

Research Article

Neostigmine as an Adjuvant to Epidural Anaesthesia With 0.5% Bupivacaine for Vaginal Hysterectomy: A Comparative Study

Dr. Mahilamani PP¹, Dr. Ranjan John²

¹Assistant Professor, Department of Anaesthesiology and Critical care Medicine, SMIMS, Kulasekharam, TamilNadu

²Senior consultant, Department of Anaesthesiology, Cosmopolitan Hospital, Thiruvananthapuram, Kerala

***Corresponding author**

Dr. Mahilamani PP

Email: drmahilamani@yahoo.com

Abstract: Various drugs have been used as epidural adjuvants to enhance the quality and duration of surgical anaesthesia. We aimed at evaluating the effects of Neostigmine, an acetylcholine esterase inhibitor, as an adjuvant to epidural anaesthesia with 0.5% Bupivacaine for vaginal hysterectomy. In this clinical comparative randomized study, 60 ASA I & II patients requiring vaginal hysterectomy were randomly divided into two groups - comprising 30 each. *Control group:* receiving epidural- 15ml of 0.5% Bupivacaine +0.6ml saline. *Neostigmine group:* receiving 15 ml of 0.5% Bupivacaine +0.6ml Neostigmine. Both groups were given an initial epidural top-up dose for postoperative analgesia. Time of onset, maximum sensory level achieved, degree of motor blockade, time of two segmental dermatomes regression, total duration of analgesia, perioperative hemodynamic changes and side effects were studied. The data obtained was compiled systematically and analyzed statistically using student-t test and chi-square test. Value of P<0.05 was considered significant. There were significant differences between the two groups (P<0.001) regarding: onset of sensory and motor blockade, time to attain maximum sensory level, all of which were earlier in Neostigmine group. The degree of motor blockade, time for 2 segmental dermatomes regression, total duration of motor block, postoperative analgesia and haemodynamic stability were comparable in both the groups. The mean arterial pressure in Neostigmine group, showed a delayed rise, though they were in the normal range. There were no major side effects noted in any of the patients. In conclusion, Neostigmine is a safe adjuvant to 0.5% Bupivacaine in epidural anaesthesia which provides early onset of sensory and motor blockade, with minimal effect on duration of blockade and perioperative hemodynamic stability, without any major side effects.

Keywords: Epidural, Adjuvant, Neostigmine, Bupivacaine, Vaginal hysterectomy

INTRODUCTION

The use of epidural blockade, a type of central neuraxial blockade, has recently become widespread and is preferred for regional anaesthesia/analgesia and for the management of acute and chronic pain. It has the advantage of providing excellent surgical anaesthesia and analgesia during postoperative period.

It is beneficial in attenuation of surgical stress response [1], faster recovery of gut function [2], reduction in thromboembolic and cardiovascular complications [3, 4] and provides superior postoperative analgesia than intravenous patient controlled analgesia [5].

Bupivacaine, a long-acting amide local anaesthetic, is most extensively used in various concentrations for epidural anaesthesia and analgesia. Its onset of action is slow and duration is longer [6].

Addition of adjuvants to local anaesthetics enhances the quality and duration of epidural blockade. Addition of adrenaline increases sensory blockade, and improves the pain relieving effect [7]. Sodabicarb hastens the onset of analgesia and enhances the degree of blockade [8]. Opioids like morphine, Buprinorphine, Fentanyl are used traditionally as adjuvant, but with side effects vomiting, pruritus, urinary retention and respiratory depression [9]. Many new adjuvants are being used like clonidine, ketamine, midazolam [10, 11, 12].

Neostigmine is an acetylcholinesterase inhibitor, universally used reversal agent and is used in the treatment of Myasthenia gravis. Acetyl choline is one of the neurotransmitter that participate in spinal cord modulation of pain processing, being rapidly hydrolyzed by acetylcholinesterase. Therefore the use

of acetylcholinesterase inhibitor such as Neostigmine was investigated with respect to the antinociceptive activity and to any potential side effects and toxicity after spinal administration [13].

