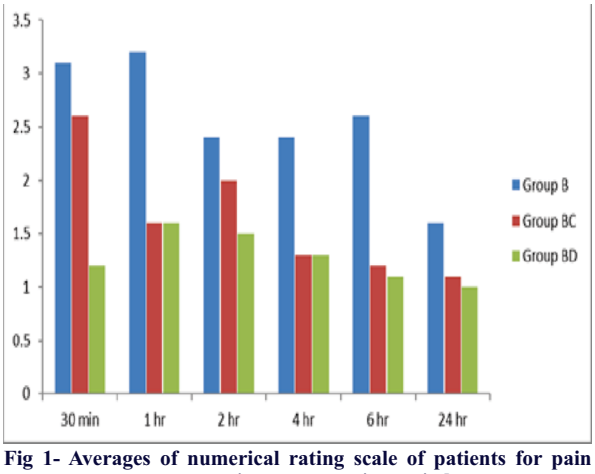


**Fig 1- Averages of numerical rating scale of patients for pain assessment among groups in post-operative period**

**Table 3- p-values for comparison (using t-test) of numerical rating scale for pain assessment of patients between groups at different time points in post-operative period**

| Groups | 30 min | 1 hour | 2 hours | 4 hours | 6 hours | 24 hours |
|---|---|---|---|---|---|---|
| Group-B Vs Group-BC | 0.05851151126 (NS) | 0.00000000075 (Sig.) | 0.1042 (NS) | 0.0000058 (Sig.) | 0.00000003 (Sig.) | 0.0002 (Sig.) |
| Group-BC Vs Group-BD | 0.00000000975 (Sig.) | 0.87551012163 (NS) | 0.04154 (Sig.) | 0.8613 (NS) | 0.1476 (NS) | 0.1602 (NS) |
| Group-B Vs Group-BD | 0.00000000008 (Sig.) | 0.00000000006 (Sig.) | 0.00015 (Sig.) | 0.0000034 (Sig.) | 0.0000000008 (Sig.) | 0.000053 (Sig.) |

NS- Not Significant Sig.- Significant

In Table-3, it is observed that the Group-B and Group-BD were significantly different to each other at every post-operative time points till 24 hours while, Group- BC & Group-BD were significantly different to each other only at the time point of 30 minutes and 2 hours. Group-B and Group BC were significantly differing to each other at every post-operative time points except the time points of 30 minutes and 2 hours; p-values (<0.05).

**Table 4- Mean±SD time to first request for analgesia (min) among the groups**

| Time | Group B | Group BC | Group BD | p-value (ANOVA) & statistical significance |
|---|---|---|---|---|
| Average time to first request for analgesia (min) | 39.4±22.2 | 50.4±39.5 | 89±38.1 | 0.00000002 (Significant) |

In Table-4, it can be observed that the time to first request of analgesia (in minutes) of patients in Group-B were lower among all the groups while average time to first request of analgesia (in minutes) Group-BD was higher among all the groups. p-value< 0.05.

**Table 5- Mean±SD total fentanyl (mcg/Kg) among the groups and their significance**

| Time | Group B | Group BC | Group BD | p-value (ANOVA) & statistical significance |
|---|---|---|---|---|
| Average of total fentanyl (mcg/Kg) | 77.5±21.6 | 62.8±4.4 | 60.6±4.2 | 0.0249260 (Significant) |

In Table 5, The mean (SD) of total fentanyl (mcg/Kg) of patients in Group B was 77.5(21.6) while in 62.8 (4.4) in Group BC and 60.6 (4.2) in Group BD. p- value< 0.05.

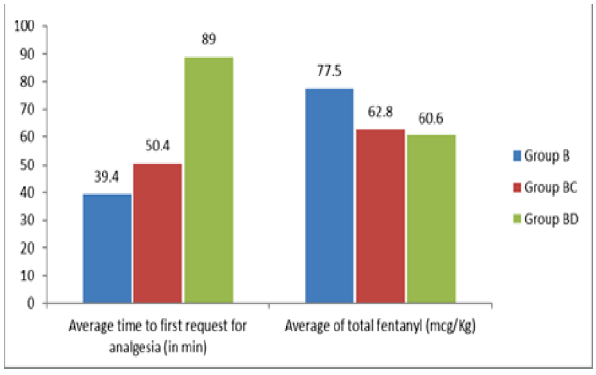


**Fig 2- Averages of time to first request for analgesia (minutes) and total fentanyl (mcg/Kg) among the groups**

**Table 6- p-values for comparison (using t-test) of time to first request for analgesia (min) of patients between groups**

| Groups | First request for analgesia (min) |
|---|---|
| Group-B Vs Group-BC | 0.15177542 (NS) |
| Group-B Vs Group-BD | 0.00000001 (Sig.) |
| Group-BC Vs Group-BD | 0.00007155 (Sig.) |

NS- Not Significant Sig.- Significant.

In Table-6, Group-B and Group-BC were not significantly different to each other based on time to first request of analgesia while Group-BC & Group-BD and Group BD & Group B were significantly different to each other based on time to first request of analgesia.

**Table 7- p-values for comparison (using t-test) of total fentanyl (mcg/Kg) of patients between groups**

| Groups | Total fentanyl (mcg/Kg) |
|---|---|
| Group-B Vs Group-BC | 0.026489 (Sig.) |
| Group-B Vs Group-BD | 0.012982 (Sig) |
| Group-BC Vs Group-BD | 0.317715 (NS) |

NS- Not Significant Sig.- Significant

In Table-7, Group-B & Group-BC and Group-B and Group-BD are significantly different to each other based on total fentanyl (mcg/Kg) as the p-values<0.05 whereas Group BC & Group BD are not significantly different to each other based on total fentanyl (mcg/Kg) in pair-wise comparison.

