Original article

A comparative analysis of the use of Clonidine Vis a Vis Fentanyl when used as an adjunct to Bupivacaine for Postoperative analgesia

Urvashi Tandon[1], Vidhu Bhatnagar[2], Kumar Kunal[3], Ajay Sharma[4]

[1]Professor and Head, Dept. of Anesthesiology, INHS Asvini, Colaba, Mumbai,

[2]Assistant Professor, Anaesthesiology, INHS Asvini, Colaba, Mumbai,

[3]Anaesthesiologist, Military Hospital, Gaya, Bihar, [4]Anaesthesiologist INHS Sanjivani, Kochi, Kerala

Corresponding author: Dr. Urvashi Tandon

Abstract

The use of adjuncts to local anaesthetics to provide analgesia during surgery is a fairly common procedure. However, not many analytical studies have been done to evaluate their postoperative efficacy. It was attempted to compare the quality of analgesia and the requirement of sedation during the postoperative period while using Clonidine with that of Fentanyl when used as adjuncts to 0.125% Bupivacaine via an epidural catheter placed at the L2- L3 intervertbral space.

60 patients undergoing lower abdominal and lower extremity surgeries under spinal anaesthesia with epidural analgesia for post operative pain relief were selected. The effects of the addition of 1µg/kg of Clonidine and 2µg/ml of Fentanyl on the efficacy and duration of epidural analgesia produced by 10 ml of 0.125% Bupivacaine for post operative analgesia were compared. The verbal numerical scale of pain assessment was explained to the patient during preoperative assessment. A bolus of 3mg of Morphine was given when the patient demanded pain relief for the first time in the post operative period and for subsequent requirements. Pain assessment in the postoperative period was done every two hours with verbal numerical scale (0-10) for 12 hours and then at 24 hours. Ramsay Sedation Scale was used for assessment of sedation. Adverse effects if any were noted. Postoperative Pain score on Verbal numerical scale and sedation scores were analyzed using non-parametric analysis (Mann-Whitney U test).

Result: The Pain score was significantly less in the Clonidine group as compared to the Fentanyl group. There was similarly a significant difference in the requirement of Morphine to be supplemented. This difference however was significant only for the first four hours postoperatively.

Key words: Epidural analgesia, Sedation, Postoperative Analgesia

Introduction

Epidural administration of analgesics is a widely used method for the treatment of postoperative pain and is justifiably popular. Since its first description by Corning in 1885, epidural block has evolved to become one of the most popular regional anaesthetic techniques (1). Although it is a versatile block one of the major limitations of the single-injection technique is the relatively short duration of postoperative analgesia (4–6 hrs) even with long-acting local anaesthetics. This problem can be circumvented by the use of a continuous catheter technique.

An established method to prolong postoperative analgesia following epidural block is to add different drugs as adjuncts to the local anaesthetic solution. During the second half of the 1980's neuraxial administration of opioids came into vogue in anaesthesia. Soon after this, the successful use of racemic Ketamine, Tramadol, Clonidine, Midazolam, Neostigmine and Dexmedetomidine was described (2,

3, 4, 5, 6, 7, 8). The non-opioid α_2 agonist Clonidine as adjunct to local anesthetics for epidural analgesia has gained popularity because of relatively lower incidence of side effects. However few studies have compared Clonidine co-administered with Bupivacaine in epidural technique for postoperative analgesia. Therefore, this study was designed to compare the effects of the addition of 1µg/kg of Clonidine and 2µg/ml of Fentanyl on the efficacy and duration of epidural analgesia produced by 10 ml of 0.125% Bupivacaine for post operative analgesia in patients undergoing lower abdominal and lower extremity surgeries under spinal anaesthesia.

Material and Methods:

The study was a prospective randomized controlled study in 60 patients undergoing lower abdominal and lower extremity surgeries under spinal anaesthesia with epidural analgesia for post operative pain relief. Approval from institutional ethical committee was obtained. Written, informed consent was taken from each of the patients.The patients aged between 18 and 60 years in ASA I or II who can understand pain scale were included in the study.