It has been demonstrated that neostigmine produces analgesia without introducing the ventilatory depression characteristic of neuraxial opioids, although nausea was common. Antinociception is brought about by the interaction with spinal noradrenergic-cholinergic neurons corresponding with neurons in laminae I and II of spinal dorsal horn.

It has been used as adjuvant intrathecally where it inhibits break down of acetylcholine and induces analgesia [14, 15]. Neostigmine added to intrathecal Bupivacain, extends the duration of postoperative analgesia, with fewer side effects without adverse effects on fetus following caesarean section [16].

Neostigmine offers the advantage of easy availability of preservative-free drug, minimal side effects, cost effectiveness and reliable post-operative analgesia.

In this study we used Neostigmine as an adjuvant to epidural anaesthesia with Bupivacaine, to assess the effects of Neostigmine in the time of onset, duration of action, degree of muscle relaxation, perioperative haemodynamic changes, side effects and as an adjuvant for initial single dose of post-operative analgesia.

Aim and Objectives of the Study

To study the effects of Neostigmine as an adjuvant on quality and efficacy of epidural Bupivacaine 0.5% for vaginal hysterectomy by studying the time of onset, duration of action, highest dermatome level achieved, degree of motor blockade, time of two segmental dermatomes regression, total duration of analgesia, haemodynamic effects and side effects.

MATERIALS AND METHODS

Source of data

This study consists of 60 patients scheduled for elective vaginal hysterectomy at Cosmopolitan Hospitals, Thiruvananthapuram, during October 2009-December 2010.

Inclusion criteria

After obtaining the approval of Institutional ethics committee and written informed consent, 60 patients of ASA physical status 1 & 2 aged 45-60 years, weighing 45-65 kg, and height 145cm-165 cm, were enrolled in this clinical study.

Exclusion criteria

Patients with history of diabetes mellitus, hypertension, preexisting severe cardiac and respiratory disease, renal and hepatic disease, spinal deformity, neurological disorders, skin infection or local infection at the site of epidural, coagulation or bleeding disorders, allergy to local anaesthetics, patients in whom the epidural block failed or when other analgesics or anaesthetic agents have been supplemented and the patients who refused the technique.

METHOD

Pre anaesthetic evaluation was done; all patients were visited on the previous day of surgery, reassured, explained in detail about the anaesthetic procedure, the method of assessing the sensory and motor blockade, and the possible complications. Tab. Ranitidine 150mg and Tab. Alprazolam 0.25mg were given at night prior to surgery. Patients were randomly divided into two groups, 30 each.

Group I: control group - received Bupivacaine 0.5% + saline, and

Group II: Neostigmine group - received Bupivacaine 0.5% with 300 mcg of Neostigmine

Drug was prepared by adding:-

1. Bupivacaine 0.5% 15ml+ 0.6ml (300mcg) Neostigmine
2. Bupivacaine 0.5%ml +0.6ml saline to maintain equivalent dilution of Bupivacaine.

On arrival to the premedication room, 18G venous cannula was secured; all patients were preloaded with 10ml/kg of Ringer lactate solution and premeditated with intravenous Ranitidine 50mg and Ondansetron 4mg.

A multiparameter monitor was attached and baseline vital parameters like heart rate, non-invasive blood pressure, respiratory rate, S_{PO_2} were recorded and monitored throughout the perioperative period.

After taking into the operation theatre patient was positioned in the left lateral decubitus position and with all aseptic precautions, epidural space was identified at L₃₋₄ or L₄₋₅ interspace with an 18G Tuohy's needle by loss of resistance to air technique, after skin infiltration with 2% lignocaine. An epidural catheter was introduced 4-5cm into the epidural space and secured. Position of the epidural catheter was checked by aspiration for blood and CSF. A test dose of 3ml 2% lignocaine with 5mcg/ml of epinephrine was administered to detect the intrathecal or intravenous injection, and patient turned to supine position. After 3 minutes the drug under study was given.

Group I: 0.5% Bupivacaine + saline
 Group II: 0.5% Bupivacaine + 300mcg Neostigmine.
 The volume of drug given was 15.6ml in both the groups, so as to provide anaesthesia up to T₇ dermatome.

