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Original Article

Comparative Study of Post-operative Analgesia Using Epidural Bupivacaine Versus Bupivacaine and Fentanyl Versus Bupivacaine and Neostigmine in Total Abdominal Hysterectomy

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Abstract

Introduction: Post-operative pains following abdominal surgeries are of major concern as they cause psychological trauma and stress to the patients. Numerous studies involving multimodal post-operative analgesics strategies have been undertaken.

Aim: This study was undertaken in assessing efficacy of using epidural bupivacaine, bupivacaine with fentanyl and bupivacaine with neostigmine for patients undergoing total abdominal hysterectomy under general anesthesia.

Materials and Methods: A prospective, randomized, triple arm, single-blind, controlled study was conducted at Government Kilpauk Medical College Hospital and Government Royapettah Hospital, Chennai, for the patients undergoing total abdominal hysterectomy under general anesthesia. Informed consent from patients was obtained. The patients were divided into three groups of 20 in each based on computerized random number into Group B, Group BF, and Group BN. The patients in Group B received 10 ml of 0.125% bupivacaine, the patients in Group BF received solution containing 10 ml of 0.125% bupivacaine with fentanyl (1 mcg/kg), and the patients in Group BN received 10 ml of 0.125% bupivacaine with neostigmine (10 mcg/kg) epidurally at the start of surgical site closure. Time to first rescue analgesia, visual analog scale and Ramsay sedation score after giving epidural bolus dose, and the mean arterial blood pressure were monitored and compared.

Results: Mean time for first rescue analgesia in Group B was 104.75 ± 1.60, Group BF was 289.25 ± 3.23, and Group BN was 261.00 ± 4.13. The visual analog scale variation in the three groups had statistically significant difference in 60, 120, 180, and 240 min.

Conclusion: It was found that post-operative analgesia and other parameters were significantly advantageous in the groups of BF and BN when compared to Group B.

Key words: Bupivacaine, Epidural, Laparotomy, Neostigmine and fentanyl

INTRODUCTION

Acute pain in the post-operative setting can have adverse physiological and psychological effects due to the stress hormone response induced by anesthesia and surgery. The main objective of providing post-operative analgesia is to make the patient comfortable without pain, promote early ambulation, and improve respiratory function and early restoration of his/her routine life. In abdominal surgeries, the incidence of post-operative pain is higher causing restriction of the diaphragmatic movements.[1] This could result in basal atelectasis, respiratory tract infections due to decreased effort in coughing out the secretions, deep venous thrombosis due to poor ambulatory effort, all of which lead to increased duration of hospital stay, expenditure, morbidity and mortality. Providing epidural

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block with local anesthetic drugs in these patients can efficiently relieve post-operative pain.[2] Bupivacaine is one of the commonly used drugs for post-operative analgesia. Bupivacaine belongs to aminoacyl group of local anesthetics. It has a Pka of about 8.1 with protein binding capacity of 95%. It is highly potent has a slow onset and longer duration of action. 0.25% and lower concentrations of bupivacaine are preferred for use in obstetric patients and out patients for day care procedures. Usage of bupivacaine alone has its own disadvantages with regards to the dosing and concentration leading to subsequent hypotension that may ensue. Thus came the need for adjuvants such as opioids and alpha-2 agonists. Neostigmine has also been used in numerous studies and found advantageous in prolonging the duration of the epidural while reducing the concentration of bupivacaine. Fentanyl is 800 times more lipid soluble than morphine and rapidly is absorbed from the epidural space and cerebrospinal fluid (CSF). Its onset of action is very rapid which is about 15-30 min and its duration of action is 2-5 h.[3,4] The initial epidural bolus dose of fentanyl is 5 mcg/kg. Pruritus is the most common side effect. Neostigmine, an anticholinesterase drug, which is used to antagonize nondepolarizing muscle relaxants, has been tried for post-operative analgesia as an off-label use. Being a quaternary amine, it does not cross blood-brain barrier. Epidural neostigmine provides analgesia through M1 and M2 receptors in the spinal cord, inhibiting the breakdown of acetylcholine. It also prolongs and intensifies the analgesia increasing cyclic guanidino-mono phosphate by generating nitric oxide. It prolongs motor blockade when combined with a local anesthetic. Neostigmine also displays peripheral and supraspinal analgesic activity, however, the dose necessary to achieve this seems to be higher. Several studies have demonstrated that the use of epidural neostigmine is associated with lesser adverse effects and the proposed mechanism of analgesia is by drug spreading into CSF at the rate of $1/10^{th}$ the epidural dose.[5,6]