**Table-8 Frequency (percentage) of adverse effect in patients among groups**

| Adverse Effect | Group B | Group BC | Group BD |
|---|---|---|---|
| Bradycardia | 0(0%) | 0(0%) | 4(11.1%) |
| Nausea | 13(36.1%) | 7(19.4%) | 5(13.9%) |
| None | 23(63.9%) | 29(80.6%) | 27(75%) |

In Table-8, it can be observed that 2 (5.6%) patients in Group B received fentanyl two times while no patient in Group BC and Group BD received fentanyl two times. 12 (33.3%) patients in Group B received fentanyl one time while 9 (25%) in Group BC and 8 (22.2%) in Group BD received fentanyl one times.

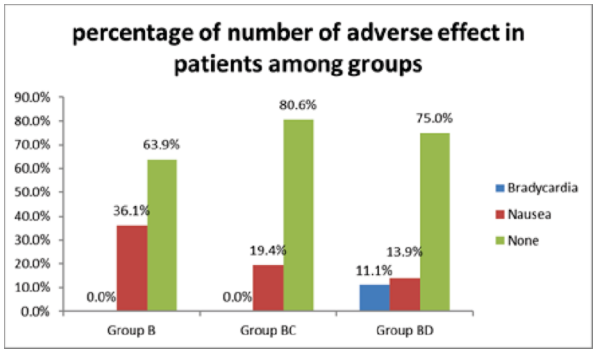


**Fig. 3 –Percentage of numbers of adverse effects in patients among groups**

## DISCUSSION

Laparoscopic cholecystectomy has various advantages over open cholecystectomy in terms of shorter hospital stay, early return to daily activities, lower morbidity, shorter operative time. There have been efforts to minimize the post-operative pain to further enhance the technique.

Intraperitoneal instillation of Local Anaesthetic drugs avoids side effects related to NSAIDs, opioids and longer post-operative pain control period as compared to repeated administration of other analgesics [3].

Numerical Rating Scale (table 1,2) for quality of post-operative pain was significantly lower in clonidine as compared to Bupivacaine alone at 1 hour, 4 hours, 6hours and 24 hours post-operative interval. Therefore, suggesting a better outcome when using Bupivacaine along with Clonidine rather than plain Bupivacaine, whereas NRS was significantly lower in Dexmedetomidine as compared to clonidine groups at 30 min and 2 hours only. This implies comparable results for quality of pain among BC and BD.

The time for 1st Request for analgesia (table 4,6) showed significant difference between Dexmedetomidine vs. Clonidine (p= 0.00007155) and Bupivacaine vs. Dexmedetomidine (p=0.00000001). However, the time for 1st analgesia Request was comparable between clonidine and Bupivacaine (p=0.15177542).

Total Fentanyl dose (in mcg) (table 5,7) used was least in Dexmedetomidine (60.6±4.2) as compared to clonidine (62.8±4.4) and bupivacaine (77.5±21.6). Moreover, significant difference in fentanyl dose was only found between bupivacaine vs. Clonidine (p=0.026489) and dexmedetomidine vs. Bupivacaine (p=0.012982).

Majority of the patients had no complication (table- 8), while a small proportion of cases in plain bupivacaine (8.3%), clonidine with bupivacaine (13.9%) and dexmedetomidine with bupivacaine (2.8%) groups had Nausea, while only a few cases in Dexmedetomidine had Bradycardia (11.1%) which were managed with intravenous fluid boluses and atropine 0.01mg/kg and monitored closely.

**Vijayaraghavalu S et al** [4] compared normal saline and plain bupivacaine (0.5%) and observed a significant (P = 0.04) reduction in postoperative pain for the first six hours postoperatively in patients; moreover, the time taken to request for rescue analgesia requirement was prolonged (P = 0.04)..

**Lakshmi praveena et al** [5] observed Visual Analog Scale score at different time intervals, overall Visual Analogue Scale in 24 h was significantly lower (1.68 ± 0.46 vs. 4.47 ± 0.94) in Ropivacaine plus dexmedetomidine group than in Ropivacaine plus, Fentanyl group.

**Jain et al**. [6], reported significantly lower Visual Analogue Scale score was observed in patients managed by adjuvant of Clonidine and Bupivacaine as compared to only Bupivacaine. **Kaarthika et al.** [7] who reported time to first request for analgesia was shortest in patients who received clonidine (64.0 ± 60.6 min) when compared to the other groups (Bupivacaine, 78.8 ± 83.4 min; Bupivacaine plus Dexmedetomidine, 112.2 ± 93.4 min; P < 0.05)

**Aanchal et al** [8] studied in groups receiving dexmedetomidine had higher number of patients developing bradycardia as compared to patients receiving clonidine.

**Govil et al.** [9] also reported that the side-effects were comparable between the patients treated with an adjuvant of clonidine with bupivacaine and bupivacaine alone.

Hence, both Clonidine and Dexmedetomidine can safely be recommended as adjuvants to Bupivacaine for prolonging the duration and better quality of analgesia, also, lower requirement of Fentanyl as rescue analgesia needed for post-operative analgesia, while having comparable adverse effects in patients undergoing laparoscopic cholecystectomy which was easily managed for the same. Dexmedetomidine proves to be a better alternative than clonidine due to its better efficacy in post-operative pain management.

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