Bilateral pin prick was used to assess sensory level using short beveled 26G hypodermic needle. Motor blockade was assessed by modified Bromagescale [17] (0 no paralysis, 1- unable to rise extended leg but able to flex knee, 2- unable to flex knee, 3 unable to flex angle), at 5-10-15-20-25-30 minutes after the epidural administration of the study drug. Duration of the motor blockade was considered as time for return to modified Bromage scale I.

After conclusion of surgery and confirming 2 segmental dermatomes regression, both the groups were given epidural top up of initial single dose for post-operative analgesia with

Group – I-0.125% Bupivacaine 10ml + 0.2ml saline
 Group – II-0.125% Bupivacaine 10ml + 0.2ml Neostigmine (100mcg)

The following parameters were observed after epidural anaesthesia:

Time of onset of sensory and motor blockade, attainment of sensory blockade at L₁, T₁₀ and maximum level, 2 segmental dermatomes regression, degree of

motor blockade with reference to time (as per, modified Bromage scale), time of complete motor blockade, and total duration of analgesia. Hemodynamic parameters heart rate, ECG, NIBP, S_{PO2}, respiratory rate were monitored continuously and recordings were made every 5 minutes till the completion of surgery and every 30 minutes during the post-operative period.

For the present study hypotension was defined as a fall in systolic blood pressure of more than 20% of base line value or less than 100 mm of Hg, and was treated with IV fluids and if required by incremental doses of ephedrine 3-6 mg iv. Bradycardia- heart rate <60/minute was treated with .6mg of Atropine. Supplemental oxygen was given. Side effects and complications were recorded and treated concurrently.

Statistical Analysis

Mean and standard deviations were calculated and we used student-t, chi-square test to compare both the groups and to find the P value, P ≤ .05 considered to be significant.

RESULT

Totally 60 patients were enrolled for the study and were randomly divided into two groups of 30 each. The demographic character in both groups in terms of age, weight, height and mean duration of surgery were comparable (Table 1).

Table 1: Demographic profile of Patients (mean±SD)

SlNo.	Parameters	Group I	Group II
1	Age in years	52.34± 5.4	51.57±3.7
2	Weight (kg)	57.62±5.38	59.42±4.28
3	Height (cm)	150.47±3.37	152.32±4.52
4	ASA (I/II)	23/7	23/7
5	Duration of procedure	114.27±8.34	117±7.45

SD= Standard deviation. ASA-American Society of Anesthesiologists

Table 2: Sensory and Motor blockade Characteristics

Parameters	Group I	Group II	P Value
Onset time of sensory blockade - (min)	5.15±4.08	2.92±2.24	0.001**
Time to attain L1	8.75±4.21	3.61±2.73	0.001**
Time to attain T ₁₀ (min)	11.53±4.9	25.77±2.71	0.001**
Maximum cephalad dermatome	T6.9±0.4	T7.7±0.3	0.07
Time to attain maximum dermatome (min)	21.23±5.59	13.05±3.23	0.001**
Two segment regression(min)	165±32.82	163.32±24.66	0.690
Onset of motor blockade (Bromage 1)	11.41±4.94	5.15±4.08	0.001**
Time taken to achieve complete motor blockade (Bromage 3)	24.35±5.45	20.13±6.94	0.002*
Total duration of motor blockade (min)	232.00±33.87	246.00±25.56	0.026*
Total duration of analgesia	392.00±82.66	372.80±55.57	0.171

Data expressed as mean ±SD. *P<0.05 statistically significant. **P<0.001 statistically highly significant. SD=Standard deviation.

The Sensory and motor blockade characteristic are shown in Table. 2.

The onset of sensory blockade was sooner in Group II than Group I (P<0.001).The time to attain L₁, T₁₀ was also shorter in Group II (P<0.001).

Though the total volume injected and the maximum sensory level achieved in both groups was comparable T₇,T₈,the time to attain maximum sensory level was sooner in Group II. (P<0.001).

The mean time of onset of motor blockade (Bromage 1), and also time to attain modified Bromage II, was faster in Group II(P<0.001).

The mean time for attaining modified Bromage3 was shorter in Group II than Group I (P=0.002)though not statistically highly significant.