Aim

The aim of the study is to compare "The post-operative analgesic efficacy of epidural bupivacaine, bupivacaine plus fentanyl and bupivacaine plus neostigmine in adults is undergoing total abdominal hysterectomy under general anesthesia" by assessing:

1. Duration of post-operative analgesia, i.e., time interval between epidural drug bolus and time for first rescue analgesia
2. Visual analog scale after giving first epidural bolus dose
3. The Ramsay sedation score after giving first epidural bolus dose
4. Mean arterial blood pressure (MAP) perioperatively extending 12 h postoperatively.

MATERIALS AND METHODS

A prospective, randomized, triple arm, single-blind, controlled study was conducted at Government Kilpauk Medical College Hospital and Government Royapettah Hospital, Chennai, for the patients undergoing total abdominal hysterectomy under general anesthesia. Informed consent from patients was obtained. Female patients aged 20-60 years, belonging to ASA PS I and II who have given valid informed consent and undergoing elective total abdominal hysterectomy under general anesthesia. The patients refusal, contraindications to epidural anesthesia, and patients with allergy or sensitivity to the drugs used were excluded from the study.

A total of 60 patients were included in the study. The patients were divided into three groups (n = 20) in each based on computerized random number into Group B, Group BF, and Group BN. The patients in Group B received 10 ml of 0.125% bupivacaine, the patients in Group BF received solution containing 10 ml of 0.125% bupivacaine with fentanyl (1 mcg/kg), and patients in Group BN received 10 ml of 0.125% bupivacaine with neostigmine (10 mcg/kg) epidurally at the starting of surgical site closure. Routine monitoring included electrocardiogram, pulse oximetry, and noninvasive blood pressure. Intravenous (IV) cannulation was done with 18 G venflon. Premedication with injection of glycopyrrolate 6 mcg/kg IV, injection of midazolam 0.01 mg/kg IV, and injection of fentanyl 2 mcg/kg IV was administered. Under sterile aseptic precautions an epidural catheter was placed at the level of T12-L1 intervertebral space with 5 cm *in situ*. After ensuring that neither blood nor CSF was aspirated via catheter, a test dose of 3 ml 2% lignocaine with adrenaline (1:2,00,000) dilution was given.

Patients' vitals including heart rate, respiratory rate, MAP, and oxygen saturation are measured at the following time intervals 15, 30, 45, 60, 90, 120, and 180 min and hourly till 12 h in the post-operative period. Only surgeries completed within 200 min were taken for this study. Time for first rescue analgesia, visual analog scale and Ramsay sedation score after giving epidural bolus dose, and MAP were observed hourly till 12 h into the post-operative period.

The patient was then made to lie in supine position. Preoxygenated with 100% oxygen for 3 min. Then, it induced with injection of propofol 2 mg/kg and atracurium 0.5 mg/kg. The patient was intubated with appropriate sized endotracheal tube and secured after ensuring bilateral air entry. Maintenance was with nitrous oxide and oxygen in the ratio of 2:1 and sevoflurane 2 vol%. Injection of fentanyl was given 1 mc/kg 1 h after start of incision.

The epidural drug administration was given at the time of wound closure according to the patient belongs to. At the end of surgery, the patient was reversed and extubated after satisfying Aldrete criteria.

Statistical Analysis

Descriptive statistics was done for all data and reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired *t*-test and ANOVA single factor test. Categorical variables were analyzed with the Chi-square test and Fisher exact test. Statistical significance was taken as $P < 0.05$. The data were analyzed using SPSS version 16 and Microsoft Excel 2007.

RESULTS

The pre-operative heart rate, respiratory rate, MAP, and oxygen saturation were recorded before administering epidural block.

Figure 1 shows mean time for first rescue analgesia in Group B was 104.75 ± 1.60, Group BF was 289.25 ± 3.23, and Group BN was 261.00 ± 4.13. The three groups were comparable with respect to the time for first rescue analgesia. Analysis of variants in Figure 1 showed they were highly statistically significant ($P < 0.05$).

Visual analog scale variation in the three groups and the analysis of variants in Table 1 showed they were highly statistically significant.

Table 2 shows the Ramsay sedation score after giving epidural bolus dose in the three groups and they were found to be comparable. Analysis of variants in Table 3 showed they were highly statistically significant.

