A Comparative Study of Two Different Doses of Epidural Neostigmine Coadministered with Lignocaine for Post Operative Analgesia and Sedation

Mamta Harjai, Girish Chandra, V.K. Bhatia, Dinesh Singh, Priyesh Bhaskar

ABSTRACT

**Background:** Adjuvants have been used to prolong analgesic effects of epidural local anaesthetics. We studied two different doses of neostigmine.

**Patients & Methods:** A randomized double blind study was conducted on ninety adult females scheduled for lower intra abdominal surgeries. The study was designed to compare two doses of epidural neostigmine co administered with lignocaine, with regard to its analgesic efficacy and its effect on sedation in postoperative period. Patients were divided into three groups of 30 each. Group I received lignocaine 1% (9ml) with normal saline (1ml), group II lignocaine1% (9ml) with neostigmine 100µg in saline (1ml) and group III received lignocaine 1% (9ml) with neostigmine 200µg in NS (1ml). Group I served as a control. In operating room, after putting epidural catheter, general anesthesia was administered with propofol (2mg kg⁻¹), succinylcholine (2mg kg⁻¹) and maintained with O₂, N₂O, relaxant technique. At the end of surgery, patients were reversed. Epidural analgesic medication was administered to after proper recovery from anesthesia. Intensity of pain relief on VAS, duration of analgesia, level of sensory block, motor blockade, sedation by sedation score and complications were assessed.

**Results:** The addition of neostigmine resulted in significant longer duration of analgesia (dose independent) and sedation (dose dependent). Sensory and motor blockade were identical in all three groups. There was no incidence of respiratory depression, pruritus, bradycardia or hypotension in any group. Two patients in control group and one, receiving neostigmine (200µg), developed nausea/vomiting.

**Conclusion:** Co administration of epidural neostigmine and lignocaine appears to be a useful technique for postoperative analgesia as it increases the duration of analgesia and provides desirable sedation at the same time.

**KEYWORDS:** Anesthesia, Epidural analgesia, Lignocaine, Neostigmine, Sedation.

Epidural anesthesia provides prolonged postoperative analgesia as safer alternative to general anesthesia. Postoperative analgesia eases patient suffering, decreases cardiovascular and respiratory complications and ensures early mobilization.

Despite disadvantages like hypotension, migration of epidural catheter into intravenous or subarachnoid space, epidural analgesia is an effective method of analgesia. Adjuvant like clonidine⁵, opioids⁵⁻⁶ and epinephrine⁴, ⁷ has been added to improve analgesia, to reduce morbidity and to reduce local anesthetic dose and side effects. More recently, epidural administration of cholinesterase inhibitor, neostigmine, as adjuvant has been suggested to produce analgesia⁸⁻¹⁲. The rationale behind the use of neostigmine is that acetylcholine is one of more than 25 neurotransmitters that participate in spinal cord modulation of pain processing¹³. Therefore, the use of epidural neostigmine with lignocaine was investigated with respect to its specific antinociceptive activity, sedation and any potential side-effects in post operative period.

**PATIENTS AND METHODS**

This double blind, prospective and randomized study was conducted during June 2006 to August 2007 after approval of institutional ethical review committee board on 90 female ASA grade I and II patients, aged (18-45 years), scheduled to undergo lower intra abdominal surgeries. Informed written consent was taken from patient or patient's kins. Patients with contraindication to epidural anesthesia, allergy to local anesthetics and pregnant females were excluded from this study. Patients were divided into following groups of 30 each, according to the epidural medication, they received:

- **Group I:** lignocaine 1% 9ml+normal saline (NS) 1 ml.
- **Group II:** lignocaine 1% 9ml+neostigmine 100µg in NS 1ml
- **Group III:** lignocaine 1% 9ml+neostigmine 200µg in NS 1ml

In operating room after intravenous access and application of monitors, epidural catheterization was performed under strict aseptic conditions, at L2-L3 or L3-L4 interspace in sitting position. A Test dose in the form of 3mL injection of lignocaine (2%) and epinephrine (1:200,000) was...
given through epidural catheter to confirm proper placement of epidural catheter.

Thereafter, the patients were premedicated with intravenously glycopyrrolate (0.005 mg kg⁻¹), ondansetron (8 mg) and fentanyl (1 μg kg⁻¹), 5 min prior to induction of anesthesia. All patients were induced with propofol (2mg kg⁻¹) and succinylcholine (2mg kg⁻¹), followed by endotracheal intubation. Anesthesia was maintained with O₂, N₂O, vecuronium, intermittently. The residual neuromuscular blockade was reversed at the end of surgery using neostigmine and glycopyrrolate (2:1). Epidural neostigmine solution was prepared, by a person who did not participate in this study any further, by mixing neostigmine and lignocaine to obtain two concentrations of neostigmine in lignocaine 1% (100 μg for Group II and 200 μg for Group III patients). In order to maintain uniformity, the volume of epidural medication was kept constant at 10ml, for all the three groups. The solution was injected through epidural catheter at the end of surgery, after recovery from anesthesia.

