

A COMPARATIVE STUDY BETWEEN EPIDURAL BUTORPHANOL, NALBUPHINE, AND FENTANYL FOR POST-OPERATIVE ANALGESIA IN LOWER ABDOMINAL SURGERIES

SWARNA BANERJEE*, SHASWAT KUMAR PATTNAIK

Department of , Institute of Medical Sciences and Sum Hospital, Bhubaneswar, Odisha, India. Email: dr.swarnabanerjee@gmail.com

Received: 27 December 2016, Revised and Accepted: 03 March 2017

ABSTRACT

Background: Achieving satisfactory post-operative analgesia with neuraxial administration of narcotics has been the subject of much research. The use of epidural opioids had become an increasingly popular technique for management of acute post-operative pain in recent times. This study evaluates post-operative analgesic benefits in patients administered epidural butorphanol, nalbuphine, and fentanyl as adjuvants with local anesthetics postoperatively for surgery under epidural anesthesia.

Methods: A total of 75 patients belonging to age groups 18-60 years who were scheduled for surgeries of lower abdomen were randomly divided into groups of 25 each. Epidural technique was adopted for surgery of the lower abdomen for all patients with 0.5% bupivacaine. In the post-operative period, the study drug was given through epidural catheter. Group A received butorphanol 2 mg, Group B received fentanyl 100 µg, and Group C received nalbuphine 10 mg with 0.125% bupivacaine diluted to 10 ml in normal saline each. Onset, duration, quality of analgesia, hemodynamic changes, and side effects – such as sedation, pruritus, nausea, vomiting, respiratory depression, and urinary retention - were recorded and compared.

Results: The demographic data were comparable in all three groups. The onset of sensory block was significantly earlier in Group B (fentanyl) than other two groups. Duration was significantly longer in Group A (butorphanol). No serious cardiorespiratory side effects were noted in any of groups.

Conclusion: Fentanyl produces the faster onset of analgesia with adverse effects like pruritus. Butorphanol administered epidurally has the advantage of longer duration of analgesia than fentanyl or epidural nalbuphine with side effects such as nausea, vomiting, and sedation.

Keywords: Epidural analgesia, Butorphanol, Fentanyl, Nalbuphine.

© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i5.16802>

INTRODUCTION

In perioperative scenario pain is now taken up as the sixth vital sign. Acute post-operative pain is associated with several adverse events. Given the multiplicity of mechanisms involved in post-operative pain, a multimodal analgesia regimen using a combination of opioid and non-opioid analgesics has become the treatment of choice for facilitating the recovery process [1,2]. Administration of analgesics through the epidural route is a more popular technique for post-operative pain management as it can be used alone or in combination with general anesthesia [3]. Epidural catheter placed in a location congruent to the incisional dermatome has been shown to provide analgesia that minimizes the need for systemic analgesics, reduces stress response to surgery and pain and facilitates early rehabilitation [4]. Epidural analgesia with local anesthetics was found to be very effective in pain management [3]. Later on, opioids were used as an adjuvant to local anesthetics. The combination was found to be synergistic [3]. Advantages of the combination include better pain relief, motor sparing and reduced overall toxicity.

Butorphanol is a synthetically derived agonist-antagonist opioid analgesic. It is an agonist on κ receptor and either antagonist or partially agonist on μ receptor. Epidural butorphanol has been employed successfully for the relief of post-operative pain. It is considered safer than pure agonist opioids because of its ceiling effect on respiratory depression, lower addiction potential, lesser nausea, vomiting, pruritus, and urinary retention. It produces sedation comparable to or more than that of morphine, which is desired in post-operative period [4].

Fentanyl, a μ opiate receptor agonist, has analgesic potency greater than morphine. It has shorter duration of action and lesser respiratory depressant effect as compared to morphine and pethidine [5].

Nalbuphine is an agonist-antagonist opioid analgesic which is also synthetically derived. It is equal in potency as an analgesic to morphine and is about one-fourth as potent as nalorphine as an antagonist. It also has a ceiling effect on respiratory depression. Sedation is commonly seen when used in post-operative period as an analgesic [3].