Table 3 shows the MAP variation in the three groups which were found comparable. There was no statistically significant difference in MAP neither intraoperatively nor postoperatively until 12 h of observation.

DISCUSSION

Out of 60 patients ($n = 20$) in this study, the results of our study showed there were no significant difference in age distribution, weight distribution, and gender status among the three groups ($P > 0.05$). The time for first rescue analgesia in Group B was 104.75 ± 1.60, Group BF was 289.25 ± 3.23, and Group BN was 261.00 ± 4.13. Based on this evaluation, the duration of post-operative analgesia in Group BF and Group BN was found to be much higher when compared to Group B. Tekin *et al.*, compare the post-operative analgesic activity of the neostigmine and fentanyl when

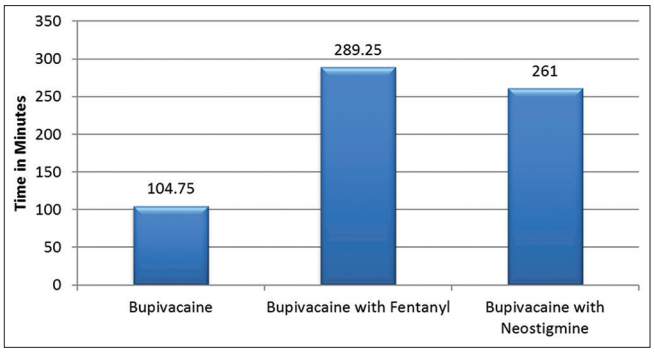

Figure 1: Comparison of average time for first rescue analgesia in Group B, Group BF, and Group BN

used as an additive to bupivacaine in patients undergoing abdominal hysterectomy under general anesthesia showed that the duration of post-operative analgesia and total analgesic consumption was better when either fentanyl or neostigmine is added as addictives to bupivacaine than bupivacaine alone.[4] Ross *et al.* did a randomized controlled study on a group of obstetric patients using bupivacaine and neostigmine as patient controlled epidural analgesia in 40 healthy patients posted for elective cesarean section. Epidural neostigmine infusion reduced bupivacaine requirement by 19% in all patients and 25% in those with >4 h of treatment ($P < 0.05$ for both). It was also found that these patients also experienced mild sedation.[5] Shehab and Salman conducted a study in women who underwent open abdominal hysterectomy for dysfunctional uterine bleeding under epidural combined with general anesthesia. The results showed that the mean duration of post-operative analgesia was significantly longer in the dexamethasone/levobupivacaine group compared with groups neostigmine/levobupivacaine and levobupivacaine, with significantly longer duration in the neostigmine/levobupivacaine group compared with group levobupivacaine.[6] Nakayama *et al.* evaluated the analgesic effects of epidural neostigmine in adult patients undergoing abdominal hysterectomy. 45 ASA I patients posted for elective abdominal hysterectomy were enrolled in this study. These patients were randomly divided into three groups. Here, the duration of post-operative analgesia was higher in the 10 μg group than 5 μg group.[7] Lauretti *et al.* compared the post-operative analgesic property of intra-articular and epidural neostigmine in patients undergoing knee surgery under combined spinal-epidural anesthesia. The time (min) for first rescue analgesia was much longer in both the 1 ug/kg epidural neostigmine (EG) Group and 500 ug intra-articular neostigmine (AG) groups ($P < 0.05$). The pre-operative hemodynamic parameters were comparable between the three groups (Group B, Group BF, and Group BN). Post-operative sedation and visual analog scores were also significantly higher in Group BF and Group BN when compared to the Group B.[8] Cossu *et al.* found that neostigmine was used as an adjuvant to local anesthetics for neuraxial blockade

Table 1: Comparison of visual analog scale after giving epidural bolus dose in Group B, Group BF, and Group BN

Time after giving epidural dosage (in min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	*P* value
60	3.55±0.95	0.25±0.12	0.45±0.14	<0.0001
120	7.85±0.41	0.60±0.18	1.15±0.17	<0.0001
180	5.50±0.36	0.75±0.16	1.25±0.18	<0.0001
240	4.75±0.23	1.55±0.44	3.75±0.68	<0.0001
300	4.80±0.26	6.30±0.65	6.55±0.47	0.028
360	4.60±0.26	4.80±0.42	4.70±0.29	0.912
420	4.80±0.24	3.90±0.24	3.90±0.22	0.009
480	4.55±0.24	3.60±0.29	4.05±0.22	0.036

