“A COMPARATIVE ANALYSIS OF NEOSTIGMINE AS AN ADDITIVE TO LIGNOCAINE FOR POSTOPERATIVE ANALGESIA IN INTRATHECAL AND EPIDURAL ANAESTHESIA”

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SUMMARY

Our aim is to evaluate the role of neostigmine as an additive to lignocaine to increase the duration of analgesia postoperatively in intrathecal/epidural anaesthesia.

We made five groups of twenty patients, each of both the sexes ranging from 25-45 years of age group of ASA-Grade I & II, selected for surgery of less than 90 minute duration. Using doses of neostigmine 50 mgm intrathecal, 100 mgm & 150 mgm epidural with one group without neostigmine (control group) along with 5% lignocaine 2 ml intrathecal and 2% lignocaine 16 ml epidural.

Intrathecal neostigmine prolongs the duration of postoperative analgesia significantly 368.1±145.4 minutes (control group 123.3±14.8 minutes), without prolonging the motor block duration too much with stability of haemodynamic parameters.

Epidural neostigmine 100 mgm dose provides equivalent analgesia without significantly increasing the side effect, eg. nausea and vomiting which was the major side effect with intrathecal neostigmine.

Keywords : Neostigmine - additive to analgesia, Technique – Intrathecal – Epidural, Monitoring – duration of analgesia & side effects.

Introduction

The postoperative pain can be relieved in better way if the nociceptive pathway is blocked pharmacologically before the intense pain stimulation is evoked. Using polypharmacologic approach to reduce postoperative pain and the morbidity, we used neostigmine methylsulphate along with lignocaine intrathecally/epidurally to prolong the duration of analgesia in continuation of surgical anaesthesia.

Neostigmine inhibits the break down of acetylcholine (endogenous neurotransmitter) which has been shown to cause analgesia. It blocks the activity of both true and pseudo-cholinesterase, and there by enhancing and accumulation binding of acetylcholine at various cholinergic sites responsible for analgesia. It also augments the activity of other anti nociceptive systems.

It is postulated that there are cholinergic receptors in the spinal cord such as those of mu and delta opioid and alfa-2 adrenoreceptor type, known to selectively alter pain behaviour.

It is also found that intrathecal analgesia by neostigmine is mediated through M1 & M2 muscrinic cholinergic receptor stimulation which can be blocked by atropine.

Analgesia by cholinesterase inhibitors depend on degree of spinal cholinergic tone in some species and the tonic spinal cholinergic activity in normal human is adequate for neostigmine to produce meaningful analgesia alone.

According to recent literature the inhibition of acetylcholine enzymatic degradation by neostigmine enhances the descending control of afferent nociceptive stimuli and provide new approach for enhancement of desirable analgesia.

Material and methods

The 100 adults of both the sexes of ASA grade I and II, between 25-45 years of age, scheduled for lower abdominal and lower limb surgery of duration less than 90 minutes, were included in the study.

All the patients were randomly divided into five groups of 20 each.

Group I Intrathecal : 5% 2ml lignocaine+1ml normal saline
Group II Intrathecal : 5% 2ml lignocaine +50 mgm. neostigmine in 1 ml normal saline.

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Group III  Epidural : 2% Lignocaine 16 ml+50 mgm
  – neostigmine In 1 ml normal saline
Group IV  Epidural : 2% Lignocaine 16ml+100 mgm
  neostigmine in 1ml normal saline
Group V  Epidural : 2% Lignocaine 16 ml+150 mgm
  neostigmine in 1ml normal saline

All the patients were preloaded with 500 ml
Ringer’s lactate solution. No premedication was given to
the patients. Intrathecal/Epidural block was performed in
left lateral position in L2-3 interspinous space with 23G
spinal/18G Touhy needle with all aseptic precautions.
Patient were then observed for the following :

a. - Time of drug administration
b. - Time of onset of analgesia
c. - Time of onset of motor block
d. - Time of recovery from motor block
e. - Time of occurrence of pain (VAS >2-3 cm)
f. - Intra and postoperative vital parameters
g. - Time of commencement and end of operation
h. - Side effects.

