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A comparative study of analgesic efficacy of buprenorphine and fentanyl as an adjuvant with bupivacaine in open cholecystectomy under thoracic epidural anaesthesia

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Abstract: Background: Thoracic epidural analgesia (TEA) remains a critical tool for anaesthesiologists to use in acute pain management. Present study was aimed to investigate the analgesic effect of buprenorphine and fentanyl as adjuvant with bupivacaine in thoracic epidural anaesthesia in patients undergoing open cholecystectomy.
Material and Methods: Present study was prospective, randomized, blinded study, conducted patients 18-50 years, of either sex, ASA physical status I and II, posted for elective open cholecystectomy under thoracic epidural anaesthesia. The patients were randomly allocated into 2 groups, A (buprenorphine) or B (fentanyl) of 30 each.
Results: Onset of analgesia in group A was 5.97 min while that of group B is 5.43 min at T10 level. There was no difference in the onset of analgesia between the two groups. Mean duration of analgesia of group A is 701.53 min while that of group B is 477.17 min, which is statistically significant with p value <0.0001. So, duration of analgesia is higher in buprenorphine compared to fentanyl as an adjuvant with bupivacaine in thoracic epidural anaesthesia. Mean two segment regression time of group A is 129.96 min while that of group B is 120.7 min, which is statistically significant with p value 0.0057. VAS is statistically significant in group B at 6th ,12th and 20th hrs. In the Group A, 20 % patients show nausea and 10% shows vomiting, while in the group B, 10% complained of nausea and 36.67% complained of pruritus.
Conclusion: Open cholecystectomy cases can be done under thoracic epidural anaesthesia with 0.5% bupivacaine and buprenorphine or fentanyl as an adjuvant. Buprenorphine having prolong duration of analgesia can be better than fentanyl even in postoperative period.

Keywords: Buprenorphine; Fentanyl; Bupivacaine; Open cholecystectomy; Thoracic epidural anaesthesia.

1. Introduction

Open cholecystectomy is a major surgery performed routinely. It is commonly done under GA. There are many draw backs of GA associated with open cholecystectomy like pulmonary infection, diaphragmatic dysfunction, basal atelectasis, and increased perioperative morbidity and mortality. Marked diaphragmatic dysfunction occurs postoperatively, caused by both reflex diaphragmatic changes and incisional pain [1].

Thoracic epidural analgesia (TEA) remains a critical tool for anaesthesiologists to use in acute pain management. TEA is particularly effective for reducing pain after thoracic and upper abdominal surgery and likely permits major surgical procedures to be performed on patients with moderate to severe comorbid diseases, who several years ago may have been determined to be too great a risk for surgery [2]. The benefit

and indication for TEA are expanding. Thoracic epidural anaesthesia offers superior perioperative analgesia compared with systemic opioids, decrease postoperative pulmonary complication, decrease the duration of postoperative ileus [3].

Bupivacaine is a widely used drug in epidural anaesthesia. Buprenorphine is a thebaine derivative, mu-receptor partial agonist and antagonist. It is effective in relieving moderate to severe pain, when placed in epidural space the high lipid solubility and affinity for opioid receptors limit the cephalad spread [4]. Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist; it is 75 to 125 times more potent than morphine [4]. Present study was aimed to investigate the analgesic effect of buprenorphine and fentanyl as adjuvant with bupivacaine in thoracic epidural anaesthesia in patients undergoing open cholecystectomy.

2. Material and methods

Present study was prospective, randomized, blinded study, conducted in Department of Anaesthesiology and Critical Care, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, India. Study duration was of 1 year (September 2020 to August 2021). Study approval was obtained from institutional ethical committee.

2.1. Inclusion criteria

Patients 18-50 years age, of either sex, ASA physical status I and II, posted for elective open cholecystectomy under thoracic epidural anaesthesia, willing to participate in present study.

2.2. Exclusion criteria

Patients displaying sign and symptoms of systemic infection, local infection in thoracic spinal region. Patients with pre-existing Diabetes Mellitus, CNS, CVS, Respiratory illness or any other major systemic illness. Bleeding diathesis or coagulopathy, spinal deformity like kyphosis, scoliosis etc., any other contraindication to neuraxial block OR Failed block. Patients having known hypersensitivity to the drugs. Unwilling patients not giving consent for operation.

All patients admitted under the department of surgery. All patients were explained regarding the type of anaesthesia and the procedure and informed consent were taken from each patient. A routine pre-anaesthetic examination was conducted on the evening before surgery, assessing History and general condition of the patient, Airway assessment, Nutritional status, height and weight of the patient, detailed examination of the Cardiovascular system, Respiratory system and Central nervous system, examination of the spine, pre-operative history of hypertension (on regular or irregular medication), insulin dependent or non-insulin dependent diabetes mellitus, myocardial infarction, respiratory disease including restrictive or obstructive pattern (with or without medication) were recorded.