Table 2: Comparison of Ramsay sedation score after giving epidural bolus dose in Group B, Group BF and Group BN

Time after giving epidural bolus dose in (min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	*P* value
Baseline	2.00±0.00	2.00±0.00	2.00±0.00	1.000
60	1.85±0.08	2.60±0.15	2.10±0.07	<0.0001
120	2.00±0.00	3.15±0.15	2.00±0.00	<0.0001
180	2.00±0.00	3.45±0.11	2.00±0.00	<0.0001
240	2.00±0.00	3.10±0.07	2.00±0.00	<0.0001
300	2.00±0.00	2.60±0.11	2.00±0.00	<0.0001
360	2.00±0.00	2.35±0.11	2.00±0.00	<0.0001
420	2.00±0.00	2.00±0.00	2.00±0.00	1.000
480	2.00±0.00	2.00±0.00	2.00±0.00	1.000
540	2.00±0.00	2.00±0.00	2.00±0.00	1.000

Table 3: Comparison of MAP changes in Group B, Group BF, and Group BN

Time (in min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	*P* value
Baseline	90.45±2.34	90.95±2.06	91.55±2.09	0.937
15	80.50±1.85	83.05±1.81	83.35±1.70	0.468
30	84.15±1.58	84.60±1.67	84.90±1.75	0.950
45	84.30±1.34	86.60±1.62	86.55±1.71	0.500
60	84.95±1.46	86.30±1.61	86.15±1.77	0.812
75	84.80±1.34	86.70±1.77	86.75±1.90	0.650
90	84.90±1.42	86.15±1.76	86.35±1.87	0.807
180	87.35±1.93	86.75±1.65	86.80±1.87	0.967
120	84.65±1.45	86.20±1.67	86.80±1.87	0.646
240	87.60±2.41	87.15±1.70	87.30±1.97	0.988
300	83.85±1.65	86.45±1.74	86.60±1.91	0.471
360	85.95±1.86	86.50±1.72	86.60±1.91	0.964
420	86.25±1.84	86.95±1.68	86.60±1.93	0.964
480	86.35±1.84	87.15±1.75	87.40±1.94	0.916
540	86.65±1.87	87.35±1.69	87.85±1.96	0.899
600	86.40±1.67	87.55±1.91	88.15±2.12	0.806
660	86.55±1.91	87.40±1.82	87.00±1.90	0.950
720	86.45±1.81	87.65±1.87	87.15±1.99	0.903

MAP: Mean arterial blood pressure

in obstetric patients to find out its efficacy in producing post-operative analgesia. From this study, they found that the epidural addition of neostigmine to local anesthetic like bupivacaine or ropivacaine resulted in greater analgesic response and greater patient tolerance when compared to the intrathecal administration of neostigmine. Post-operative requirement of subsequent doses of local anesthetics was also significantly reduced ($P < 0.05$).[9] Kaya *et al*. found that in patients posted for elective cesarean study under combined spinal-epidural using epidural neostigmine showed that total duration of post-operative analgesia and global pain satisfaction scores were reduced in the neostigmine group. There were no significant MAP variations found. The parameters were also statistically

significant when compared to the baseline values. Adverse effects such as pruritus and gastrointestinal side effects such as nausea and vomiting were significantly less in Group BN and Group B, but increased in Group BF where fentanyl was used.[10] Roelants and Lavand'homme studied the use of neostigmine and clonidine for labor analgesia in obstetric patients. They found that the post-operative analgesia was similar in both groups, the patients in neostigmine group had fewer side effects like hypotension.[11] In 2012, Jain *et al.* did a study in 45 patients posted for total knee replacement surgery. They compared the post-operative analgesic efficacy of low dose intrathecal neostigmine as an adjuvant to fentanyl and bupivacaine for total knee replacement and found out that the total duration of post-operative analgesia was significantly high in fentanyl and neostigmine group ($P < 0.001$). The total number of rescue analgesia required was significantly higher in bupivacaine group ($P < 0.05$). They also found that epidural neostigmine did not cause any adverse gastrointestinal side effects such as nausea and vomiting.[12]

CONCLUSION

The duration of post-operative epidural analgesia was prolonged when either fentanyl or neostigmine was used as an adjuvant to epidural bupivacaine. However, it was found that fentanyl caused adverse effects such as pruritus, nausea, and vomiting. Thereby, epidural neostigmine may be considered as a safe adjuvant to bupivacaine, since the duration of post-operative analgesia was comparatively similar in both groups (Group BF and Group BN).

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