Before giving drug through epidural catheter, blood pressure, heart rate, VAS, sensory level and level of motor blockade was assessed. After 15 minutes of first epidural dose VAS, sensory level and level of motor blockade was reassessed. Intramuscular diclofenac, 75 mg, was used for rescue analgesia.

In post anesthetic recovery room, patients were assessed for:
(a) Wound pain using VAS (0 mm = no point), 100 mm = worst pain
(b) Duration of analgesia (Time between first dose of epidural medication given and when patient demanded first rescue analgesic dose in post-operative period.)
(c) Level of sensory block
(d) Motor blockade according to Bromage scale¹⁴, ¹⁵.
   *0 = No Motor Block  
   *1 = Inability to raise extended hip  
   *2 = Inability to flex knee  
   *3 = Inability to flex ankle joint
(e) Sedation by the following Sedation score
   *0 = Awake (absent)  
   *1 = Drowsy but responding to verbal stimuli (mild)  
   *2 = Responding to moderate touch (moderate)  
   *3 = Responding to firm touch (severe)

When patient complained of pain in post operative period local anesthetic in diluted concentration was given through epidural catheter for analgesia.

These observations were performed at 3, 6, 9, 12 and 24 hr from the end of surgery for first 24 hr post operatively. Vitals of all the patients were recorded every 15 minutes for first 2 hrs postoperatively and hourly for next 22 hours.

Patients were monitored for side effects like respiratory depression, hypotension, nausea, vomiting and pruritus. Since patients were catheterized preoperatively, urinary retention, as a side effect, was not taken into consideration. Statistical tests used were student ‘t’test and ANOVA test.

Sample size estimation was performed with the help of PS and Sample Size calculator developed by Vanderbilt University's Clinical and Translational Science Award (CTSA) program (grant UL1 RR024975 from the NCCR/NIH). We planned a study of a continuous response variable (VAS for pain) from three experimental groups with equal proportion of patients in each. In a previous study the response within each subject group was normally distributed with standard deviation 1. If the true difference in the two experimental groups’ means is 1, we will need to study 17 subjects in each group to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. However, in order to enhance the power and reliability of study we have selected 30 patients in each group which is statistically not a small sample.

RESULTS

The patient characteristics age, height and weight were comparable. There was no significant difference in age, height and weight.

In current study, duration of analgesia i.e the time (min) to first rescue analgesic was significantly longer in group II (200 mins) and group III (210 mins) than group I (130 mins) which was also statistically significant (p<0.001) (Table 1). When group II was compared with group III, no significant difference was found. The number of intramuscular diclofenac injections ([median, 25th-75th percentile]) during the first 24 h postoperatively was less for the group II (1 or 2) and group III (1 or 2) as compared to the control group (3 or 4). (P < 0.05)

Regarding level of sensory blockade, no significant difference was found among three groups (Mean sensory block in Gr I was 8.33±0.48, Gr II 8.50±0.78 and in Gr III 8.60±0.77). The average level of sensory block was around T8.

Comparison of motor blockade after 3hrs between three groups showed no significant difference (Table 2).

The baseline VAS at the end of surgery was comparable among three groups. Pain decreased significantly after 15 mins of epidural injection in all three groups and was statistically significant (p<0.001) when VAS was assessed after 15 mins. (Table 3).

Table 4 shows comparison of sedation score after 3hrs. Group I patients did not show any sedation while group II and III patients showed mild sedation which was significantly higher than group I. When comparison between group II and group III was done the latter showed higher sedation score
which was statistically significant (p<0.001).

Regarding hemodynamic changes none of the patients in any group had fall in blood pressure more than 15% of baseline. No significant difference was found in readings from baseline during different time intervals in three groups.

At baseline and 15 mins, no significant difference in heart rate was observed in the any of the groups. During 30 to 120 mins, heart rate decreased significantly from baseline in all the three groups (p<0.001), but this decrease was found to be more in group III. No significant difference in heart rate changes were seen in any of the groups during 3hr to 24 hr. Bradycardia was not seen in any patient at any time.