Every patient received tablet alprazolam 0.25 mg (<40 kg) or0.5 mg (>40 kg body wt.) and tablet pantoprazole 40 mg in the night before surgery. The patients were asked to stay nil orally for at least 6 hours prior to the operation. All the patients were explained about the evaluation of postoperative pain with the use of VAS scores.

The patients were randomly allocated into 2 groups, A (buprenorphine) or B (fentanyl) of 30 each by block randomisation, with 5 patients in each block; a total of 6 such blocks. Both the observer and the patients were blinded to the study drugs. In operation theatre, baseline pulse rate, Respiratory rate, systolic and diastolic pressure was recorded and the mean arterial pressure (MAP) calculated. Patient were connected to multichannel monitor and baseline heart rate, non-invasive blood pressure (SBP, DBP & MAP), temperature and Spo2 were recorded.

After insertion of 18G IV cannula a ringer's solution were connected and continued. Each patient was given inj Midazolam 0.02mg/kg prior to operation. Epidural anaesthesia was administered in sitting position. Proper cleaning and identification of space done, 2ml 2% lignocaine with adrenaline used to infiltrate the skin and subcutaneous tissue at T8-9 or T9-10 interspace. For epidural anaesthesia, an 18 G Tuohy needle introduced by loss of resistance technique with saline. Epidural catheter insertion done and the needle is withdrawn. Catheter was placed 3-4 cm inside the epidural space. After negative aspiration, a test dose of 3ml of 2% lignocaine with adrenaline (1: 2,00,000) was given to rule out intravascular or intrathecal placement. Five minutes after test dose, in the absence of any adverse sequelae,

- Group A: graded epidural in incremental doses with 0.5% Bupivacaine with 150 mcg buprenorphine till a block height of T4 dermatome is achieved.
- Group B: graded epidural in incremental doses with 0.5% bupivacaine with 50 mcg fentanyl till a block height of T4 dermatome is achieved

After injection of the drug, the epidural catheter was secured in place with adhesive tapes and sterile gauge, then bacterial filter was added and patient was placed to undergo operation. All the patients were given oxygen @5lit/min via face mask. Assessment of sensory blockade done at the end of each minute with the patient in supine position after completion of the injection of the study drug, the time at which epidural injection of the study drug completed would be considered as zero (t=0). The onset time and the time for maximum sensory block was recorded. Sensory blockade was assessed using a cold swab bilaterally. The level of motor block was considered two segments below the level of sensory block.

Post-operative we assessed the patient in post op ward in half an hour interval to see analgesic efficacy of the drug till patient complains of pain or VAS score will be more than 4. To maintain post op analgesia intermittent top-up was given through epidural catheter with 0.125% bupivacaine. Catheter is removed after 48 hours.

Vital parameters such as the heart rate, blood pressure, respiratory rate, and oxygen saturation was continuously monitored for every 3 minute for first 15 minutes, then every 5 min till 30 minutes, then every 10 minutes for 2 hrs., thereafter every 30 minutes till patient complains of pain. Complications like nausea, vomiting, headache, dizziness, hypotension, bradycardia, urinary retention, shivering and respiratory depression were also being recorded. Postoperative analgesia assessed by VAS (Visual Analogue Scale-numeric pain scale 0-10). Where 0 being no pain and 10 being the worst possible pain.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

3. Results

A total of 60 patients of both sex selected randomly for the study. Mean age of Group A was 35.06 $\pm$ 7.04 years and mean age of Group B was 35.7$\pm$6.35. Maximum patients belong to age group of 30-40 years. Difference of age in both the group was statistically insignificant (p=0.7129). In Group A total male patient is 14 and female patient is 16 while is group B total male and female patient is 15. Mean weight of Group A is 60.13$\pm$7.57 kg and mean age of Group B is 58.63$\pm$5.41 kg, difference was statistically insignificant (p=0.3809). Mean height of Group A is 163.13$\pm$9.25 cm and mean age of Group B is 163.9$\pm$10.09 cm, difference was statistically insignificant (p=0.7591).

Table 1. General characteristics

	Group A	Group B	p value
Age groups (in years)			
20-30	6	4	
30-40	15	18	
40-50	9	8	
Mean age (mean $\pm$ SD)	35.06$\pm$7.04	35.7$\pm$6.35	0.7129
Gender			
Male	14	15	
Female	16	15	
Mean Weight (kgs)	60.13$\pm$7.57	58.63$\pm$5.41	0.3809
Mean Height (cm)	163.13$\pm$9.25	163.9$\pm$10.09	0.7591

It is observed that onset of analgesia in group A is 5.97 min while that of group B is 5.43 min at T10 level. At T4 level onset of analgesia in group A is 15 min and in group B is 14.3 min; which is statistically not significant. There was no difference in the onset of analgesia between the two groups.