This study was conducted to evaluate post-operative analgesic benefits in patients administered epidural butorphanol, nalbuphine, and fentanyl as adjuvants with local anesthetics postoperatively for surgery under epidural anesthesia and to compare their post-operative efficacy with respect to increase in duration of analgesia, reduction in total requirements of analgesics postoperatively and study side effects and complications, if any attributable to these drugs.

METHODS

This study was conducted after its approval by the Ethical Committee of Institute of Medical Sciences and Sum Hospital, Bhubaneswar; Odisha, India. After explaining in details about the study protocols to all the patients and his/her attendants, sometime with multiple interactions, written informed consent was obtained from all the patients of all the study groups. A total of 75 patients were selected for the study, conducted from January 2015 to September 2015.

Type of study

It is a prospective randomized double-blind study.

Patient profile

The study was confined to the hospital inpatients only who were scheduled for surgeries of lower abdomen. 75 patients of age ranging from 20 to 60 years (25 in each group) of the American Society of

Anesthesiologists (ASA) I and ASA II group were selected on the basis of inclusion and exclusion criteria outlined below.

Inclusion criteria

- ASA I and II patients.
- Surgeries of the lower abdomen.
- Patients were eligible for enrolment in the study if they were >18 years old, within $\pm 50\%$ of their ideal body weight, had no clinically significant cardiovascular or central nervous system diseases.

Exclusion criteria

- Pregnant patients
- Breastfeeding patients
- ASA III and IV patients
- Local infection
- Known allergy to study drugs
- Coagulopathies
- Vertebral anomalies
- Neurological diseases
- Spinal level blockade above T₆
- Renal insufficiency
- Peptic ulcer disease
- History of drug abuse
- Patients in whom epidural anesthesia was not adequate and supplemented with other types of anesthesia.

Patients were randomly divided into three groups of 25 each.

- Group A - Butorphanol group
- Group B - Fentanyl group
- Group C - Nalbuphine group.

Pre-anesthetic evaluation

Patients were visited on the previous day of the surgery. A detail clinical history was taken, Detail general and systemic examinations were done. Basic laboratory investigations such as complete hemogram, bleeding time, clotting time, blood sugar, blood urea, serum creatinine and urine analysis, electrocardiography (ECG), and chest X-ray were carried out routinely in all patients.

The patients were explained about the epidural technique with catheter *in situ* and its advantages and disadvantages. They were also educated about the usage of linear visual analog scale (VAS) for assessment of the intensity of post-operative pain and were instructed to mark on the scale at the point which he/she felt was representative of their level of discomfort.

A written informed consent was taken from each patient.

Premedication

To allay the anxiety and apprehension, all patients were premedicated with Tablet Alprazolam 0.25 mg on the night before the surgery. The patients were also kept nil orally for 6 hrs before surgery.

Anesthesia

Epidural technique was adopted for surgery of the lower abdomen for all patients with 0.5% bupivacaine. The patient was made to lie supine on the operation table. An intravenous line was secured with 18 G canula and infusion of 5% Ringer lactate was started. Routine monitors such as ECG, noninvasive blood pressure (NIBP), and pulse oximetry were connected for every case, and basal vital signs were recorded before starting the epidural technique. Drugs and equipment necessary for resuscitation and general anesthesia administration were kept ready.

An autoclaved epidural tray was used. The patient was placed in sitting or lateral position. Under aseptic precautions, a skin wheal was raised at L2-L3 or L3-L4 interspace with 2 ml of 2% lignocaine. The epidural space was identified using 18 G disposable Tuohy needle with loss of resistance technique. Then, 20 G catheter was passed through the

epidural needle till about 2-3 cm of the catheter was in the space. The needle was withdrawn keeping the inserted epidural catheter *in situ* and was fixed to the back using adhesive tape. 3 ml of 2% lignocaine with adrenaline 1:2,00,000 was injected through the catheter as a test dose and observed for any untoward reactions including drug interactions as well as intravascular or intrathecal injection.

After confirming correct placement of the catheter, epidural anesthesia was activated using 16-18 ml bolus dose of 0.5% bupivacaine. Subsequent top up doses were given depending on the duration of surgery and intensity of pain. No narcotics were administered throughout the intraoperative period.

Fluid management

The patients were infused and maintained with crystalloids and colloids. Blood was transfused only when indicated.

The following observations were made.