The mean time for two segment dermatomes regression was comparable in both the groups (P = 0.690).

Total duration of motor blockade in Group II was longer than in Group I, but was not statistically significant (P=0.026). Total duration of analgesia in Group I was prolonged but not statistically significant (P=0.171)

Hemodynamic Parameters

Both the groups were comparable with respect to the pulse rate, with P values ranging between 0.16 and 0.97, at no time <0.001 (Fig 1.)

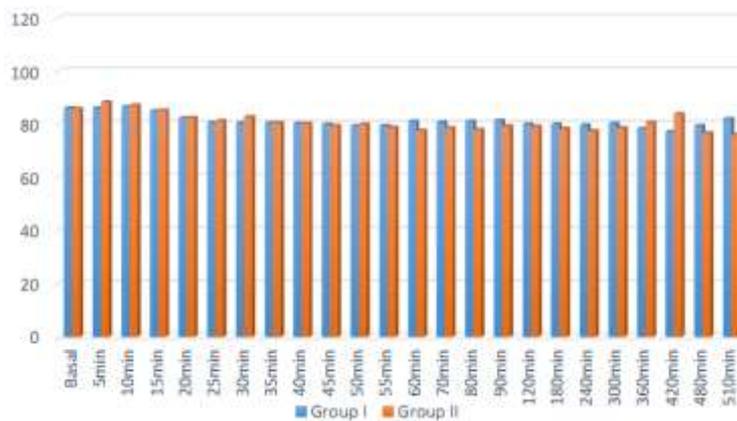


Fig. 1: Comparison of Pulse rate in groups

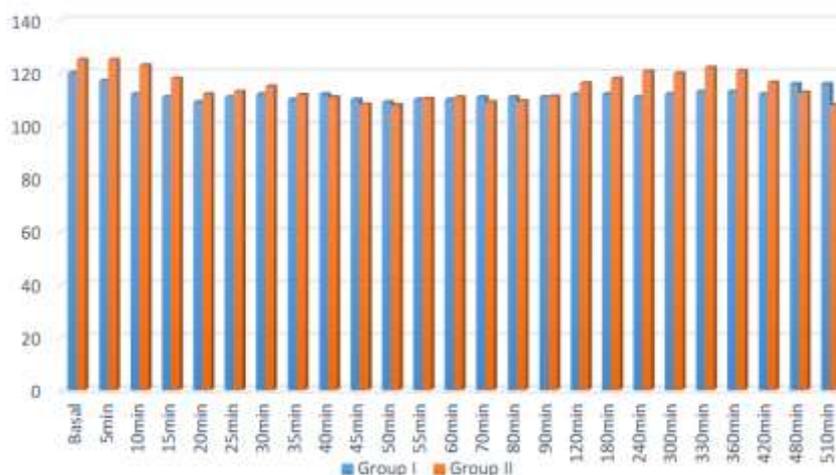


Fig. 2: Comparison of Systolic BP of Groups

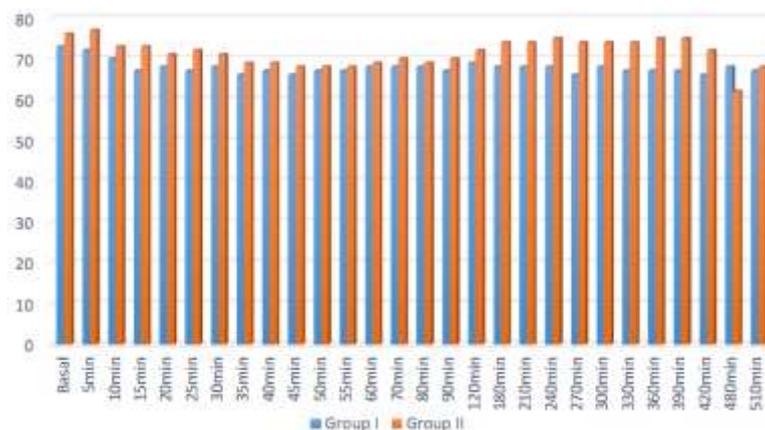


Fig 3: Comparison of Diastolic BP of Groups

The Systolic, Diastolic, mean arterial pressure were within normal range, though in group II the systolic pressure was significantly higher at 10min, 240min and 330 min. $P < 0.001$ and was within normal range between 240 and 330min.

