Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-nahrain.edu.iq

Effect of adding Neostigmine to Lidocaine on the Onset of Epidural Anaesthesia

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Abstract

Background Shortening the onset time of sensory block is a practical goal to improve the quality of epidural anesthesia. The addition of Neostigmine to a local anesthetic solution is one of the ways used during epidural anesthesia to perform this goal.

Objective To examine the onset time of sensory block and intensity of motor block during epidural lidocaine anesthesia with and without Neostigmine addition to the epidural solution and to compare haemodynamic changes and any associated side effects.

Methods We made two groups of twenty patients, each of both the sexes ranging from 20-80 years age group of American Society of Anaesthesia (ASA) Grade I & II, selected for abdominal surgery; group I (epidural administration of 17 ml of 2% Lidocaine plus 1 ml of normal saline); group II (epidural administration of 17 mL of 2% Lidocaine plus 500 µg Neostigmine in 1 ml of normal saline). The sensory block was assessed by pinprick method; the motor block was assessed by using Bromage scale. The hemodynamic changes, post epidural shivering, and side effects of epidural Neostigmine were also recorded.

Results The onset time of sensory block up to T_{10} dermatome was significantly more rapid in the group II (8.95±2.44 minutes) than that of the group I (25±4.32 minutes). The upper level of sensory block was also significantly higher in group II, regarding intense motor block it was significantly in group II (13.11± 5.52 minutes) while in group I it was 30.2± 6.4 minutes; this represents the stage of just being able to flex knee but full flexion of foot (Bromage Scale). Post epidural arterial blood pressures and heart rates were not statistically different between both groups. No significant difference was also noticed considering associated side effect (nausea, vomiting, hypotention and shivering).

Conclusions Addition of Neostigmine 500µg to 2% Lidocaine shortened the onset of sensory block with rapid cephaled spread with more potent motor block without increasing side effect.

Key Words Epidural, Neostigmine, Lidocaine, Onset of sensory block and Motor block.

List of Abbreviation: ASA: American society of Anesthesia, L_2:Second lumbar dermatomal nerve supply, L2: Second lumber inter-vertebral space, L3: Third lumber inter-vertebral space, L4: Fourth lumber inter-vertebral space, LA: Local anesthetic, S_5: Fifth sacral dermatomal nerve supply, T_{10}: Tenth thoracic dermatomal nerve supply, T_6: Sixth thoracic dermatomal nerve supply.

Introduction

Local anaesthetic agents can produce unwanted side effects such as motor and autonomic block. Their onset may be slow and have limited duration of action. At higher doses, there is a risk of cardiotoxicity and central nervous system side effects. For these reasons, other drugs are sometimes co-administered to utilize their synergistic analgesic properties and to limit the local anesthetic dose requirement [(1)]. A variety of drugs have been studied more recently to try to improve the quality of neuraxial blockade, and speed the onset of action. Neostigmine, a cholinesterase inhibitor, is more recent addition to the list of epidural

anesthesia for analgesia. Recently, epidural Neostigmine was studied for analgesia during labor [2-4]. It acts by inhibiting acetyl cholinesterase and preventing the breakdown of acetylcholine, increases the concentration of acetylcholine available to bind muscarinic and nicotinc receptors, in the dorsal horn of spinal cord provides analgesia, and also it enhances the duration and intensity of epidural anesthesia [5].

All previous studies were designed to evaluate the effects of adding Neostigmine to mixture of Lidocaine for epidural analgesia. The onset of action is 10-15 minutes [6] (10-20 minutes) [7]. Alkalizations of local anesthetic solutions has also been used to increase the speed of onset of local anesthetic by increasing the concentration of the nonionic form of the drug; more drugs are available to penetrate the lipid nerve cell membrane to produce more rapid intramural diffusion [5].

Methods

This prospective randomized clinical study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq in the period of 1st of November 2012 to 1st of March 2013 on 40 patients ASA classes I, II of either sex, age ranged 20-80 years old, height 160-180 cm. and weight 60-100 Kg. Scheduled for elective operation under epidural anaesthesia.