1. The following patients were excluded from the study :-
   - A. Unwilling Patients.
   - B. Patients with known hypersensitivity to any drugs which were being used (Bupivacaine, Clonidine, Fentanyl, Morphine)
   - Patients with any contradiction to spinal or epidural block.
   - Patients who were receiving any analgesics 24 hrs prior to the surgery.
   - Patients suffering from epilepsy, liver disease, renal disease, suffering from any chronic pain syndrome, or having any psychiatric illness.
2. The verbal numerical scale of pain assessment was explained to the patient during preoperative assessment. In all the patients' weight, pulse rate, blood pressure, respiratory rate, relevant history and clinical signs if any were recorded. Investigations like hemoglobin % and urine examination were performed. Special investigations like blood sugar, ECG, and chest X- ray were ordered whenever required.
3. Each patient was randomly assigned to one of two groups – group Bupivacaine Clonidine (A) and group Bupivacaine Fentanyl (B).
4. In the operating room, patients received 15 ml/kg of intravenous crystalloid solution for preloading. Combined spinal epidural technique was performed. Groups and Bupivacaine-Clonidine (A) and Bupivacaine-Fentanyl (B) received preservative-free Clonidine 1µg/kg and preservative free Fentanyl 2µg/ml respectively in 10ml of 0.125% Bupivacaine at L2-3 space and were the study groups. Surgical intervention started 10-15 min after the block injection. Surgery was done under spinal anaesthesia with 3 ml of 0.5% hyperbaric Bupivacaine at L2-3 space.
5. Intraoperative monitoring included heart rate, non-invasive blood pressure, ECG and Oxygen saturation and sedation level.
6. Significant hypotension (defined as >20% fall) was treated with Inj Ephedrine and intravenous crystalloids.
7. Post-operative pain was managed with Morphine administration. A bolus of 3mg of Morphine was given when the patient demanded pain relief for the first time in the post operative period and also for further analgesic requirements.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

8. Post-operative monitoring and assessment was done by an assigned nurse in the ward who was not aware of the assigned group of the patient. It included :-

Pain assessment every two hours with verbal numerical scale (0-10) for 12 hours and then at 24 hours.

Consumption of Morphine every four hours and cumulative amount in 24 hours post-operative period.

Any side effects such as nausea, vomiting, sedation, dizziness.

Ramsay Sedation Scale was used for assessment.

9. **Statistical analysis:**-

a.Demographic data like Age and weight were analyzed with unpaired't test.

b.The duration of anaesthesia and the time of first rescue analgesia were also analyzed with unpaired't' test.

c.Sex and ASA grading were analyzed with Chi- square test.

d.Postoperative Pain score on Verbal numerical scale and sedation scores were analyzed using non-parametric analysis (Mann-Whitney U test).

e.The difference was considered significant when probability is $p < 0.05$.

Statistical analysis was done using SPSS 14 windows processor.

Result

Comparative study of Clonidine (1µg/kg) and Fentanyl (2µg/ml) as adjunct to 10 ml of 0.125% Bupivacaine in epidural analgesia for post operative pain relief was undertaken in 60 ASA class I and II patients of either sex, between 18-60 years, scheduled for elective surgeries.

Observations were drawn on following aspects:-

1. Demography
2. Type of surgeries
3. Mean duration of surgeries
4. Mean duration of first analgesia requirement
5. Sedation Scores at 2, 4, 8 and 24 hrs post spinal anaesthesia
6. Pain scores at 2, 4, 8, 12 and 24hrs post spinal anaesthesia
7. Mean total morphine consumption postoperative