The diastolic pressure in Group II was significantly high between 180min to 390min than Group I and MAP being significantly higher in Group II at 240,330 minute $P < 0.001$.

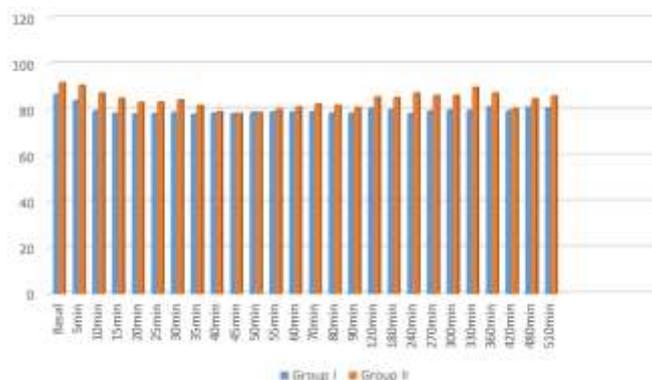


Fig 4: Comparison of MAP in the groups

Oxygen Saturation

The SPO₂ in both groups were in normal range throughout. Respiratory rates were also comparable and within range.

Side effects

The side effects noted amongst the patient were bradycardia, hypotension, and nausea, vomiting and shivering. They were noted equally on both the groups. Respiratory distress, excessive sweating or sedation was not seen in any of the patients.

Table 3: Intra and Postoperative side effects

Side effects	Group I	Group II
Bradycardia	1	1
Hypotension	1	1
Nausea, vomiting	2	3
Shivering	3	2

DISCUSSION

Epidural technique has the advantage of providing excellent anaesthesia intraoperatively, analgesia post operatively, attenuation of physiologic response to surgery [18] and improving the post-operative outcome. Various adjuvants have been used for enhancing the quality of block and to reduce the side effects. The present study evaluated the efficacy and safety of neostigmine as an adjuvant to epidural anaesthesia and analgesia with Bupivacaine. Neostigmine used as an adjuvant for epidural anaesthesia has shown to produce improved analgesia with sedation and low incidence of nausea and vomiting [19, 20].

In our study we observed an early onset of sensory and motor blockade in neostigmine group. Chittora et al [21] in their study observed that the onset of analgesia in patients receiving 100&150 µgm. Neostigmine was sooner than in patients receiving 50 µgm neostigmine. Kiran et al [22] in their study found no difference in onset of analgesia in the control group. In our study the hastening could have been due to the

higher dosage of (300mcg) neostigmine as adjuvant and the control drug being plain bupivacaine.

Though the maximum sensory level attained were comparable (T7-T8), the time taken to attain the maximum sensory level was earlier in neostigmine group. Roelant F et al [23] noted comparable maximum sensory level in both the groups after 30mts of epidural and Kiran et al [22] noted no difference in the time to attain maximum sensory level.

In this study we observed the degree of motor blockade was comparable and that there was no significant difference in the duration of motor blockade in both groups. This was similar to the results observed by Roelant et al [23] and Harjai M. et al [24]. In our study we noted no prolongation in duration of analgesia in the neostigmine group, but there was good relaxation. Chittora et al [21] in their study observed that in patients receiving 100 and 150 mcg neostigmine epidurally, duration of analgesia was prolonged in lower limb surgeries, but was less in lower abdominal surgeries with poor relaxation. Kiran M et al [22] also noted prolongation of duration of analgesia. They used neostigmine with mixture of lignocaine and Bupivacaine while in our study its addition to plain Bupivacaine failed to do so.

