A comparative evaluation of three different doses of Epidural Neostigmine co-administered with Levobupivacaine for postoperative analgesia after lower limb Orthopedic surgeries

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Abstract

Background: Intrathecal neostigmine produces analgesia but its utility is limited by increased incidences of nausea and vomiting. However, epidural neostigmine has been investigated to produce postoperative analgesia without nausea and vomiting. The purpose of the current study was to define the dose range for analgesic effectiveness of epidural neostigmine co-administered with levobupivacaine and side effects in patients after lower limb orthopedic procedures.

Patients & Methods: After Institutional Ethical committee approval and informed written consent, 120 patients (n = 30) undergoing lower limb orthopedic surgery were randomly allocated to one of four groups and studied in a prospective way. Patients were randomized to receive either saline or 50, 100, or 150 µg neostigmine in 1ml as adjuvant to Levobupivacaine 0.5%, 20 ml (n = 30 per group), epidurally. Onset and duration of analgesia and motor block was assessed using pin prick, visual analogue scale (VAS) and bromage scale for 22 hrs. peri-operatively. Any side effects were also observed.

Results: Groups were demographically the same and did not differ in intraoperative vital characteristics (heart rate and respiratory rate), however there was some protection from hypotension observed in neostigmine 100 and 150 µg group. Addition of neostigmine resulted in significant longer duration of analgesia in group III (490±105.2 mins) and group IV (542±133.6 mins) than control group I (335±101.3 mins). The time of onset of analgesia (7.2 mins versus 9.2 mins in control) and motor block (12.4 and 11.5 mins versus 17 mins in control) was also decreased significantly. Two patients in control and one patient in group III developed nausea/vomiting which was statistically insignificant. There was no other incidence of increased side effects in any group.

Conclusion: Co-administration of epidural neostigmine and levobupivacaine appears to be a useful technique for perioperative analgesia as it increases duration of analgesia without increasing side effects.

Keywords: Neostigmine, Epidural, Postoperative analgesia, Levobupivacaine.

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-4994.2016.00041.X

Introduction

The goals of perioperative pain management are to relieve suffering, achieve early mobilization after surgery, reduce length of hospital stay, and achieve patient satisfaction. Traditionally, acute perioperative pain management has relied solely on opioid medications to target central mechanisms involved in the perception of pain[1]. Opioids have been successfully used in bolus, continuous or patient-controlled epidural analgesia (PCEA) for postoperative epidural analgesia. However, opioids have some undesirable side effects such as nausea- vomiting, urinary retention, pruritus, respiratory depression and decreased bowel motility[2]. Due to these side effects, non-opioids analgesics have been extensively investigated.

Neostigmine is a parasympathomimetic agent, a quarternary amine, unable to cross blood brain barrier, has been recently investigated for use as an adjunct to neuraxially administered local anaesthetics in the perioperative period. While the intrathecal injected neostigmine produced useful analgesic effects in the postoperative period, the high incidence of adverse events, mainly nausea and vomiting limits the clinical usefulness of this route of administration. Conversely, epidural neostigmine appeared to improve postoperative analgesia in several studies without increasing the incidence of adverse effects, it warrants further research about optimum dosing required without clinical side effects.

Epidural anaesthesia is commonly used in lower limb orthopedic procedures as it is safe way of providing anaesthesia intraoperatively as well as is a good way to provide postoperative analgesia. We studied neostigmine as an additive along with local anaesthetic levobupivacaine in epidural space to prolong postoperative analgesia.

Patients & Methods

This randomized double blind prospective study was conducted on 120 adult patients of either sex of ASA grade I or II, between age group 20-45 years, at tertiary level teaching institution associated hospital in Udaipur. After obtaining institutional ethical committee approval and written informed consent, the patients were scheduled for lower limb orthopedic surgeries. Patients

with contraindication to epidural anesthesia, allergy to local anesthetics and any bleeding or coagulation abnormalities were excluded from this study. All patients were explained about procedure and about visual analogue scale (VAS) when they visited for pre-anaesthetic check-up. Only patients with surgery less than 120 minutes of duration were included in the study. To ensure double blind nature of the study, the medication was prepared and coded by a separate observer who was not participating in other parts of the study, while the anaesthetist who gave epidural block did not participate in taking parameters intra and postoperatively and was blinded to study drugs as well as its outcome. Patients were randomly assigned into following four groups of 30 each as per computer generated randomization.