Intraoperative:

- Onset of analgesia.
- Level of sensory blockade (maximum sensory level after 30 minutes).
- BP monitoring (NIBP).
- Heart rate (HR).
- Respiratory rate (RR) and SpO₂.

Duration of surgery was also noted.

- Onset of analgesia (sensory block): The time interval between administrations of local anesthetic (0.5% bupivacaine) epidurally to the loss of pinprick sensation at the site of surgical incision.
- Level of sensory blockade: The maximum sensory dermatome level after 30 minutes of administering the local anesthetic (0.5% bupivacaine) in the epidural space. The local anesthetics usually get fixed to their respective receptors by 20 minutes, and regression of two dermatomes usually occurs after 30 minutes.

During intraoperative period, NIBP, HR, RR, and SpO₂ were recorded before activating epidural anesthesia and subsequently at every 5 minutes till the end of the surgery.

After the surgery, the patients were shifted to recovery room and monitoring was continued. When patients recovered from motor blockade, they were shifted to post-operative ward.

Post-operative period

In the post-operative period, when the patients first complained of pain, intensity of pain was assessed using VAS scale. When the VAS score was >5, study drug was given through epidural catheter after confirming its proper position as:

- Group A - Received butorphanol 2 mg with 0.125% bupivacaine diluted to 10 ml in normal saline.
- Group B - Received fentanyl 100 µg with 0.125% bupivacaine diluted to 10 ml in normal saline.
- Group C - Received nalorphine 10 mg with 0.125% bupivacaine diluted to 10 ml in normal saline.

The intensity of pain and pain relief was assessed using VAS at 5,10,15,30,60 minutes and thereafter hourly for 8 hrs and then at 4 hrs interval for 24 hrs postoperatively. As and when the patient complained of pain during the period of observation, intensity of pain was assessed again using VAS to know the effect of the study drug given earlier. If it was >5, an intramuscular non-opioid analgesic as per the institutionally approved protocol was given.

VAS consisted of a 10 cm line, marked at 1 cm each on which the patient makes a mark on the line that represents the intensity of pain he/she was experiencing. Mark "0" represents no pain and mark "10" represents worst possible pain. The numbers marked by the patient was taken as units of pain intensity.

Linear VAS score

VAS score	Intensity of pain
0-2	No pain to slight pain
2-5	Mild pain
5-7	Moderate pain
7-9	Severe pain
10	Worst possible pain (intolerable)

Following observations were recorded:

1. Onset of analgesia
2. Duration of analgesia
3. Quality of analgesia
4. Cardio- respiratory effects: HR, BP and RR were
5. Side effects such as sedation, pruritis, nausea, vomiting, respiratory depression and urinary retention, and hypotension.

Onset of analgesia

The time interval from administration of the study drug (VAS score of >5) till VAS score came down to <5.

Duration of analgesia

The time interval between onset of analgesia (VAS score <5), till patient complained of pain (VAS score >5) when rescue medication was given.

Quality of analgesia was assessed during the duration of analgesia using pain score and compared between all the three groups.

Quality of analgesia

Pain score	Pain relief
0	No pain relief
1	Poor pain relief
2	Fair pain relief
3	Good pain relief
4	Excellent pain relief

Side effects

Sedation - quality of sedation after giving the study drug was based on sedation scoring.

- Grade 0 - No sedation, patient wide awake.
- Grade 1 - Mild sedation, patient awake but drowsy.
- Grade 2 - Moderate sedation, sleepy but arousable.
- Grade 3 - Severe sedation, unarousable.

Hypotension - Defined as a fall of systolic BP by 20% from basal systolic BP.

Respiratory depression - Bradypnea appears to be a more reliable clinical sign of early respiratory depression and a RR<10 breaths/minutes was recorded as respiratory depression.

Bradycardia - A fall of HR by 20% from the basal HR.

Other side effects that were observed and compared were pruritis, nausea, and vomiting.

Statistical analysis

All data recorded was analyzed using statistical package for social sciences (SPSS version 17). Data are expressed as mean with a standard deviation. Discrete data are expressed as frequency with percentage of total. ANOVA with post hoc test was used to compare continuous variables. A $p < 0.05$ was considered significant.

RESULTS

All the three groups were comparable in terms of age, sex and weight, duration and type of surgery (Tables 1 and 2).