Only two patients (6.7%) in group I and one (3.3%) in group III developed nausea and/or vomiting. No patients in group II developed nausea and/or vomiting. No patient developed pruritus or respiratory depression in our study (Table 5).

Table 1
Comparison of duration of analgesia

| Group   | Mean duration of analgesia ± S.D (minutes) |
|---------|------------------------------------------|
| I       | 130 ± 0.50                               |
| II      | 200 ± 0.24                               |
| III     | 210 ± 0.35                               |

| Comparison | 't'  | 'p'   |
|------------|------|-------|
| Group I vs. Group II | 10.91 | <0.001 |
| Group II vs. Group III | 10.81 | <0.001 |
| Group II vs. Group III | 1.30 | 0.20 (NS) |

Table 2
Comparison of Motor Blockade. (At 3hrs)

| Group   | Mean Motor Blockade ± S.D (muscle power grade) |
|---------|-----------------------------------------------|
| I       | 1.67±0.76                                     |
| II      | 1.50±0.48                                     |
| III     | 1.56±0.38                                     |

| Comparison | 't'  | 'p'   |
|------------|------|-------|
| Group I vs. Group II | 1.04 | NS    |
| Group II vs. Group III | 1.71 | NS    |
| Group I vs. Group III | 0.54 | NS    |

NS = p > 0.001

Table 3
Comparison of VAS

| Group   | Baseline | At 15 minutes |
|---------|----------|---------------|
| I       | 50.6±5.20| 12.40±2.42    |
| II      | 52.0±4.60| 5.6±1.20      |
| III     | 51.5±6.20| 8.00±3.20     |

Baseline vs. 15 minutes (p) <0.001 <0.001 <0.001

Table 4
Comparison of sedation score (3 hrs)

| Group   | Sedation score |
|---------|----------------|
| I       | 0.00± 0.00     |
| II      | 0.17± 0.38     |
| III     | 1.17± 0.70     |

| Comparison | 't'  | 'p'   |
|------------|------|-------|
| Group I vs. Group II | 2.46 | <0.05 |
| Group II vs. Group III | 9.19 | <0.001 |
| Group I vs. Group III | 6.90 | <0.001 |

DISCUSSION

Epidural block is widely accepted technique for post operative analgesia. It eases patient's discomfort and results in early mobilization. Many additives like clonidine, opioids and epinephrine have been investigated in epidural space and the results showed improvement in duration, intensity of analgesia and reduction in local anesthetic dose. The current study determined the analgesic effectiveness of two different doses of epidural neostigmine with lignocaine, along with its effect on sedation. The results showed encouraging clinical performance.

The current study established that addition of epidural neostigmine 100µg or 200µg to lignocaine 1% increased the duration of analgesia as compared to control group. The effect seems to be dose independent because comparison of duration between group II and group III was stastically insignificant. Nakayama et al. (2001) also concluded that duration of analgesia was significantly increased with epidural neostigmine 5µg kg⁻¹ or 10µg kg⁻¹ with bupivacaine and effects were dose independent. The improvement in duration of analgesia was also explained by Lauretti et al. (1999) who stated that neostigmine causes analgesia by increasing endogenous acetylcholine levels to act on muscarinic M1 receptors.

Pain intensity assessed by VAS was similar in all three groups at the end of surgery, but after 15 minutes it was significantly less in group II and III when compared to group I. The results show that addition of epidural neostigmine is associated with better pain relief, though in a dose independent manner. The similar results have been reported by other workers.

In current study, we found that level of sensory block was not affected by addition of neostigmine. The height of sensory block did not increase with higher dose of neostigmine. This could be due to volume of drug, which was kept constant in our study.

The current study also inferred that different doses of epidural neostigmine do not affect the motor blockade. Maximum score was obtained at 30 mins after the epidural loading dose which decreased gradually with passage of time.

Higher doses of intrathecal neostigmine can cause sedation. Post operative sedation was increased by epidural neostigmine but in a dose independent manner. Conversely in our study, the addition of epidural neostigmine produced mild sedation in both the neostigmine groups but sedation was statistically significant with high dose of neostigmine (Group III). The effects were found to be dose dependent in our study. It may be due to difference in type of anesthesia (general anesthesia in our study vs. combined spinal epidural technique), difference in doses of neostigmine (200 µg vs. 300µg) and addition of intrathecal fentanyl in study by Nurkaya.
et al.  

In the present study, the mean arterial pressure and heart rate were assessed in three groups at every 15 minutes for the first 2 hours and then hourly during the next 24 hours. None of the patients had a fall in blood pressure more than 15% of baseline, which was statistically insignificant on comparison between the three groups. The fall in heart rate from baseline was highest in group III, which was statistically significant. Bradycardia below 50 bpm was not noticed in any patient, so atropine administration was not required. The change in heart rate was more in group III during the first hour. This may be explained by cholinergic side effects at higher doses of neostigmine, secondary to systemic absorption.