From the above observations the following indices
were made:
1. Onset of analgesia and relaxation
2. Duration of analgesia and relaxation
3. Duration of operative procedure

The onset of analgesia was evaluated by pin-prick
method in intrathecal anaesthesia, at 1 minute and then
every 5 minute. In epidural after 10 minute and then
every 5 minutes and then surgery was started once
anaesthesia was achieved.

Duration of analgesia was recorded using Visual
analogue scale (VAS) 0 to 10 cm score from no pain to
worst pain on marked paper strip.

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

The time of recovery from motor block was
assessed using Bromage scale (Table A).

<table>
<thead>
<tr>
<th>Bromage scale</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full flexion of Knee and Foot No Block</td>
</tr>
<tr>
<td>2</td>
<td>Just able to flex Knee but full flexion of Foot possible Partial Block</td>
</tr>
<tr>
<td>3</td>
<td>Unable to Flex knee but flexion of foot possible Almost Complete Block</td>
</tr>
<tr>
<td>4</td>
<td>Unable to Flex Knee and Foot Complete Block</td>
</tr>
</tbody>
</table>

All the patients were observed for vital parameters
in the entire perioperative period upto 4-6 hours and the
side effects of neostigmine were noted at various intervals.
(Table-B).

| Side effects | [A] NAUSEA & VOMITING
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Nausea &amp; Vomiting</td>
</tr>
<tr>
<td>1</td>
<td>Mild Nausea</td>
</tr>
<tr>
<td>2</td>
<td>Mild to Moderate Nausea</td>
</tr>
<tr>
<td>3</td>
<td>Vomiting Single episode</td>
</tr>
<tr>
<td>4</td>
<td>Recurrent Vomiting</td>
</tr>
<tr>
<td>[B] SWEATING – Above/Below the level of sensory block.</td>
<td></td>
</tr>
<tr>
<td>[C] OTHERS</td>
<td></td>
</tr>
<tr>
<td>- Abdominal Cramp</td>
<td></td>
</tr>
<tr>
<td>- Genito-Urinary Urinary retention / urgency / incontinence, Ejaculation, Faeces incontinence, vaginal contraction</td>
<td></td>
</tr>
<tr>
<td>- Neurological Effect : Motor Strength and deep Tendon reflexes.</td>
<td></td>
</tr>
<tr>
<td>- Tachycardia &amp; Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

Statistical values

All the data were analysed statistically and the
significance was measured as probability of occurrence
by students ‘t’ Test.

<table>
<thead>
<tr>
<th>‘t’ Value</th>
<th>‘P’ Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.02</td>
<td>0.05</td>
<td>&gt; 0.05 (non significant)</td>
</tr>
<tr>
<td>2.7</td>
<td>0.01</td>
<td>Significant</td>
</tr>
<tr>
<td>3.55</td>
<td>0.001</td>
<td>Highly Significant</td>
</tr>
</tbody>
</table>

Observations

In vital parameters (RR,BP,HR) no significant
alterations were noted.

Table I shows the inter relationship of duration of
analgesia with duration of surgery alongwith type of surgery.
In lower limb surgeries where relaxation was less needed, the duration of analgesia was prolonged in relation to duration of surgeries both in intrathecal and epidural groups.

However the duration of analgesia in epidural group was more in Group IV and V wherein high doses of neostigmine were administered for lower limb surgeries. Duration of analgesia was less in lower abdominal surgical group with poor relaxation.

Table-II Shows onset and duration of analgesia and relaxation (Mean±SD)

Intrathecal and epidural neostigmine decreased the onset of analgesia and relaxation in intrathecal (II Group) and epidural (IV and V) but not in epidural III Group.