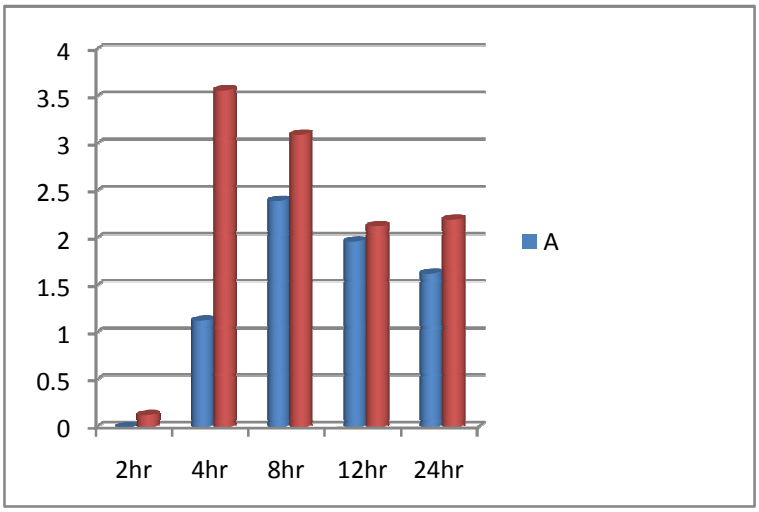
Comparison of Postoperative Pain Scores between the Two Groups

Variables	Group A (n = 30)	Group B (n = 30)	p-value
Total pain score	7.13 (2.27)	11.13 (1.99)	< 0.05 Significant

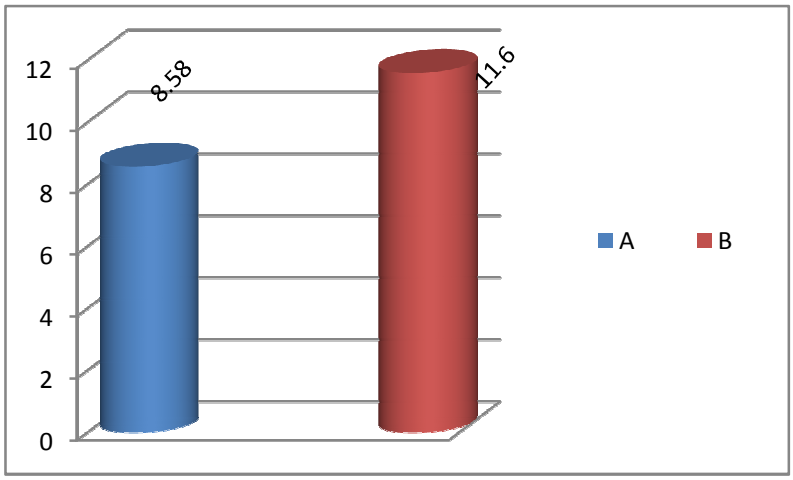
The statistical difference in mean pain score on Verbal Numerical Scale was extremely significant (p value < 0.05) between the two groups.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Pain scores comparison at different intervals



The statistical difference in mean total Morphine consumption was significant between the two groups (p value < 0.05).



Comparison of Total Morphine Consumption between the Two Groups

VARIABLES	GROUP A (n = 30)	GROUP B (n = 30)	P-value
Total morphine requirement (mg)	8.58 (3.92)	11.6 (4.44)	< 0.05 significant

Discussion:

The present study was conducted to compare the efficacy and safety of Clonidine and Fentanyl administered as adjuncts to epidural bupivacaine. The results of the study demonstrate that addition of Clonidine (1µg/kg) produced more prolonged analgesia than addition of Fentanyl (2µg/ml) to 10ml of 0.125% Bupivacaine provided by single shot epidural block in patients undergoing lower abdominal and lower extremity surgeries under spinal anaesthesia. This is evident by prolongation of the time to first analgesic administration viz 517.67 min and 322 min for group A and B respectively which was statistically significant (9). Also, addition of Clonidine resulted in lesser pain score (7.13) as compared to that achieved with addition of Fentanyl (11.13) on verbal numerical scale which was statistically significant.