Onset of analgesia

The mean time of onset of analgesia was 11.24 minutes, 6.32 minutes, and 14.64 minutes in Groups A-C, respectively. Statistical analysis

Table 1: Demographic data

	Group A	Group B	Group C
Age in years	34.4±11.9	33.8±10.53	34.67±10.80
Sex (female:male)	22:3	23:2	23:2
Weight (kg)	54.47±5.491	54.30±6.35	53.92±5.25
Duration of surgery (minutes)	98±54.56	96±56.54	98±53.78

Table 2: Block characteristics

Time (minutes)	Group A	Group B	Group C
Onset of analgesia	11.24±2.989	6.320±3.555	14.64±2.234
Range	7-18	5-9	10-19
Level of analgesia	T9	T10	T9
Duration of analgesia (minutes)	481.68	178.60	294.68

showed that onset of analgesia was faster in fentanyl group compared to other two groups ($p < 0.05$).

Duration of analgesia

The mean duration of analgesia was 481.68 minutes in Group A, 178.60 minutes in Group B and 294.68 minutes in Group C. The duration was thus significantly longer in butorphanol group.

Hemodynamic changes

Fig. 1 shows in all the three groups there was no change observed in pulse rate and mean arterial pressure.

The mean RR increased 6-8 hrs onward postoperatively in Group I, 4 hrs onward in Group B and immediately postoperatively in Group C. This hyperventilation was probably due to the onset of pain after analgesic effect of respective drugs curtailed off over time. The rate came down after administration of rescue analgesic, further confirming the assumption.

Comparison of mean pain score

Fig. 2 shows the mean pain score recorded was significantly lower in Groups A and B than in Group C. All the patients in Groups B and C required analgesic supplementation within first 2-4 hrs and 4-6 hrs, respectively. Whereas, 9 patients of Group A required supplementation within 6-8 hrs, 16 patients between 8 and 10 hrs.

Complications

Table 3 shows, in this study, 12% patients in Group A, 16% patients in Group B and 48% patients in Group C had nausea and vomiting. The high female proportion in the study group and the fact that pain and opioids themselves are emetogenic may be the underlying reasons.

Sedation

This was the main side effect in butorphanol group which constituted 32% and 20% of the patients in fentanyl group had sedation. The majority of the patients had mild sedation, patient awake but drowsy. This was statistically significant ($p < 0.001$) as compared to nalbuphine group.

Pruritus

In this study, no patients in nalbuphine group and butorphanol group had pruritus whereas eight patients in fentanyl group had pruritus. Pruritus induced by epidural opioids is likely due to interaction with trigeminal nucleus in medulla.

DISCUSSION

Post-operative pain is acute pain, which starts with the surgical trauma and usually ends with tissue healing. It diminishes with time after surgery and responds to analgesics. The effective relief of pain