The onset of analgesia decreased to (1.05±0.15 minute) in II Group in comparison to control group (1.72±0.34 minutes). The onset of analgesia in III Group with epidural is the usual onset of epidural effect (14.2±2.01 Minute) while in IV and V Group it has decreased to (7.6±1.2 minute) and (7.6±1.02 Minutes) respectively. These findings are statistically highly significant (p<0.001).

Duration of analgesia increased in intrathecal neostigmine (368.1±145.4 min) in comparison to control (123.3±14.8 min) which is highly significant (p<0.001).

The 50 mgm neostigmine epidurally (group III) did not increase significantly the duration of analgesia (193.9±21.78 min) than control group while 100 mgm & 150 mgm (IV Group and V Group) neostigmine increased the duration of analgesia upto 355±105 min in group IV and 410.7±153.8 min in group V which are highly significant (p<0.001). The duration of relaxation did not increase significantly as compared to duration of analgesia but the duration of relaxation in Group I is highly significant (p<0.001).

The duration of relaxation increased only 1.25 times than control in comparison with duration of analgesia which increased 3-4 times in comparison to control.

The interrelationship of neostigmine doses with of analgesia duration and side effects has been shown in Table III. Duration of analgesia with 50 mgm intrathecal neostigmine is increased significantly (368.1±145.4 minute) but at the cost of higher side effects (50%) viz. nausea, vomiting and sweating. Epidural neostigmine 50mgm although has no side effects but duration of analgesia remains equal to control group. Neostigmine

Table No. II : Onset & Duration of Analgesia and Relaxation (Mean ± SD)

The side effects viz. nausea, vomiting and sweating were less with epidural neostigmine than intrathecal neostigmine. In lower abdominal surgery where relaxation was less needed, the side effects were more viz. hypotension (20%), bradycardia (5%). But neostigmine groups in comparison to control group, which increased 3-4 times in comparison to control.

The Table IV show the incidence of side effects in different groups. Incidence of hypotension was less in all neostigmine groups in comparison to control group, which shows the antihypotensive property of neostigmine.

The side effects viz. nausea, vomiting and hypotension were less with epidural neostigmine in comparison to control. In Group III shows minimal side effects. viz. hypotension (20%), bradycardia (5%). But neostigmine
duration of analgesia is not much prolonged, while Group IV shows good prolongation of analgesia with comparable side effects. In Group V, the duration was prolonged as much as in Group IV but with more side effects.

Graph No. I shows that 100 mgm neostigmine epidurally (Group IV) proved to be good and safe in regard to prolonging duration of analgesia with less side effects (15%) in comparison to 150 mgm neostigmine epidurally (25%, side effect) and 50 mgm intrathecally 50% side effects.

Discussion

The changes in vital parameters of both cardiovascular and respiratory system by different doses of neostigmine with lignocaine were studied by Altinatas,\(^1\) De-Rosa,\(^3\) Klamt\(^8\) and Minovsky.\(^9\) Their results correlate well with our studies, as heart rate, blood pressure and respiratory rate, remained stable.

Considerable evidence exists to implicate the role of cholinergic agonists and anti cholinesterase agents in the spinal inhibition of nociceptive transmission. Cholinergic receptors have been found in spinal cord and have been shown to have a potent antinociceptive action, an effect that can be mimicked by spinal cholinesterase inhibitors.\(^10\)

Neostigmine inhibits breakdown of an endogenous spinal neurotransmitter, acetylcholine. Thus spinal cholinergic stimulation is deemed to be associated with analgesia,\(^12\) which is further substantiated by animal studies.\(^8\)

In our study we have noticed the enhancement of post operative analgesia when we injected neostigmine as an additive to lignocaine which was confirmed by Pin Prick and VAS pain score.

The study of De-Rosa\(^3\) shows the significant increase in postoperative analgesia from 85±10 minutes to 270±43 minute in bupivacaine – neostigmine group compared to bupivacaine alone.