Group I: Levo-bupivacaine 0.5% (20 ml) + normal saline (NS) 1 ml.

Group II: Levo-bupivacaine 0.5% (20 ml) + neostigmine 50µg in NS 1ml

Group III: Levo-bupivacaine 0.5% (20 ml) + neostigmine 100µg in NS 1ml

Group IV: Levo-bupivacaine 0.5% (20 ml) + neostigmine 150µg in NS 1ml

Group I served as a control. In operating room after intravenous access, application of monitors and preloading with 10 ml/kg Ringer lactate solution, epidural block was performed under strict aseptic conditions, at L2-L3 or L3-L4 interspace in sitting position. After confirmation of epidural space with loss of resistance technique, syringe containing test solution prepared by investigator blinded to the groups were injected. Immediately after injection, following observations were taken. Vital parameters - Heart rate, Blood Pressure and respiration rate just after block till end of the surgery. Time of onset of analgesia measured by pin prick after 5 mins of epidural injection and then every minute till onset while duration of analgesia was measured using visual analogue scale (VAS) with paper strip marked 0 to 10 cm [0= no pain, 10 = worst pain]. Duration was noted with time of onset of pain (VAS $\geq$ 3) or need for rescue analgesic. Time of onset and duration of motor block was assessed using Bromage scale [0=No Motor block, 1= Inability to raise extended hip, 2= Inability to flex knee, 3= Inability to flex ankle joint]. Observations were performed at 3, 6, 9, 12, 15, 18, 22 hrs. from the end of surgery for first 22 hrs. post-operatively. Blood pressure of all patients were recorded every 3 minutes for first fifteen minutes thereafter every 5 mins non-invasively till end of the surgery. Then, every hourly for next 22 hours. Heart rate and SpO2 was measured continuously peri-operatively. Patients were monitored for side effects like respiratory depression, hypotension, nausea, vomiting and pruritus. Statistical analysis were performed using paired and unpaired student 't' test as applicable. A value of $p<0.05$ was considered statistically significant while $p<0.001$ considered highly significant.

Results

The groups did not differ significantly in terms of demographic data. There was no significant statistical difference in age, weight and sex distribution (Table 1).

Table 1: Demographic Characteristics

Groups(n=30)	Age (Yrs.)	Weight (Kg.)	Sex	
			M	F
I	44.1±11.5	59.22±4.45	11 (55%)	9(45%)
II	43.4±10.2	56.94±6.99	14 (70%)	6 (30%)
III	39.1±14.2	55.5±7.60	15 (75%)	5 (25%)
IV	42.1±12.5	57.7±8.22	12(60%)	8 (40%)

There was no significant difference among groups in heart rate except in control group where heart rate was decreased significantly from baseline after block, intra and post-operative period which is a usual finding after local anaesthetic neuraxial blockade (Table 2).

Table 2: Comparison of Heart Rate changes (Mean±SD)

Heart Rate/ min	Group I (Control)	Group II (50)	Group III (100)	Group IV (150)
Pre Op.	88.7±3.3	84.7±4.3	86.7±5.3	82.7±7.5
After Block	81.9±2.54*	83.1±5.1	85.1±4.3	82.2±8.4
Intra Op.	80.7±5.07*	82.6±3.7	84.7±5.4	81.6±5.7
Post Op.	81.0±4.1*	82.8±4.2	85.4±2.3	82.1±5.0

Comparison from Pre Op. (Baseline). *$p<0.05$; **$p<0.001$

Table 3 shows comparison of blood pressure changes from baseline amongst different groups after block and intra and post op period. Statistically significant hypotension was observed in control and group II while neostigmine in

higher doses in group III and IV prevented fall in blood pressure. Table 4 shows no significant different amongst control and test groups. Respiratory rate significantly decreased from baseline preop levels in all groups.