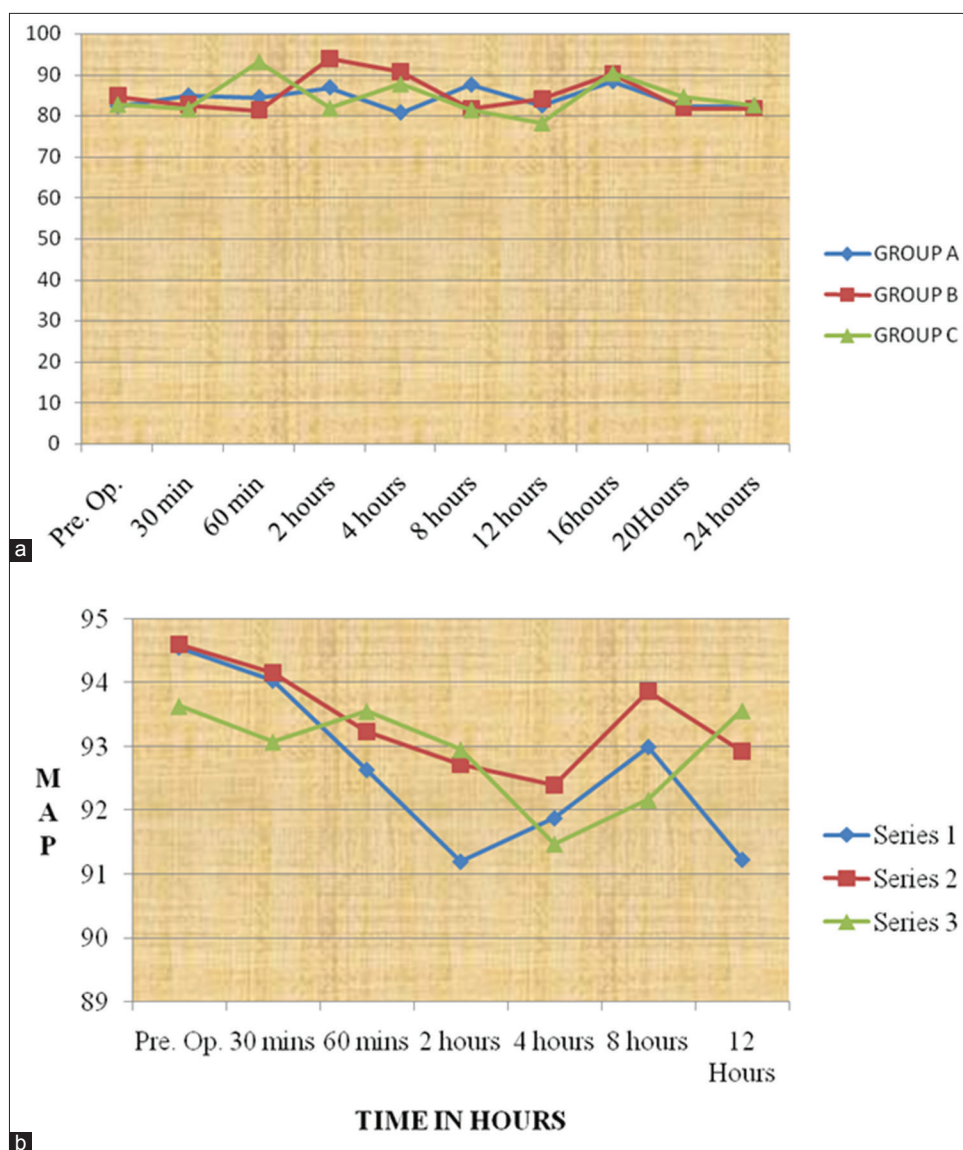


Fig. 1: (a and b) Changes in pulse rate, mean arterial pressure and respiratory rate in post-operative period

Table 3: Complications

Complication	Group A (%)	Group B (%)	Group C (%)	p value
Nausea and vomiting	3 (12)	4 (16)	12 (48)	0.484
Urinary retention	4 (16)	1 (3.3)	0 (0.0)	0.6
Respiratory depression	0 (0.0)	0 (0.0)	0 (0.0)	-
Sedation	8 (32)	7 (20)	2 (8)	0.001
Pruritus	0	8	0	<0.001

to the patients undergoing surgery is essential and is of paramount importance both on humanitarian grounds and also in reducing post-operative morbidity, hence should be duly imparted by the treating anesthesiologist.

Severe pain can result in splinting, with resultant atelectasis and hypoxia. In addition, poor control of pain may result in increased catecholamine secretion in response to pain, which may in turn increase myocardial oxygen demand. A number of studies in the past have proved that improved post-operative analgesia may reduce the incidence of cardiac and pulmonary morbidity and mortality in patients undergoing major abdominal surgery.

Since the discovery of opioid receptors in the spinal cord, the action of narcotics through opioid receptors has become more clearly understood. One of the opioid receptors, kappa are mainly involved with the mediation of visceral pain. After this, achieving satisfactory post-operative analgesia with epidural and intrathecal administration of narcotics has been the subject of much research. The use of epidural opioids had become an increasingly popular technique for management of acute post-operative pain in recent times. However, there are disadvantages associated with narcotics as they are not always simple to use and may be associated with some unpleasant adverse effects such as nausea and vomiting (post-operative nausea and vomiting), pruritus, respiratory depression, and urinary retention.

Stimulation of spinal opiate receptors (kappa, κ) can also produce spinal analgesia but with fewer side effects. Therefore, a drug such as butorphanol, a mixed narcotic agonist/antagonist, acts as a mu (μ) agonist/antagonist and kappa agonist, also produces analgesia, associated with fewer side effects and also low abuse potential. Its high lipid solubility and high affinity for opioid receptors are additional factors that contribute to paucity of side effects with its use.

