A PROSPECTIVE RANDOMIZED DOUBLE BLIND CONTROL STUDY OF DURATION OF ANALGESIC EFFECT OF EPIDURAL LIGNOCAINE 1.5% WITH ADRENALINE AND NEOSTIGMINE IN TWO DIFFERENT DOSES FOR LOWER ABDOMINAL SURGERIES

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Summary

A prospective double blind randomized controlled trail was conducted on 30 patients scheduled to undergo elective lower abdominal surgeries. The patients were allocated to three groups and received epidural anaesthesia with 1.5% lignocaine with 90μg adrenaline with either saline, neostigmine 10μg/kg. and 15μg/kg. The onset of sensory block, duration of postoperative analgesia and associated hemodynamic changes and sequelae between the three groups were studied. 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. Thus, postoperative pain management plays a vital role in deciding the overall outcome of any surgery. Epidural analgesia with local anesthetics (LA) and opioids 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 LAs 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 techniques and strategies wherein intraoperative analgesia is extended into postoperative period. With the introduction of multi-modality approach to pain management, newer agents like clonidine, ketamine, tramadol, fentanyl, midazolam, neostigmine etc have been all tried as adjuvants to LAs , with varying success rates.

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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 the 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 Institution ethical committee and informed consent from each patient, 30 ASA I and II patients of either sex, aged 18 to 60 years,

undergoing lower abdominal surgeries were enrolled for the study. Before surgery, each patient was instructed on evaluation of pain using the visual analog scale (VAS, 0 cm = no pain to 10 cm = the worst possible pain). Patients were randomly assigned via the computer generated randomization table to one of three groups to receive epidural neostigmine (0, 10 and 15 μg/kg in group G1, group G2 and 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 sized cannula, all patients were preloaded with 15 ml/kg of Ringer Lactate within 15 minutes before the block.

Non invasive monitors (viz ECG, NIBP, pulse oximeter) were attached and epidural block was performed in lateral position at L3 & L4 space using 18 G Tuohey epidural needle, using loss of resistance technique. A test dose with 3 ml of the respective solution for the group was injected. 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 to less than 60 per min and hypotension was defined as fall in B.P more than 20% below base line, and were treated with Inj. Atrpine 0.6 mg. IV bolus (0.3 mg increments if necessary) and incremental doses of I.V. Ephedrine 6mg. 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 enquired and observed for any nausea, vomiting, shivering, pain and any discomfort.

Postoperatively patients were 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 / doses given
5) Side effects if any

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

Statistics :

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

Observations 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 (yrs)	29± 2.21	29± 2.91	29± 3.2
Weight (kgs	52± 2.75	50.4± 5.23	51.2± 6.05
Duration of Surgery (Mins)	53± 6.75	52.5± 6.34	53±6.74

Table 2 : Onset and Duration of analgesia (in mins)

Group	G1	G2	G3
Onset of analgesia	12.45 ± 1.04	3.35± 0.33	2.45± 0.28
Duration of analgesia	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	Durationof 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 highlysignificant.

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

Group	Duration of analgesia in min	Nausea/vomiting		Sweating		Bradyeardia	
		No	%	No	%	No	%
G1	144 ± 11.73	-		-		-	
G2	664 ± 35.02	-		-		2	30%
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 guanidion-monophosphate by generating nitric oxide. Autoradiographic studies have shown muscarinic binding in substanita gelatinosa and to a lesser extent in lamina 2 and lamina 5 of dorsal gray matter of spinal cord. Neostigmine also displays peripheral and supraspinal analgesia activity ; however the dose necessary to achieve this seems to be higher. However intrathecal 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 1/ 10th 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 minutes in control group which was prolonged to 245±76.1 minutes and 225±49.7 minutes in the intrathecal neostigmine (50 μg) and epidural neostigmine (100 μg) 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 minutes in control group, which was prolonged to 368.1±145. 4 minutes in intrathecal neostigmine 50 μg group, 139.3±21.78 minutes in epidural neostigmie 50 μg group, 225±105 minutes in 100 μg group and to 410.7±153 minutes in 150 μg group.

A study of Lauretti et al showed that 1 to 4 μg / 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 5 μg/kg and 10μg epidurally, analgesic effect seen in 10 μg group was significant but not in 5 μg/kg group.

The result of all the above studies correlate well with our study, where we used neostigmine with lignocaine 1.5% epidurally compared with control group (G1). The onset of analgesia was 12.45± 1.04 minutes in control group G1 which was reduced to 3.35±0.33 minutes and 2.1±0.28 minutes in group G2 and G3 respectively.

The duration of analgesia was 144±11.73 minutes in control group G1 which was prolonged to 664±35.02 minutes in G2 and 814±20.65 minutes in G3. All these findings are statistically highly significant.

The major side effects we observed were nausea and vomiting in 10% and bradycardia in 30% of patients 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 neostigmine decreased the onset of analgesia and prolongs the duration of postoperative analgesia when injected as an additive to lignocaine for epidural blocks. Epidural neostigmine at 15 μg / kg dose is more effective in prolonging the duration of post operative analgesia compared to 10 μg / kg. Higher dose of neostigmine (15 μg / kg) results in prolonged duration of post operative analgesia but at the cost of increased incidence of side effects.

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CONGRATULATIONS !!

The members of Indian Society of Anaesthesiologists (I S A), Karnataka State Branch are proud to have three senior colleagues elected to the national body of I S A , during the ISACON 2006 held at Mysore. We heartily congratulate the three on the great achievement , this being the first time we have such a big representation in the national body of the ISA. It is for all of us to utilize their services to strengthen our state branch and increase our participation at the national level.

Dr. P F Kotur (Belgaum), President , I S A (National)

Dr. S S Harsoor (Bellary) , Member , Governing Council , I S A (National)

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