Table 3: Comparison of Blood Pressure changes (Mean±SD)

Blood Pressure (Systolic in mmHg)	Group I (Control)	Group II (50)	Group III (100)	Group IV (150)
Pre - Op	143.6 ±12.2	140 ±8.35	137 ±14	144 ± 12.5
After Block	122.9 ± 14.32**	129 ±9.15**	132 ±13	140 ±20.5
Intra - Op.	120.3 ± 9.84**	131.8 ±6.8**	133 ± 9.9	139 ± 14.6
Post - Op.	125.5 ±9.67**	132.5 ±7.1**	135 ±8.1	140 ±12.4

Comparison from Pre Op. (Baseline). *p<0.05; **p<0.001

Table 5 shows neostigmine has decreased the onset of analgesia in group III and IV but not significantly in group II. The onset of analgesia in group II is the usual onset of epidural effect (8.9±2.1 min) while in group III and IV it decreased to (7.2±1.2 min) and (7.1±1.3 min) respectively. These findings are statistically significant (P < 0.05). Onset of motor block is also decreased in group III (12.5±2.67) and IV (11.4±1.92) than control group (17±3.71) which is highly significant.

Table 4: Comparison of Respiratory Rate changes (Mean±SD)

Respiratory Rate per min.	Group I (Control)	Group II (50)	Group III (100)	Group IV (150)
Pre - Op	16.4 ±1.43	17.7 ±3.6	17.2 ±5.1	17.4 ±4.4
Intra - Op.	15.0 ±2.3*	15.6 ±1.56*	15.1 ±1.34*	15.7 ±2.1*
Post - Op.	15.4 ±2.1*	15.8 ±1.75*	15.3 ±2.3*	15.4 ±2.4*

Comparison from Pre Op. (Baseline). *p<0.05; **p<0.001

Table 5: Onset and Duration of Analgesia and Motor Block

Group	Onset time of sensory block (min) Mean±SD	Duration of sensory block (min) Mean±SD	Onset time of motor block (min) Mean±SD	Duration of motor block (min) Mean±SD
I (C)	9.2± 5	335±101.3	17±3.71	175±68.2
II (N 50)	8.9±2.1	361±98.4	16.6±2.89	183±38.5
III (N100)	7.2 ±1.2*	490±105.2**	12.5±2.67**	238±44.3**
IV (N150)	7.1±1.3*	542±133.6**	11.4±1.92**	251±46.7**

Compared with Control *p<0.05; **p<0.001

Sensory block or the duration of analgesia (VAS ≥3) was significantly longer in group III (490±105.2 mins) and group IV (542±133.6 mins) than group I (335±101.3 mins) which was statistically significant (p<0.001). However, group II (50 µg) has not shown significant increase in duration of analgesia (361±98.4).

Duration of motor block was 238± 44.3 mins in group III and 251± 46.7 mins in group IV as compared to 175±68.2 mins in control group. Duration of motor block increased marginally to 183±38.5 mins in group II. Duration of motor block is also significantly increased in comparison to control (P < 0.001), although magnitude of increase is not as high as duration of analgesia. It increased only 1¼ time than control while duration of analgesia increased about twice in comparison to control.

Only two patients in control and one patient in group III developed nausea/vomiting which was statistically insignificant. No other major side effect like sweating, pruritus or respiratory depression were observed.

Discussion

It is well known fact that postoperative pain is undertreated and the conventional way of providing intermittent analgesics on patient demand is ineffective method of pain relief. Long acting local anaesthetic levobupivacaine, the S (−) isomer of bupivacaine, is less cardiotoxic and neurotoxic than racemic bupivacaine. Studies show that postoperative analgesic effects of bupivacaine cannot be increased by addition of epinephrine[3]. Common adjuvants used to prolong postoperative analgesia are opioids and alpha 2 adrenergic agonists but are not devoid of side effects. Clonidine added to levobupivacaine enhances the quality of analgesia, the motor block tends to be denser but arterial hypotension occurs[4].