Fentanyl was chosen for the study for advantages such as no neurolytic preservatives, highly lipophilic, so better retained within the epidural

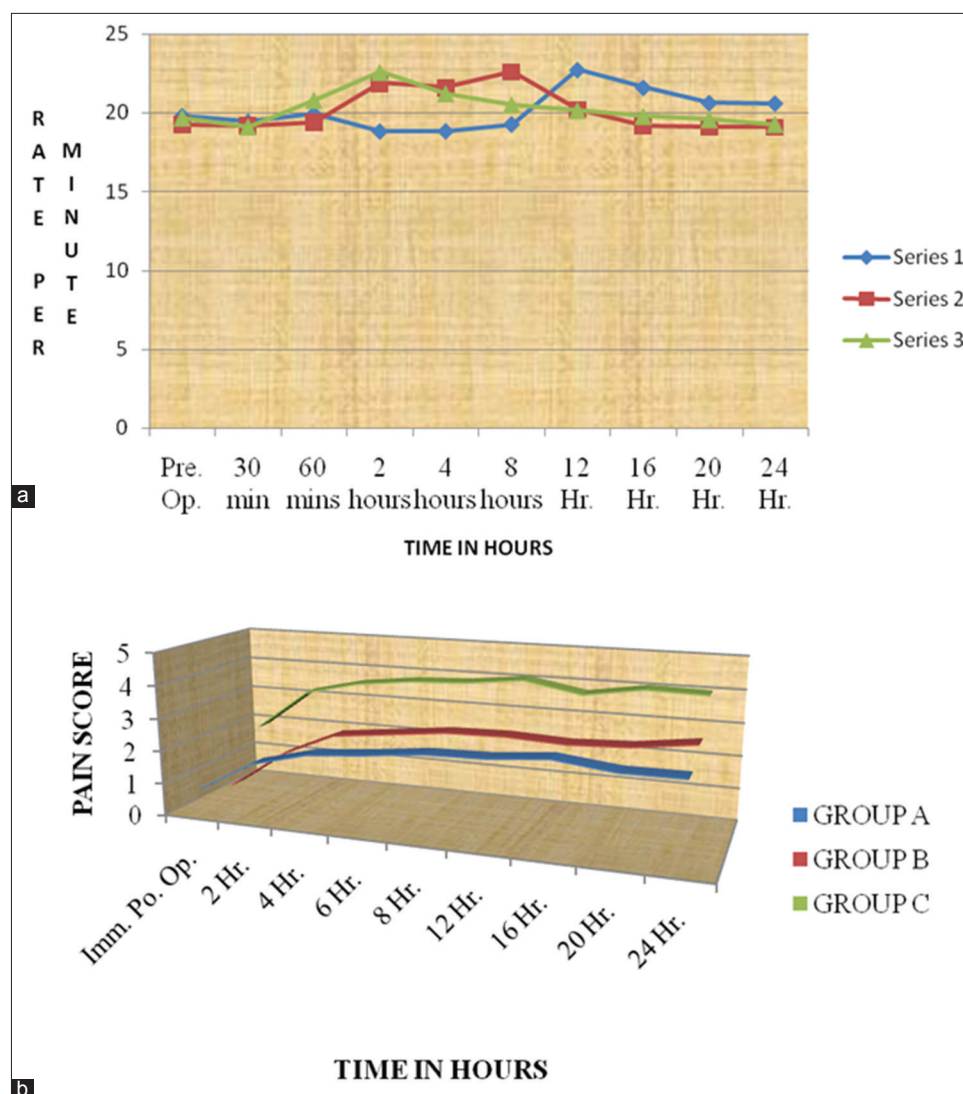


Fig. 2: (a and b) Comparison of mean pain score

space, short half-life, so less circulating blood levels resulting from absorption and finally because it is stable in salt solutions for more than 72 hrs.

Nalbuphine is an agonist - antagonist, equipotent to morphine also has a low abuse potential. It is known to produce profound analgesia and is known to be associated with side effects like sedation. It commonly finds its place in clinical practice as it has a ceiling effect on respiratory depression.