Abdulatif M and EF Sanabary M [18] in their study observed that the time for first analgesic after recovery was longer in Bupivacaine neostigmine group compared to Bupivacaine alone or neostigmine alone group indicating that neostigmine is a potent analgesic through epidural route in combination with Bupivacaine rather than alone. In our study we observed total duration of analgesia were comparable with no prolongation. Nakayama et al [25] in their study observed that time for rescue analgesia was significantly prolonged in patients who received 10mcg/kg compared to control group and 5mcg/kg group. They concluded that only at higher doses (10mcg/kg) Neostigmine, duration was prolonged. In our study the dosage of neostigmine was 300 mcg (about 5-7mcg/kg) comparable to their 5 mcg/kg group, so no prolongation. Shoji K et al [26] in their study observed no difference in time for rescue analgesia in accordance to our observation of no difference in duration of analgesia.

Haemodynamic parameters were comparable in both the groups. The heart rate, respiratory rate and SPO₂ were comparable. There was a delayed increase in mean arterial pressure compared to control group but within acceptable range. Chittora et al [21] also noticed the antihypotensive property of neostigmine. Caliskan Esra et al [27], Abdulatif M and El sanabary M [18], Tekin S et al [28], Roelants F et al [24] in their studies also observed no hemodynamic variations. The delayed

increase in MAP was seen to be due to the antihypotensive property of the neostigmine.

In our study we observed no increase in incidence of side effects like shivering, sedation, nausea and vomiting in neostigmine group. Kaya FN et al [20] in their study observed that intra operative shivering and sedation were more common with patients receiving higher doses (300mcg) of neostigmine than with lower doses, but nausea and vomiting did not differ with neostigmine. Omias M. et al [29] in their study also observed that the incidence of adverse effects were similar among the groups. In our study too adverse effects did not differ much between groups.

CONCLUSION

We concluded that neostigmine is a safe adjuvant to 0.5% Bupivacaine in epidural anaesthesia, which enhanced time of onset of sensory and motor blockade, with little/no effect on duration of blockade, and perioperative haemodynamic stability without any major adverse effects.

REFERENCES

1. Liu S, Carpenter RL, Oneal J.; Epidural anaesthesia and analgesia: Their role in postoperative outcome. *Anesthesiology*, 1995; 82:1474-1506.
2. Basse L, Jakobsen DH, Billesbølle P, Werner M, Kehlet H; A clinical pathway to accelerate recovery after colonic resection. *Ann Surg.*, 2000; 232: 51-7.
3. Myles PS, Power I, Jamozik K; Epidural block and outcome after major surgery. *MJA*, 2002; 177:536 - 537.
4. Celleno D et al; Combined epidural/General anaesthesia: Safety and outcome. *Anesth: Esia-Italia* Gennaio, 2002; 12(2); 2002.
5. Wu CL; Efficacy of postoperative patient controlled and continuous infusion epidural analgesia versus intravenous patient controlled analgesia. *Anesthesiology*, 2005; 103(5): 1079-88.
6. Riaz A, Yasin B, Malik AS; Epidural anaesthesia; Single-shot for day-case knee arthroscopy using a 50-50 mixture of lignocaine and Bupivacaine. *Professional Med J.*, 2010; 17(2):318-324.
7. Niemi G, Brevivik H et al; Adrenaline markedly improves thoracic epidural analgesia produced by a low dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomized, double-blinded, cross-over study with and without adrenaline. *Acta Anaesthesiol Scand.*, 1998; 42(8): 897-909.
8. Curatolo M, Peterson Felix M, Arendt-Nielsen L, Lauber R, Hogstrom H, Scaramozzino P et al; Adding Sodium bicarbonate to lidocaine enhances the depth of epidural anaesthesia. *Anesth Analg.*, 1988; 86:341-347.