Selection of subjects was made after excluding patients who had: absolutecontra indications for epidural anaesthesia such as, coagulation disorder, spine deformities, allergy or anaphylaxis to drugs, history of drug abuse, psychological disorder, and uncooperative patients. The patients were divided into 2 groups each group included 20 patients:

Group I received 2% Lidocaine hydrochloride 17 ml with 1 ml normal saline.

Group II received 2% Lidocaine hydrochloride 17 ml +Neostigmine 500 µg in 1 ml normal saline.

A complete preanaesthetic evaluation was carried out, baseline pulse rate, blood pressure, ECG, SPO_2 were recorded. All patients were preloaded 15 minutes prior to epidural anesthesia with 500 ml ringers lactate solution. No premedication was given to the patients. The epidural procedure was done while the patients were in sitting position, under full aseptic technique and after skin infiltration with 2% plain Lidocaine, then epidural block was performed at level (L_2 – L_3) or (L_3 – L_4) interspaces with a touhy needle size 16 then epidural catheter was advanced 5 cm into the space, the test dose with separated syringe from main dose contain 3 ml 2% Lidocaine with 15 mcg epinephrine (1:200,000) was 1st administrated to exclude possible of occurrence of accidental intrathecal or intravenous injection and then followed after 3 minute interval by main dose. Patient's age, weight, height, and duration of surgery were recorded, patients were then observed for the following:

1. Time of drug administration (test dose, main dose).
2. Time of onset of sensory block at several level dermatomes (S_1, S_5, L_2, T_{10}, T_6).
3. Time of motor block.
4. Intraoperative vital parameters.

The sensory block was assessed by pin prick method at 2 minutes intervals for 20 minutes, using 21 gauge needles in cephalic to caudal fashion along the left anterior axillary line by a blinded observer. The onset of sensory block was defined as loss of sensation to a bilateral pin prick which was tested every 2 minutes at level of dermatomes mentioned above. Time of maximum cephalic spread was defined as time from onset of analgesia up to highest level of sensory analgesia achieved. The time of occurrence of motor block was assessed using bromage scale (Table 1) [8]. Surgery was permitted only when the block was adequate in density and spread an upper sensory level of T_6 and lower S_5 were considered to be appropriate. Any need to intravenous sedation or analgesia was recorded. Side effect such as nausea and vomiting, shivering were recorded during surgery. Fluid management was done according to requirements including fluid deficit, maintenance, and blood loss.

Table 1. Bromage Scale

No.	Grade of Motor Block	Degree of Motor Block
1	Full flexion of knee and foot	No Block
2	Just able to flex knee but full flexion of foot possible	Partial Block
3	Unable to flex knee but flexion of foot possible	Almost Complete Block
4	Unable to flex knee and foot	Complete Block

Results

With taking in consideration patients' age (years), weight (Kg), and height (cm), ASA status, surgical time and the distribution of the surgical procedures, demographic data were compared in both two groups; there was no significant difference between them.

Anesthetic characteristics of the two groups regarding the onset time of sensory block up to T_{10} dermatome was significantly more rapid in group II as shown in Table 2 and Fig. 1. Also the time to maximum cephalic spread to the level of T_6 was also significantly more rapid and intense in group II; there was no excessively higher block in either group.

Table 2. Sensory Block in Different Times

Level of Dermatome	Group	Mean±SD	*P* Value
S_5	I II	20.0±3.74 6.53±2.39	0.002*
S_1	I II	15.0±3.22 4.63±2.41	0.003*
L_2	I II	10.0±2.44 3.65±2.09	0.009*
T_{10}	I II	25.0±4.32 8.95±2.44	0.008*
T_6	I II	32.0±4.53 13.26±3.43	0.016*

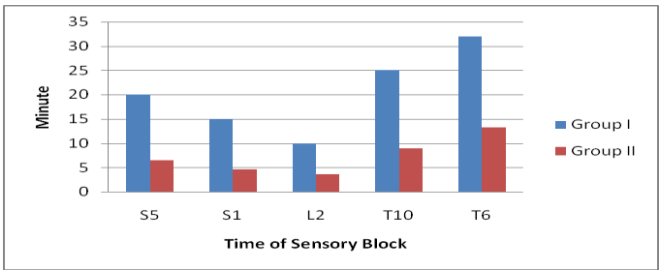

Fig. 2. Time of Sensory Block in Different Times

Regarding motor block, which was assessed by Bromage Scale, the motor block was significantly more intense and there was loss of motor function in group II as shown in table 3 and Fig. 2.