This study is a prospective randomized controlled clinical comparative study done to assess the efficacy and safety of epidural butorphanol, epidural fentanyl and epidural nalbuphine, each combined with 0.125% bupivacaine for the management of post-operative pain. A total of 75 patients belonging to age groups 18-60 years were taken, out of which majority of patients belonged to 20-50 years of age. The patients undergoing elective lower abdominal surgeries in general surgery, gynecology, urology, and plastic surgery were selected.

The observations of the study were analyzed, and results revealed that onset of analgesia was faster in fentanyl group compared to other two groups. This could be correlated with the studies conducted by Mok and Tsai [9] who did a study to evaluate the analgesic efficacy and safety of epidural butorphanol (4 mg) in comparison to that of epidural morphine 5 mg in patients with post-operative pain. In their study, it was observed that the onset of pain relief with epidural

butorphanol appeared at 15 minutes and peaked at 30 minutes. Kaur *et al.* [1] also studied epidural butorphanol and fentanyl as adjuvants in lower abdominal surgeries and demonstrated earlier onset with fentanyl when used with bupivacaine epidurally (mean 10.80 minutes) than with butorphanol used with bupivacaine epidurally (mean 11.08 minutes).

As regarding the duration of analgesia, the duration was thus significantly longer in butorphanol group. The above observation correlates with the works of Malik *et al.* [5] who used 2 mg butorphanol epidurally for post-operative analgesia after orthopedic surgeries and found duration to be 5.59 ± 1.15 hrs after the first dose. Abboud *et al.* [10] noted the duration of analgesia to be 4.82 ± 0.77 hrs, 5.53 ± 0.86 hrs, 8.05 ± 0.97 hrs after use of the first dose of 1 mg, 2 mg, and 4 mg butorphanol used epidurally. Chatrath *et al.* [2] used 10 mg epidural nalbuphine along with 0.25% bupivacaine and found the duration to be 380 ± 11.4 minutes after lower limb and hip surgeries. Kaur *et al.* [1] noted the duration of epidural fentanyl 100 µg with 20 ml bupivacaine was 3-9 hrs, mean duration being 5.96 hrs. Their study demonstrated that the duration was significantly greater in butorphanol group with a mean duration of 7.64 hrs.

Side effects of opioids include sedation, nausea, vomiting, pruritus, urinary retention, and respiratory depression. Pruritus was seen in 8 patients of fentanyl group. This is in accordance with findings of Abboud *et al.* [10] who found paucity of side effects with epidural

butorphanol given after cesarean section and attributed this to high lipid solubility of butorphanol thus limiting its cephalic spread to the brainstem. Chatrath *et al.* [2] studied the effects of epidural nalbuphine and tramadol for post-operative analgesia in orthopedic surgeries and concluded that patients were more comfortable after nalbuphine epidurally since they complained of lesser side effects. Sedation was observed in butorphanol group consistent with the study of Venkatraman *et al.* [4] who observed sedation in patients receiving epidural butorphanol.

CONCLUSION

Opioid analgesics with local anesthetics are extremely safe, effective and reliable method of post-operative pain relief. The addition of fentanyl produces faster onset of analgesia with adverse effects like sedation and pruritus than butorphanol and nalbuphine when given epidurally along with 0.125% bupivacaine. Butorphanol administered epidurally has advantage of longer duration of analgesia than fentanyl or epidural nalbuphine with side effects like nausea vomiting and sedation. Although none of the patients in this study developed respiratory depression, it is strongly recommended in concurrence with other authors that monitoring for clinical respiratory depression be made in all patients during the period of analgesia.