Transmission of pain from peripheral tissues to higher centres in brain is modulated in the dorsal horn of the spinal cord. After noxious stimulation, excitatory neurotransmitters are released from afferent fibres. Compensatory inhibitory neurotransmitters include

norepinephrine (NE) and acetylcholine. Pain and systemic opioids trigger release of endogenous norepinephrine from bulbospinal descending neurons, which in turn stimulates postsynaptic α-2 adrenoceptors in the spinal cord to produce analgesia[5]. Alpha 2 adrenergic agonists like clonidine and dexmedetomidine mimics this effect of NE to produce analgesia. When clonidine is added to local anaesthetics, a decrease in blood pressure 20% off baseline is expected due to additional sympathetic blockade caused by even small doses of clonidine, whereas large doses (75-150 µg) reduces heart rate and blood pressure[6].

Spinally administered neostigmine causes analgesia by preventing the breakdown of synaptically released acetylcholine, which acts on muscarinic and nicotinic receptors in spinal cord[5]. Lauretti [7](1999) et al also stated that neostigmine causes analgesia by increasing endogenous catecholamine levels to act on muscarinic M1 receptors. Neostigmine is not a sole analgesic but acts primarily an adjunct drug in prolonging local anaesthetic analgesia.

In our study, we have noticed significant prolongation of perioperative analgesia when we injected neostigmine as an adjunct to levobupivacaine which was confirmed by pin prick and VAS pain scores.

In line with our study, Dadu[8] (2011) et al compared 100 µg neostigmine with 50 mg ketamine as an adjunct to 20 ml 0.5% bupivacaine in epidural anaesthesia for infra-umbilical surgeries and reported that both neostigmine and ketamine demonstrated better haemodynamic stability with less incidence of hypotension, neostigmine prolonged postoperative analgesia more [543.3±133.4 minutes] compared to ketamine [292±71.9 minutes] although both were significant in prolonging it than control [212.8±62.4].

Chittora[9] (2003) et al studied neostigmine as an additive to lignocaine in intrathecal and epidural anaesthesia and found that both intrathecal 50 µg (368 mins) and epidural neostigmine 100 (355mins), 150 µg (410 mins), prolonged postoperative analgesia in dose dependent manner. 50 µg neostigmine dose epidurally failed to prolong duration of postoperative analgesia. This correlates well with our findings. In their study, 45% cases of intrathecal neostigmine showed nausea/vomiting.

Harjai[10] (2010) et al co-administered epidural neostigmine with lignocaine after recovery from general anaesthesia postoperatively and compared two doses with control and reported significant prolongation of analgesia with 100 µg (200 mins) and 200 µg (210 mins) than control (130 min) however this prolongation was independent of dose while our study demonstrated dose dependent increase in postoperative analgesia without increasing any major side effects.

The study of Mahajan[11] (2004) also shows that Caudal neostigmine compared in 3 doses of 2,3 and 4µg/kg with bupivacaine in children produced dose independent analgesic effect for 16-17 hrs. without increasing incidence of side effects (Mahajan).

In our study, we found epidural neostigmine in low dose of 50 µg as ineffective in augmenting postoperative analgesia which is supported by studies of Chittora[9] but Omais[12] (2002) et al noticed combination of low doses of neostigmine (60 µg) and morphine (0.6 mg) epidurally as an adjunct to 15 mg of bupivacaine resulted in postoperative analgesia of 11 hours devoid of side effects showing that they act synergistically.

Only 2 patients (6.66%) in group I (control) and one patient (3.33%) in group III developed nausea/vomiting. No patient in group II developed nausea/vomiting. No patient in any group developed pruritus, sedation or respiratory depression.

Conclusion

Epidural neostigmine as an adjunct to levobupivacaine prolongs the duration of analgesia. Epidural neostigmine (50, 100, or 150 µg) in levobupivacaine produced a dose-dependent analgesic effect (8-9 hours) compared to the control group (approximately 5.0h), 50 µg dose increased duration of analgesia marginally suggesting it as an ineffective dose epidurally. There was no incidence of major side effects. Thus it can be concluded from above study that in the dose of 100-150 µg epidural neostigmine is safe and effective for prolongation of postoperative analgesia without increasing the incidence of side-effects.

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