Fentanyl mediates extradural analgesia primarily via interaction with the opioid receptor in the dorsal horn of spinal cord (10). Gozard et al found combination of 0.125% Bupivacaine 2µg/ml Fentanyl to result in significant prolongation of postoperative analgesia without an increase in incidence of side effects.

Clonidine exerts its extradural analgesic effect by stimulating α-2a adrenoceptors in substantia gelatinosa of dorsal horn of spinal cord inhibiting firing of nociceptive neurons stimulated by peripheral A-δ and C fibres(11) . In a study of 50 children (6 months to 6 years age) Upadhyay et al compared caudal Bupivacaine 0.25% (0.75 ml/kg) and Clonidine (1 µg/kg) coadministered with Bupivacaine(12). They found an increase in mean analgesia time from 5.59 to 10.33 hr which is similar to our result. Several studies have also demonstrated that Clonidine added to Bupivacaine or Lidocaine increases the duration and quality of postoperative analgesia provided by epidural anaesthesia (13). Besides, the optimal extradural dose of Clonidine is not well documented. Dosage regimens of 1µg/kg, 2µg/kg or 3µg/kg have been used without major adverse respiratory or haemodynamic effects, while a decrease in blood pressure and heart rate was observed after a dose of 5µg/kg (14,15,16). Moreover increasing the dose of Clonidine beyond 1 µg/kg did not lead to a substantial increase in duration of postoperative analgesia.

The total post operative requirement of additional analgesia in first 24 hrs was 8.58mg and 11.6mg of Morphine for group A and B respectively. This observation is understandable given the fact that addition of Clonidine and Fentanyl prolonged post-op analgesia (Clonidine significantly more than Fentanyl) but subsequent relief of post-op pain relied on IV morphine.

In our study the sedation scores displayed increased sedation in group A and B, with more sedation in A

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

group in the first four hours post spinal, though well within the realm of safety i.e. all patients were arousable. After four hours the difference in sedation scores was not significant (17). The relative lack of residual sedation could be attributed to a mean of 3 hr elapsing between the epidural injection and first sedation score and the modest epidural doses of the additives. Respiratory depression is an expected yet undesirable side effect of epidural additives especially opioids (18). It has also been described in patients receiving epidural Clonidine ≥5 µg/kg and receiving extradural Clonidine 300 mg (19). In our study there was no incidence of excessive sedation or respiratory depression thus further validating the safety of epidural Clonidine (1µg/kg) and Fentanyl (2µg/ml).

There was no significant nausea, vomiting or pruritus in either of the study groups. While the emetic effect of extradural opioids is well known and involves supraspinal mechanisms, extradural Clonidine exhibit reduced potential for nausea and vomiting (20). In fact Clonidine exhibits antiemetic properties when administered by the oral or IV route. There were no adverse sequelae of epidural block in any patient which exemplifies the justifiable popularity of epidurals.

In summary, addition of Clonidine (1µg/kg) to 10ml of 0.125% Bupivacaine produced better analgesia after a single shot epidural injection in adults than addition of Fentanyl (2µg/ml). Thus this technique may be recommended for surgery lasting 60–120 min and could be a safe and cheap alternative to extradural catheter placement for infra-abdominal surgical procedures of intermediate duration in ASA I and II adults.

Conclusion:

The findings of this study suggest that Fentanyl and Clonidine administered as adjuncts to epidural Bupivacaine is effective in reducing postoperative pain and rescue analgesic requirement. The combination of Clonidine to epidural Bupivacaine produces better analgesia in comparison to combination of Fentanyl to epidural Bupivacaine. In summary this study has shown that, analgesia achieved with single shot epidural dose of Clonidine with Bupivacaine is better as compared to Fentanyl with Bupivacaine. Onset of pain after the surgery is delayed more by epidural Clonidine-Bupivacaine combination as compared to Fentanyl -Bupivacaine combination. Moreover, use of Bupivacaine- Clonidine combination results in reduced pain score and reduced Morphine requirement for rescue analgesia. Hence it can be concluded that epidural analgesia with Clonidine as adjunct to upivacaine is an effective and better tool in treatment of perioperative pain.

