A prospective randomized double blind control study of duration of analgesic effect of epidural lignocaine 1.5% with adrenaline and neostigmine in 2 different doses for lower abdominal surgeries.

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Summary

Several studies using neostigmine as an adjuvant to local anesthestics (LA) for intrathecal anaesthesia are available in literature all claiming obvious advantages; but neostigmine as an adjuvant to local anaesthetics for epidural anesthesia has not been studied yet. We have conducted a prospective double blinded randomized controlled trial on 30 ASA I and II patients of both sexes who were scheduled to undergo elective lower abdominal surgeries. The patients were allocated to three groups and received epidural anesthesia with 1.5% lignocaine with 90μg adrenaline with either saline (G1), neostigmine10μg/kg (G2) and 15μg/kg (G3). The onset of sensory block, duration of postoperative analgesia and associated hemodynamic changes and sequelae between the three groups were studied. Pain was assessed using a 10cm visual analog scale (VAS). Addition of neostigmine to lignocaine resulted in decrease in onset of analgesia but prolonged the duration of analgesia with no sequelae.

Introduction:

Acute pain in the postoperative setting can have adverse physiological and psychological effects due to the stress hormone response induced by anesthesia and surgery. This postoperative pain management plays a vital role in deciding the overall outcome of any surgery. Epidural analgesia with local anesthetics and opioid is one of the recommended techniques for control of postoperative pain. This at times may prove to be inadequate and may also be associated with side effects of the adjuvant opioid. Compounding of local anesthetics for epidural administration is an accepted technique, which combines the advantages of individual constituents. Many a times this will not be enough to alleviate postoperative pain and so there is a continuous search for newer technique and strategies wherein intraoperative analgesia is extended into postoperative period. With the introduction of multi-modality approach to pain management, newer adjuvants like clonidine, ketamine, tramadol, fentanyl, midazolam, neostigmine etc have been all tried as adjuvants to local anesthetics agents, with varying success rates. But studies are scarce with adjuvant added to local anesthetic agents for epidural block.

Several studies have demonstrated the analgesic effects of intrathecal injection of neostigmine in volunteers and patients with acute postoperative pain. However there have only been a few reports on the effectiveness of epidural neostigmine for postoperative analgesia. In current study we evaluated onset and duration of analgesia and also side effects of epidurally administered neostigmine in patients undergoing lower abdominal surgeries.

The objective of the study were to evaluate the effects of epidurally administered neostigmine on 1.Onset analgesia and 2.Duration of analgesia

Material and methods:

After obtaining approval from the Institutional ethical committee and informed consent from each patient, 30ASA I and II patients of either sex, aged 18 to 60 years, undergoing lower abdominal surgeries were enrolled in this study. Before surgery each patient was instructed in the evaluation of pain using the visual analog scale (VAS, 0cm =no pain to 10cm =the worst possible pain) patients were randomly assigned via the computer generated randomization table to one of three equal groups to receive one of three doses of epidural neostigmine (0, 10 and 15μg/kg in the control group G1, 10 μg/kg group G2 and 15μg/kg group G3 respectively).

Patients with coagulopathy, neurological diseases, spine deformities, diabetes mellitus, hypertension, allergy to study drugs and pregnant or lactating women were excluded from the study.

After securing an I.V access with appropriate size cannula all patients were preloaded with 15 ml/kg of ringer lactate within 15 minutes before the block.

Non invasive monitors (viz ECG, NIBP, pulseoximeter) were attached and epidural block was performed in lateral position at L3 & L4 space using 18 G Tuohy epidural needle, using loss of resistance technique and test dose with 3ml of the respective solution for the group was injected in all the patients. The patients were monitored for subjective signs of any inadvertent intravascular/ intrathecal injection. Patients were asked to report any unusual subjective sensation during epidural injection and also monitored for objective signs on ECG, NIBP, SpO2 and respiratory rate. In their absence the total volume of drug mixture as allocated to the groups was injected by anesthesiologist who was blinded to the drug composition.

The time of administration of the drug into epidural space was noted. The onset of sensory analgesia was defined as loss of sensation to bilateral

pin prick which was tested every 2 minutes in the initial 30 minutes and then every 5 minutes until surgery started.

Throughout the procedure B.P was monitored every 5 min, pulse and SpO2 were monitored continuously. Onset of bradycardia was defined as fall in heart rate less than 60 per min and hypotension was defined as fall in B.P more than 20% below base line, both were treated with Inj. Atrpine 0.6 mg IV bolus, 0.3 mg increments if necessary and incremental doses of I.V. Ephedrine 6 mg respectively.

Surgery was permitted only when the block was adequate in density and spread. An upper sensory level of T6 and lower level of S5 were considered to be appropriate. General anesthesia was instituted, whenever the block was inadequate. Fluid management was done according to requirements including fluid deficit, maintenance, blood loss etc. throughout the procedure patients were asked for any nausea, vomiting, shivering, pain and any discomfort.

Postoperatively patients observed for

1) Time of onset of pain
2) Assessment of pain by VAS at timed intervals
3) Time of first analgesic administered on request by patient
4) Number of analgesics given
5) Side effects if any

In postoperative period the occurrence of pain after 90 min of block at the interval of 15 min, 30min, 1 hr, 2 hr, 4 hr and 6 hr were recorded.