We did not encounter the bothering problems of pruritus or respiratory depression usually occurring with epidural opioids. The incidence of nausea and vomiting was observed both in control as well as neostigmine group (200µg). This was statistically significant and may be attributed to type of surgery (laparotomy). It may be inferred that nausea & vomiting seen after intrathecal administration is not so prominent after epidural neostigmine.

It may be concluded that neostigmine, as an adjuvant to epidural lignocaine (1%), prolongs the duration of analgesia (dose independent) and causes mild sedation (dose dependent), with almost negligible associated side effects. Further, the investigated doses of epidural neostigmine are safe and useful for clinical use.

Authors disclosure: Authors have no conflict of interest or financial considerations.

REFERENCE
1. Glynn C, O’Sullivan K. A double-blind randomized comparison of the effects of epidural lignocaine and the combination of clonidine and lignocaine in patients with chronic pain. Pain 1996; 64(2): 337-43.
2. Fung BK, Gislifoss AJ, Ho ES. Continuous epidural morphine and lignocaine for post-operative pain control in obstetric and gynaecologic operation. Acta Anaesthesiol Scand. 1994 Dec.; 32(2): 247-50.
3. Wong CS, Lu CC, Cherng CH, Ho SI. Preemptive analgesia with ketamine, morphine and epidural lignocaine prior to total knee replacement. Can J Anaesth 1997; 44(1): 31-7.
4. Lam DT, Ngan Kee WD, Khaw KS. Extension of epidural blockade in labour for emergency caesarean section using 2% lignocaine with epinephrine and fentanyl, with or without alkalinization. Anaesthesia 2001; 56(8): 790-4.
5. Cherng CH, Wong CS, Ho ST. Epidural fentanyl speeds the onset of sensory block during epidural lignocaine. Reg Anesth Pain Med. 2001; 25(6): 523-6.
6. Reinoso-Baribio F, Saavedra B, Herville S, de Vicente J, Tabares B, Gomez-criado MS. Lignocaine with fentanyl, compared to morphine, marginally improves post-operative epidural analgesia in children. Can J Anaesth 2002; 49(1): 67-71.
7. Abboud TK, David S, Nagappala S, Costandi J, Yanagi T, Haroutunian S, Yeh SU. Maternal, fetal and neonatal effects of lignocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 1984 Nov; 63(11): 973-9.
8. Sakura S, Sumi M, Morimoto N, Saito Y. The addition of epinephrine increases intensity of sensory block during epidural anesthesia with lignocaine. Reg Anesth Pain Med 1999; 24(6): 541-67.
9. Lauretti GR, de Oliveria R, Resi MP, Julino MC, Pereira NL. Study of three different doses of epidural neostigmine coadministered with lignocaine for postoperative analgesia. Anesthesiology 1999; 90(6): 1534-8.
10. Nakayama M, Ichinoise H, Nakabayashi K, Satoh O, Yamamoto S, Namiki A. Analgesia effect of epidural neostigmine after abdominal hysterectomy. J Clin Anesth 2001; 13(2), 86-9.
11. Chia YY, Chang TH, Liu K, Chang HC, KONH, Wang YM. The efficacy of thoracic epidural neostigmine infusion after thoracotomy. Anesth Analg 2006 Jan; 102(1): 201-8.
12. Nurkaya, Sukran Sahin, Medge O. Owen, James C Eisenbach. Epidural neostigmine produces analgesia but also sedation in women after caesarean delivery. Anesthesiology 2004; 100: 381-4.
13. Gurvinder Kaur, Narjeet Osahan, Lalita Afjal. Effect of Transdermal Nitroglycerine patch on analgesia of low dose intrathecal neostigmine. J Anesth Clin Pharmacol 2007; 23(2): 159-162.
14. Bromage PR. A Comparison of bupivacaine and tetracaine in epidural analgesia for surgery. Can Anaesth Soc J 1969; 16: 37-45.
15. M.Akawa, Y.Aoyama, Y.Ohe. Block of the sacral segments in lumbar epidural anaesthesia. Br J Anaesth 2003, Vol 90, No. 2; 173-178.
16. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine methylsulphate in humans. Anesthesiology 1995; 82: 341-343.
17. Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G. Evaluation of a single dose, extended release epidural morphine formulation for pain after knee arthroplasty. J Bone Surg Am 2006; 88(2): 273-81.