Table 2. Onset of Analgesia in minutes

Dermatome level	Group A (mean ± SD)	Group B (mean ± SD)	t	P value	
T10	5.97 ± 1.22	5.43 ± 0.97	1.898	0.0627	NS
T8	8.13 ± 1.65	7.73 ± 1.46	0.994	0.3242	NS
T6	10.8 ± 1.86	10.07 ± 1.70	1.587	0.1180	NS
T4	15 ± 2.54	14.3 ± 1.79	1.234	0.2222	NS

Mean duration of analgesia of group A is 701.53 min while that of group B is 477.17 min, which is statistically significant with p value <0.0001. So, duration of analgesia is higher in buprenorphine compared to fentanyl as an adjuvant with bupivacaine in thoracic epidural anaesthesia. Mean two segment regression time of group A is 129.96 min while that of group B is 120.7 min, which is statistically significant with p value 0.0057.

Table 3. Other characteristics

	Group A (mean ± SD)	Group B (mean ± SD)	P value
Mean duration (min)	701.53 ± 138.26	477.17 ± 142.39	<0.0001 Significant
Two segment regression time (min)	8.13 ± 1.65	7.73 ± 1.46	0.0057 Significant

VAS is calculated in post of period for post-operative analgesia. Up to 4 hrs. VAS is not significant in both the group. At 6th hrs., VAS is statistically significant as Group B receiving inj fentanyl is starting having pain at the site of surgery. Top up dose of epidural analgesia is given at that point. Again, VAS is statistically significant at 12th hr. and 20th hrs.

Table 4. VAS

Time Interval	Group A		Group B		P Value	Significance
	Mean	SD	Mean	SD		
1	0.5	0	0.51	0.09	0.547	Not significant
2	0.52	0.12	0.83	0.84	0.051	Not significant
4	0.74	0.4	1.13	1.1	0.073	Not significant
6	0.78	0.4	2.95	1.82	<0.000	Significant
8	1.77	1.47	1.58	1.45	0.616	Not significant
12	2.13	1.64	0.55	0.27	<0.000	Significant
16	1.08	1.33	0.96	0.34	0.633	Not significant
20	0.53	0.12	2.01	1.39	<0.001	Significant

In the Group A, 20 % patients show nausea and 10% shows vomiting, which are mild in nature and did not require any treatment. While in the group B, 10% complained of nausea and 36.67% complained of pruritus, which was mild in nature and did not require any medication to treat. No patient of either group shows urinary retention or hypotension.

Table 5. Side effects

Side effects	Group A		Group B	
	NO	%	NO	%
NAUSEA	6	20	3	10
VOMITING	3	10	-	
URINARY RETENTION	-		-	
PRURITUS	-		11	36.67
HYPOTENSION	-		-	

4. Discussion

Surgical pain is very severe immediately after surgery and gradually reduces over the next 24 hours. Existence of pain has been a constant stimulus to the discovery of both drugs and procedures for relief of pain [5]. There is also increased incidence of nausea and vomiting following cholecystectomy augmented by GA, which requires administration of postoperative anti-emetics. These factors can in turn lead to a prolonged hospital stay [6].

Epidural anaesthesia is better than general anaesthesia in open cholecystectomy cases as there are fewer side effects and less exposure to aerosol produced during laryngoscopy. Moreover, it is safer than general anaesthesia in patient with cardiopulmonary complications. Epidural analgesia also provides better pain relief in post-operative period than commonly used intravenous analgesics. To fulfil this demand, there is a need for local anaesthetic with desirable properties like longer duration of sensory blockade and shorter duration of motor blockade [7]. The role of TEA as either a primary anaesthetic or as an adjuvant to GA for cardiac, thoracic, abdominal, colorectal, genitourinary, and gynecologic surgery is expanding [3].

Zenz *et al.*, [8] studied morphine (5 mg) and buprenorphine (0.15 mg) given by the epidural route and both substances produced thorough analgesia with short latency (2-6 min) of long duration (8-9 h). Total lack of side effects with buprenorphine favours its application in epidural pain relief.

Reddy [9] found addition of 50 mcg fentanyl to 0.5 % bupivacaine (group B) resulted in faster onset of sensory and motor blockade which was statistically insignificant compared to 150mcg buprenorphine with 0.5% bupivacaine (group A).