References:

1. Corning JL. Spinal anaesthesia and local medication of the cord. NY Med J 1885; 42: 483–5.
2. Choe H, Choi YS, Kim YH, Ko SH, Choi HG, Han YJ, Song HS. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. *Anesth Analg* Mar *1997*;84(3):560-63.
3. Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. Can J Anaesth. Apr 1993; 40(4):308-13.

4. Torben Mogensen, Kirsten Eliasen, Ellen Ejlersen, Palle Vegger, Ingrid K. Nielsen, and Henrik Kehlet. Epidural Clonidine Enhances Postoperative Analgesia From a Combined Low-Dose Epidural Bupivacaine and Morphine Regimen Anesth Analg. October 1992; 75:607-610.
5. Nishiyama T, Hirasaki A, Odaka Y, Mikane T, Kobayashi O, Seto K. Epidural midazolam with bupivacaine--optimal dose for postoperative pain relief. Masui. Jul 1992;41(7):1113-8.
6. Kaya FN, Sahin S, Owen MD, Eisenach JC. Epidural neostigmine produces analgesia but also sedation in women after cesarean delivery. Anesthesiology. Feb 2004;100(2):381-5.
7. Sule Akin, Anis Aribogan and Gulnaz Arslan. Dexmedetomidine as an adjunct to epidural analgesia after abdominal surgery in elderly intensive care patients: A prospective, double-blind, clinical trial. Current Therapeutic Research, 2008;69(1): 16-28.
8. Scott, David A, Beilby, David S, McClymont, Calum Postoperative Analgesia Using Epidural Infusions of Fentanyl with Bupivacaine: A Prospective Analysis of 1,014 Patients. Anesthesiology: October 1995 ;83 (4):727-737.
9. Kizilarslan S, Kuvaki B, Onat U, Sağiroğlu E. Epidural fentanyl-bupivacaine compared with clonidine-bupivacaine for analgesia in labour. Eur J Anaesthesiol. 2000 Nov;17(11):692-7.
10. Gozard Sveticic MD. Combination of bupivacaine and fentanyl for lumbar epidural Postop analgesia. ASA, 2004:1381-93
11. Eisenach JC, et al. Alpha 2 –adrenergic agonists for regional anaesthesia: a clinical review of clonidine(1984-1995) Anaesthesiology 1996;85:655-674.
12. Upadhyay KK, Handa R, Prabhakar T, Beena Haridas. Study of the efficacy and safety of Clonidine as an adjunct to Bupivacaine for caudal analgesia in children. Indian J Anaesth 2005;49(3):199 – 201.
13. Nishikawa T, Dohl S. clinical evaluation of clonidine added to lidocaine solution for epidural anaesthesia. Anaesthesiology 1990;73: 853-9.
14. Bouguet D. Caudal clonidine added to local anaesthetics enhances post operative analgesia after anal surgery in adults. Anaesthesiology, 1994; 81:942.
15. Cigarini I et al. Epidural clonidine combined with bupivacaine for analgesie in labour. Reg anaesth, 1995; 20:113-20
16. Tryba M 7 Gehling M. clonidine- a potent analgesic adjuvant. Curr Opin Anaesth, 2002;15: 511-7.
17. Vieira AM, Schnaider TB, Costa FA, Costa ED. Analgesia and sedation with epidural clonidine associated to 0.75% ropivacaine in the postoperative period of open cholecystectomy. Rev Bras Anestesiol. Sep 2003;53(5):586-90
18. Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. Anesthesiology 1995; 83:727–737.
19. Penon C, Ecoffey C, Cohen SE. Ventilatory response to carbon dioxide after epidural clonidine injection. Anesthesia and Analgesia 1991;72:761–764.
20. Schmerzther. Effectiveness of clonidine and fentanyl addition to bupivacaine in postoperative patient controlled epidural analgesiaAnasthesiol Intensivmed Notfallmed. 2005 Sep;40(9):521-5.