Statistics

Allowing 5% type I error and a power of 80% a sample size calculated was 30 viz 10 patients in each group. A p value of <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The three groups were comparable with respect to age, weight, ASA status and duration of surgery as shown in table 1.

Table: 1 Demographic variables

	G1	G2	G3
Age in yrs	29 ± 2.21	29 ± 2.91	29.1 ± 3.2
Weight in kgs	52 ± 2.75	50.4 ± 5.23	51.2 ± 6.05
Duration of surgery in mins	53 ± 6.75	52.5 ± 6.34	53 ± 6.74

Table: 2 Onset and Duration of analgesia

Group	G1	G2	G3
Onset of analgesia in min	12.45 ± 1.04	3.35 ± 0.33	2.45 ± 0.28
Duration of analgesia in min	144 ± 11.73	664 ± 35.02	814 ± 20.65

Epidural neostigmine decreased the onset and prolonged the duration of analgesia in G2 and G3.

Table: 3 Bonferroni multiple comparison

Intergroup comparison	Onset of analgesia p value	Duration of analgesia p value
G1-G2	0.0001	0.0002
G1-G3	0.0001	0.0001
G3-G2	0.014	0.0001

p value of Inter group comparison of onset and duration of analgesia are highly significant.

Table: 4 Interrelationship of neostigmine dosage with analgesia duration and side effects

Group	Duration of analgesia in min	Nausea/vomiting No %	Sweating No %	Bradycardia No %
G1	144 ± 11.73	-	-	-
G2	664 ± 35.02	-	-	2 20%
G3	814 ± 20.65	1 10%	-	3 30%

Side effects were more in G2 and G3, but were easily treatable.

Discussion

Neostigmine, an anticholinesterase drug, which is used to antagonize non-depolarizing muscle relaxants, has been tried for post-operative analgesia as an off-label use. Being a quaternary amine, it does not cross blood-brain-barrier and by intrathecal (IT) route provides analgesia via M1 and M2 receptors in the spinal cord, inhibiting the break down of acetylcholine (Ach). Ach induces analgesia by increasing cyclic guanidino-monophosphate by generating nitricoxide. Autoradiographic studies have shown muscarinic binding in substantia gelatinosa and to a lesser extent in lamina 2 and lamina 5 of dorsal gray matter of spinalcord. Neostigmine also displays peripheral and supraspinal analgesic activity however the dose necessary to achieve this seems to be higher. However IT neostigmine also carries dose dependent side effects like nausea and vomiting.

Several studies have demonstrated that the use of epidural neostigmine is associated with lesser adverse effects and proposed mechanism of analgesia is by drug spreading into Cerebro Spinal Fluid (CSF) at the rate of $1/10^{th}$ the epidural dose.

Minovsky et al studied analgesic duration and side effects of neostigmine as an additive in spinal and epidural anesthesia with lignocaine for orthopedic surgery. He found that duration of analgesia was 120±13.8 mins in control group which was prolonged to 245±76.1 mins and 225±49.7 min in the intrathecal nesotgmine (50μg) and epidural neostigmine (100μg) group respectively.

Dr.S.P.Chittora et al studied the role of neostigmine as an additive to lignocaine to increase the duration of analgesia post operatively in intrathecal / epidural anesthesia. The duration of analgesia was 123 ± 14.8 mins in control group, which was prolonged to 368.1 ± 145.4 mins in intrathecal neostigmine 50μg group, 139.3±21.78 mins in epidural neostigmine 50μg group, 255±105 mins in 100μg group and to 410.7±153 mins in 150μg group.

A study of Lauretti et al showed that 1 to 4μg /kg of epidural neostigmine in lignocaine produced a dose independent analgesic effect in patients after minor orthopedic procedures, another study by Masayasu et al, where they used larger doses of neostigmine using 5μg/kg and 10μg /kg epidurally, analgesic effect seen in 10μg group was significant but not in 5μg/kg group.

The results of all the above studies correlate well with our study. Where we used neostigmine with ligocaine 1.5% epidurally comparing with control group G_1. The onset of analgesia was 12.45±1.04 mins in control group G_1 which was reduced to 3.35±0.33 mins and 2.1±0.28 mins in group G_2 and G_3 respectively.

The duration of analgesia was 144±11.73 mins in control group G_1 which was prolonged to 664 ± 35.02 mins in G_2 and 814± 20.65 mins in G_3 . These all findings are statistically highly significant.

The major side effects we observed were nausea and vomiting in 10% and bradycardia in 30% of points which were easily treatable which is supported by the above studies. The incidence of side effects was less with lower doses of

neostigmine that parallely increased with the increase in doses as we observed in our study.

Thus the results of our study establish that neostigmine is an effective additive in epidural anesthesia for decreasing the onset and prolonging the duration of postoperative analgesia.

Conclusion:

From the above study it can be concluded that the neostigmine decreased the onset of analgesia and prolongs the duration of postoperative analgesia when injected as an additive to lignocaine for epidural blocks.

The neostigmine 15μg/kg is more effective in prolonging the duration of post operative analgesia than the 10μg/kg neostigmine group.

The increased dose 15μg/kg of neostigmine prolongs the duration of post operative alangesia more but at the cost of increased incidence of side effects.

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