Dhalae *et al.*, [10] studied epidural Bupivacaine and epidural Bupivacaine with Fentanyl for peri-operative analgesia, they concluded that Fentanyl 50 mcg with Bupivacaine has longer duration of analgesia (256.66 mins) and ideal for postoperative analgesia with minimum side effects.

Parate *et al.*, [11] found that addition of 50 mcg fentanyl to epidural 0.5% bupivacaine significantly reduces the VAS score. It also reduces intra-operative analgesia supplementation and prolongs the duration of postoperative analgesia without altering the other characteristics of block in elective LSCS cases.

Padhy *et al.*, [12] found a statistically significant difference in the mean time of onset of analgesia between 9.5 mins in the fentanyl group as compared to 13.2 mins with buprenorphine. The difference in findings from our study may be due to the different site of placement of epidural catheter.

In our study mean duration of analgesia in group A was 701.53 min which was significantly longer compared to group B of mean duration of analgesia was 477.17 min. Buprenorphine has high affinity for spinal receptors & smaller doses produced a high concentration at spinal receptors so lower drug dose is required. Higher lipid solubility of buprenorphine favours its diffusion in to spinal cord. The diffusion from the spinal cord in to the blood stream is slow and does not approach the bulbar centers. Hence high lipid solubility, strong opiate receptor binding and intense and prolonged activity was responsible for longer duration of action [13].

Gupta *et al.*, [14] found that mean time of onset of analgesia was 8.43mins in the fentanyl group as compared to 13.70 mins in case of buprenorphine. The longer onset of action from our findings may be because they have used the opioids alone without any local anaesthetics. Reddy JS9 found duration of was significantly longer in Group A (766.6 minutes) as compared to 471 min in Group B. These findings are close to the present study.

Two segment regression time is the time interval from injection of local anaesthetic solution until the maximum level of sensory blockade has regressed by two segment. In our study mean two segment regression time of group A is 129.96 while that of group B is 120.7, which was statistically significant. Manjula *et al.*, [15] found the two-segment regression time of buprenorphine group to be 135.4$\pm$6.11. Which is close to our observation.

The four classic side effects of neuraxial opioids are nausea and vomiting, pruritus, depression of ventilation and urinary retention. Side effects are due to presence of drug in either CSF or systemic circulation. Side effects are dose dependent. Naloxone, an opioid antagonist can be used to treat these side effects.

Patients were observed for side effects like nausea and vomiting, urinary retention, pruritus, sedation and hypotension in our study. In group A, 6 patients 20%) developed nausea and 3 patients (10%) had vomiting while in group B, only 3 patients (10 %) developed nausea with no vomiting. In Group B, 11 patients (36.67%) developed pruritus compared to none in Group A in our study.

Hayashi *et al.,* [16] noted that there was no difference between the analgesic efficacies, but incidence of nausea or vomiting and dizziness was significantly less in fentanyl group, which concurs with our study. D. Kumar and co-workers and Hayashi H and co-workers study on buprenorphine also correlate with our study [17].

Reddy [9] observed no significant respiratory depression in either fentanyl or buprenorphine groups. The incidence of Nausea and vomiting was more in buprenorphine (40 %) compared to fentanyl (10 %). Mild pruritus was more in fentanyl group (10%) which did not require any treatment. Lytle *et al.,* [18] studies on fentanyl concluded with same findings with our study. Patients were comfortable and composed throughout the procedure and did not require any further medication in either of the groups.

TEA was not a preferred technique for the open cholecystectomy, but slowly with practice and better understanding, its efficacy in providing adequate operating condition with better hemodynamic stability and extension of its benefit in early post op recovery are being increasingly realized by clinical anaesthetist [3]. Thoracic epidural anaesthesia provides selective blockade of the surgical site and advantages like preservation of spontaneous respiration, contracted intestine due to sympathetic blockade helps the surgeon, avoids intubation, reduced incidence of paralytic ileus, minimizes alteration in body physiology, reduces wound bleeding [19].

Short- and long-term complications need to be evaluated with appropriate follow up and large population based multicentric studies could provide more accurate result. The effect of motor block in thoracic epidural anaesthesia with the study drugs need to be evaluated.

5. Conclusion

Both buprenorphine and fentanyl along with bupivacaine 0.5% can be given in TEA for perioperative analgesia; which provide faster onset of analgesia and good motor and sensory block with minimal side effects and many advantages over general anaesthesia in open cholecystectomy cases. Buprenorphine having prolong duration of analgesia can be better than fentanyl even in postoperative period. Open cholecystectomy cases can be done under thoracic epidural anaesthesia with 0.5% bupivacaine and buprenorphine or fentanyl as an adjuvant.

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