Bromage Scale	Group	Mean±SD	*P* value
Full flexion of the knee	I II	25.23±4.12 10.4±2.83	0.034*
Just able to flex knee but full flex foot	I II	30.2±6.4 13.11±5.52	0.020*
Unable to flex knee but full flex foot	I II	33.4±7.22 16.74±6.73	0.008*
Unable to flex knee and foot	I II	42.0±8.32 22.42±7.03	0.002*

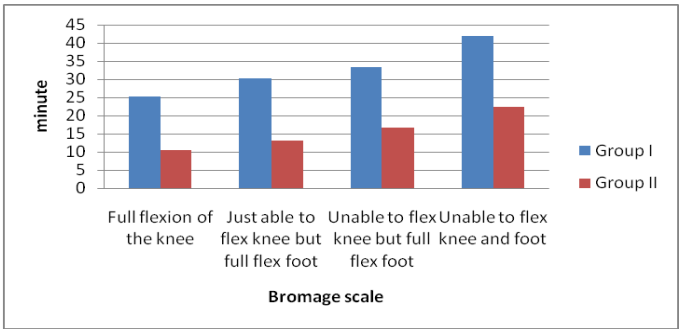

Fig. 2. Assessment of Motor Block in Different Times

The haemodynamic changes regarding arterial blood pressure and heart rate show no difference between both groups as demonstrated in the table 4 and 5.

Regarding associated side effects, there was no significant difference between both groups, in fact 4 patients complain from nausea and they have received IV medication (metoclopramide, dexamethasone, and ranitidine), 2 patients complain from vasovagal attack and they have received IV atropine. The incidence of hypotension was less the same in both groups, only 2 patients received 6mg IV ephedrine no

vomiting and no shivering was recorded in both groups (Table 6).

Table 4. Arterial Blood Pressure Monitoring in Different Times

Systolic Blood Pressure	Group I Mean±SD	Group II Mean±SD
Pre-induction	130.43±23.66	140.79±27.03
After 5 minutes	140.54±21.7	136.47±24.45
After 10 minutes	130.49±18.84	130.74±24.22
After 30 minutes	120.86±21.65	129.47±21.97
Diastolic blood pressure	**Group I**	**Group II**
Pre-induction	80.23±9.7	78.05±11.54
After 5 minutes	60.22±6.88	74.37±9.69
After 10 minutes	72.12±7.34	70.95±9.94
After 30 minutes	74.22±6.4	71.74±12.19

Table 5. Pulse Rate in Different Time Intervals

Pulse rate	Group I Mean±SD	Group II Mean±SD
Pre-induction	80.30±13.55	80.21±14.44
After 5 minutes	84.86±16.44	85.32±17.22
After 10 minutes	88.23±17.43	80.53±15.66
After 30 minutes	84.55±15.34	77.74±14.56

Table 6. Associated Side Effect

Complication	Group I		Group II	
	Count	%	Count	%
Hypotension	2	20	2	20
Vasovagal Attack/Bradycardia	0	0	2	20
Nausea	2	20	2	20
Vomiting	0	0	0	0
Shivering	0	0	0	0

Discussion

The result of our study shows that the addition of 500 µg Neostigmine as adjuncts with Lidocaine in Epidural anaesthesia reveals significant finding regarding accelerating the onset of sensory block and intensity of motor block.

The mechanism by which Neostigmine speed the onset in epidural anesthesia is not clear. As we know, alkalization of the local anesthetic solutions is known to shorten the onset time of sensory block [(5)]. The pH values of the 2% Lidocaine solutions used in this study, Lidocaine and Neostigmine, normal saline-Lidocaine solutions, were not different. Therefore, the pH changes cannot explain this result. Neostigmine is an anticholinesterase drug and several studies have demonstrated that the use of epidural Neostigmine is associated with less adverse effects and the proposed mechanism of analgesia is by drug spreading into cerebrospinal fluid (CSF) at the rate of 1/10th the epidural dose [(9-11)].