9. Gedney JA, Liu EH; Side effects of epidural infusions of opioid Bupivacaine mixtures. *Anaesthesia*, 1998; 53(12): 148-55.
10. Huang YS, Lin LC, Huh BK, Sheen MJ, Yeh CC, Wong CS, Wu CT; Epidural Clonidine for postoperative pain after Total Knee Arthroplasty: A doses response studies. *AnesthAnalg.*, 2007; 104:1230-5.
11. Shobary HME, Sonbul Z, Schricker TP; Epidural Ketamine for postoperative analgesia in elderly.M.E.J ANESTH 19(6) 2008; 1369-78.
12. Nishiyama T, Hirasaki A, Odaka Y, Mikane T, Kobayashi O, Seto K; Epidural midazolam with bupivacaine- optimal dose for postoperative pain relief. *Masui.*,1992; 41(7): 1113-8.
13. Vadalouca AN; Adjuvant drugs. Prithvi raj Text book of Regional Anaesthesia. New York: Churchill Livingstone,2003; 254-255.
14. Brown DL; Spinal, Epidural and Caudal Anaesthesia. In:Miller RD, Erikson L, Fleisher LA, et al., editors.Millers Anaesthesia 7thed. New York. ChurchillElsevier, 2010;2:1624.
15. Klampt JG, SlullitelA, Garcia IV, Prado WA; Postoperative analgesic effect of intrathecalneostigmine and its influence on spinal anaesthesia. *Anaesthesia*, 1997; 52(6): 547-551.
16. Hye M.A et al;IntrathecalNeostigmine for postoperative analgesia in caesarean section.Mymensingh Med J., 2010; 19(4): 286-93.
17. Bromage PR, Burfoot MF, Crowell DE, Pettigrew RT; Quality of epidural blockade influence of physical factors.Br. J. Anesthe., 1964; 36:342-52.
18. Abdulatif M, El-Sanabary M; Caudal Neostigmine,Bupivacaine, and their combination for Postoperative pain management after hypospadias surgery in children. *AnesthAnalg.*, 2002; 95:1215-8.
19. Lauretti GR, Oliveira R, Perez MV et al; Study of three different doses of epidural Neostigmine co-administered with lidocaine for postoperative analgesia. *Anesthesiology*, 1999; 90(6) 1534-8.
20. Kaya FN et al; Epidural Neostigmine Produces analgesia but also sedation in women after caesarean delivery. *Anesthesiology*, 2004; 100(2): 381-5.
21. Chittora SP, Ahmed F, Sharma RA; Comparative analysis of neostigmine as additions to Lignocaine for postoperative analgesia in intrathecal and epidural anaesthesia. *Indian J. Anesthe.*, 2003; 47(3): 185-189.
22. Kiran MD, Sanikop CS, Kotur PF; Randomized control trial of Neostigmine and placebo as adjuvants to compound mixture of Lignocaine and Bupivacaine for epidural analgesia in abdominal surgeries. *Indian J. Anaesthesia*, 2006; 50(6):448-451.
23. Roelants F, Lavand'homme PM; Epidural Neostigmine combined with sufentanil provides balanced and selective analgesia in early labor. *Anesthesiology, Pain and Regional Anesthesia*, 2004; 101(2):439-444.
24. Harjai M, Chandra G, Bhatia VK, Singh D, Bhaskar P; A comparative study of two different doses of epidural Neostigmine co-administered with Lignocaine for postoperative analgesia and sedation. *J AnesthesiolClin Pharmacol.*, 2010; 26(4):461-64.
25. Nakayama M, Ichinose H, Nakabayashi KI, Satoh O, Yamamoto S, Namiki A; Analgesic effect of epidural Neostigmine after abdominal hysterectomy. *J Clin Anesth.*, 2001; 13(2): 86-9.
26. Shoji K, Saito H, Masaki E; Epidural neostigmine co-administered with Ropivacaine does not improve stress responses, or postoperative pain status. *Jikeikai Med J.*, 2004; 51:91-6.
27. Caliskan E, Turkoz A, Sener M, Bozdogan N, Gulcan O, Turkoz R; A prospective randomized double-blind study to determine the effect of thoracic epidural Neostigmine on postoperative ileus after abdominal aortic surgery. *AnesthAnalg.*, 2008; 106: 959-64.
28. Tekin S, Topeu I, Ekici NZ, Caglar H, Erincler T; Comparison of analgesic activity of the addition to neostigmine and fentanyl to bupivacaine in postoperative epidural analgesia. *Saudi Med J.*, 2006; 27(8):1199-1203.
29. Omais M, Lauretti GR, Paccola CAJ; Epidural Morphine and Neostigmine for postoperative analgesia after orthopedic surgery. *AnaesthAnalg.*, 2002; 95:1698-1701.