REFERENCES

1. Kaur J, Bajwa SJ. Comparison of epidural butorphanol and fentanyl as adjuvants in the lower abdominal surgery: A randomized clinical study. *Saudi J Anaesth* 2014;8(2):167-71.
2. Chatrath V, Attri JP, Kaur S. Epidural nalbuphine for post-operative analgesia in orthopaedic surgery. *Anesth Essays Res* 2015;9(3):326-30.
3. Camann WR, Hurley RH, Gilbertson LI, Long ML, Datta S. Epidural nalbuphine for analgesia following caesarean delivery: Dose-response and effect of local anaesthetic choice. *Can J Anaesth* 1991;38(6):728-32.
4. Venkatraman R, Sandhiya R. Evaluation of efficacy of epidural butorphanol tartarate for post-operative analgesia. *Int J Pharm Pharm Sci* 2015;7(2):52-4.
5. Malik P, Manchanda C, Malhotra N. Comparative evaluation of epidural fentanyl and butorphanol for post-operative analgesia. *J Anesthesiol Clin Pharmacol* 2006;22:377-82.
6. Saxena AK, Arava SK. Current concepts in neuraxial administration of opioids and non-opioids: An overview and future prospectives. *Indian J Anaesth* 2004;48(1):13.
7. Tripathi DC, Mehta VS, Jha PS, Shah KS, Trivedi LP. A comparative study of epidural tramadol versus butorphanol for post-operative pain relief in abdominal hysterectomy. *Indian Soc Study Pain* 2009;.
8. Rutter DV, Skewes DG, Morgan M. Extradural opioids for post-operative analgesia. A double-blind comparison of pethidine, fentanyl and morphine. *Br J Anaesth* 1981;53(9):915-20.
9. Mok MS, Tsai YJ, Ho WM. Efficacy of epidural butorphanol compare to morphine for the relief of post-operative pain. *Anaesthesiology* 1986;65:A175.
10. Abboud TK, Moore M, Zhu J, Murakawa K, Minehart M, Longhitano M, *et al.* Epidural butorphanol or morphine for the relief of postcesarean section pain Ventilatory responses to carbon dioxide. *Anaesth Analg* 1987;66(9):887-93.
11. Naulty JS, Weintraub S, Mcmahon J, Hunt OC, Chantigian R. Epidural butorphanol for postcesarean delivery pain management. *Anesthesiology* 1984;61:A415.
12. Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* 2001;87(1):47-61.
13. Lippmann M, Mok MS. Epidural butorphanol for the relief of postoperative pain. *Anesth Analg* 1988;67(4):418.
14. Hunt CO, Naulty JS, Malinow AM, Datta S, Ostheimer GW. Epidural butorphanol-bupivacaine for analgesia during labor and delivery. *Anesth Analg* 1989;68(3):323-7.
15. Palacios QT, Jones MM, Hawkins JL, Adenwala JN, Longmire S, Hess KR, *et al.* Postcesarean section analgesia: A comparison of epidural butorphanol and morphine. *Can J Anaesth* 1991;38(1):24-30.
16. Welchew EA. The optimum concentration for epidural fentanyl. A randomized, double-blind comparison with and without 1:200000 adrenaline. *Anaesthesia* 1983;38:1037-41.
17. Kim DH, Kim TJ, Park NH. Comparison of butorphanol and fentanyl administered with bupivacaine for patient controlled epidural analgesia after cesarean section. *Korean J Anesthesiol* 1998;34(1):126-31.
18. Hwang KB, Chung CJ, Lee JH, Lee SC, Oh SH. Comparison of butorphanol and fentanyl for patient-controlled epidural analgesia after gastrectomy. *J Korean Pain Soc* 2004;17(1):24-48.
19. Pokharel K, Rahman TR, Singh SN, Bhattarai B, Basnet N, Khaniya S. The efficacy and safety of low dose epidural butorphanol on postoperative analgesia following cesarean delivery. *JNMA J Nepal Med Assoc* 2008;47(170):57-61.
20. Salomäki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. *Anesthesiology* 1991;75(5):790-5.
21. Etches RC, Sandler AN, Lawson SL. A comparison of the analgesic and respiratory effects of epidural nalbuphine or morphine in postthoracotomy patients. *Eur J Anesth* 2007;.
22. Parker RK, Holtmann B, White PF. Patient-controlled epidural analgesia: Interactions between nalbuphine and hydromorphone. *Anesth Analg* 1997;84(4):757-63.
23. Baxter AD, Langanière S, Samson B, McGilveray IJ, Hull K. A dose-response study of nalbuphine for post-thoracotomy epidural analgesia. *Can J Anaesth* 1991;38(2):175-82.
24. Bakhshi RG, Bobby NK, Jagtap SR. Comparative study of intrathecal fentanyl versus intrathecal clonidine with low dose bupivacaine for lower abdominal and lower limb surgery. *ISSP J* 2009;