Other studies show the effect of using Neostigmine in intravenous regional anaesthesia (IVRA), the addition of Neostigmine in (IVRA) produced significantly reduced onset times of sensory and motor blocks while prolonging their recovery times. These findings are in agreement with those of Turan et al. [(12)]. However, McCartney et al [(13)] observed merely a reduced motor block onset time in their Neostigmine group. Prolongation of the sensory block may be related to the newly discovered acetylcholine-mediated sensory regulatory mechanism controlled by the motor system [(14)], and the prolonged motor block may be the result of the nicotinic agonistic effect of Neostigmine at the neuromuscular junction [(15,16)].

Lauretti et al, have proven that epidural Neostigmine in lignocaine produces dose independent analgesia [(11)].

Chittora et al in their study have concluded that epidural Neostigmine with lignocaine at a dose of 100 mg provides prolonged analgesia with lesser adverse [(17)]. We found much difference in the onset of anaesthesia between the two groups, which was not comparable to onset time recorded by Harjai et al who used 100 µg and 200 µg of Neostigmine and showed no much difference in onset of sensory block with control group in their study; mean time of onset was found among three groups (Mean sensory block in control group was 8.33 ± 0.48, 100 µg Neostigmine 8.50 ± 0.78 and in 200 µg Neostigmine 8.60 ± 0.77) .The average level of sensory block was around T8 [(18)].

In this result the time to maximum cephaled spread was definitely shortened in group II and it was statically significant, while in Kiran et al study [19], the time of maximum cephaled spread was also shortened but statically not significant. The intensity of motor block as shown in our study was significantly more potent in Group II, in comparison to other study, which was done by Chittora et al shows using Neostigmine induce more potent analgesia in epidural anesthesia [17]. The mechanism by which Neostigmine acts to speed the onset of sensory block is not clear; this may be due to synergistic effect between Lidocaine and Neostigmine, as Neostigmine 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 breakdown of acetyl choline (ACh) [20], ACh induces analgesia by increasing cyclic guanidino-mono phosphate by generating nitric oxide [21], 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 spinal cord [22]. Neostigmine also displays peripheral and supraspinal analgesic activity, however the dose necessary to achieve this seems to be higher [23].

Kirota et al reported that Lidocaine dose-dependently inhibited the cyclic adenosine monophosphate formation in Chinese hamster ovary cells [24]. Moreover, Li et al showed that Lidocaine inhibited both substance P binding and substance P–evoked increases in intracellular calcium [25]. Therefore, the combination of local anesthetics and Neostigmine may effectively inhibit multiple areas of neuronal excitability. The changes in vital parameters of both cardiovascular and respiratory system by different doses of neostigmine with lignocaine were studied by Altintas, Klamt and Minovsky their results correlate well with our studies, as heart rate, blood pressure and respiratory rate, remained stable [26,29]. The associated incidence of nausea and vomiting in our study was remarkably reduced about 2% in comparison to Kirota et al study [24] which was (5-10%) while it was the same as our study in comparison with the study of Kiran et al which was (2%) [19].

In conclusion, addition of Neostigmine 500 µg to 2% Lidocaine shortened the onset time of sensory block, rapid cephaled spread with more potent and more rapid onset motor block without significant increase in side effect.

We recommend to study a larger number of patients with longer duration of monitoring to evaluate the analgesic and sedative effect of Neostigmine as adjuncts in epidural anaesthesia through the use of the drug in different doses and to encourage the use of Neostigmine as adjuncts in epidural anaesthesia for its efficacy in speed the onset of sensory block and its potent motor block.

Acknowledgments

The authors are grateful to Dr. Haider F. Ghazi in the Department of Microbiology, Al-Nahrain College of Medicine for his help in statistical study, and to the nursing staff of Al-Yarmouk Teaching Hospital for invaluable assistance and finally thanks to Dr. Israa Al-Ani whose her comments improved the quality of this work.

Author contributions

Study conception and design by Dr. Sabah N. Al-Sa'ad and Dr. Zinah M. Mnati, acquisition of data by Dr. Tariq T. Atta and Dr. Zinah M. Mnati., and analysis and Interpretation of data by Dr. Zinah M. Mnati.

Conflict of interest

The authors declares no conflict of interest.

Funding

By Al-Yarmouk Teaching Hospital and Iraqi Council of Medical Specialization.

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Received 26th Sep. 2013: Accepted 16th Feb. 2014