Klamt\(^8\) also reported prolonged duration of analgesia 10.7±4.3 hours but associated with severe nausea and vomiting. He found that spinal neostigmine with bupivacaine as effective as morphone and significantly prolonged the duration of analgesia compared with saline. It was 4.5±1, 15.3±7.1 and 10.7±4.3 hours for saline, morphine (100 mgm) and neostigmine (100 mgm) groups respectively.

Minovsky\(^9\) evaluated the analgesic duration and side effects of neostigmine as an additive in spinal and epidural anaesthesia with lignocaine for orthopaedic 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 intrathecal neostigmine (50 mgm) and epidural neostigmine (100 mgm) groups respectively.

The results of all of the above studies\(^3,8,9\) correlate well with our study, where we used neostigmine with lignocaine 5% intrathecally and lignocaine 2% epidurally comparing with control (Group–I). The duration of analgesia was 123.3±14.8 minute in control (Group I) which was prolonged to 368.1±145.4 minutes in intrathecal neostigmine 50 mgm (Group II), 139.3±21.78 minutes in epidural neostigmine 50 mgm (Group III), 355±105 minutes in epidural neostigmine 100 mgm (Group IV) and to 410.7±153 minutes in epidural neostigmine 150 mgm (Group V). These all findings are statistically highly significant. The epidural neostigmine 50 mgm has not caused desired prolongation in comparison to Group I and Group II, although statistically highly significant. (p<0.001)

The neostigmine 100 mgm epidurally provided the comparable prolongation of analgesia (355±105 minutes) to intrathecal group (368.1±145.4 minute), these findings are also statistically highly significant and are similar to the finding observed by Minovsky.\(^5\) Further we observed increased duration of analgesia upto 410.7±153 minutes with neostigmine 150 mgm epidurally and 368.1±145.4 minutes with 50 mgm neostigmine intrathecally (p< 0.001) but the duration of prolonged analgesia was less in comparison to study of Klamt\(^8\) (10.7±4.3 hours with neostigmine 100 mgm and bupivacain intrathecal) and De-Rosa\(^3\) (270±43 minutes with neostigmine – bupivacaine intrathecelly).

In intrathecal neostigmine group nausea in 25%, vomiting in 20% hypotension and sweating in 5% of total cases were observed.

Among these side effects, only nausea and vomiting were found significant when compared to control group.

In epidural neostigmine 50 mgm the side effect were comparatively less than in Group I or groups II.

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### Table No. IV: Side Effects and Complications

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Side Effects</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Vomiting</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Hypotension</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Bradycardia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Sweating</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Numbness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
(hypotension 20% and bradycardia 2%) which was not different from control group.

In epidural 100 mgm, we observed hypotension in 5%, vomiting in 5%, and nausea in 10%, of cases which was not much different from control group. In epidural 150 mgm hypotension in 5%, nausea in 15% and vomiting in 10% cases observed.

The major side effects we observed were nausea and vomiting in 45% cases in group II which is supported by studies of Minovsky\(^9\) and De-Rosa\(^3\) who observed nausea and vomiting in 60% and 86% patients respectively with intrathecal 50 mgm neostigmine – bupivacaine.

The higher incidences of nausea & vomiting may be because of hypotension as they did not preloaded their patients with I.V. Fluids. In our study we preloaded our patients with 500 ml Ringer’s lactate to counteract this causative factor.

Incidence of side effects were less with lower doses of neostigmine that increases parallelly with the increase in doses as we observed in our study.

In our study we observed nausea and vomiting in 15% patients with neostigmine 50 mgm (epidurally) which correlates with the studies of Minovsky,\(^9\) who observed less of side effects with similar dose.

In our study we observed sweating in only one patient of Group II, which is supported by studies of Altintas\(^1\) and Klamt\(^8\) who explained it as sympathetic stimulation above the block.

Thus, the results of our study establish that neostigmine is an effective additive in intrathecal and epidural anaesthesia for prolonging the duration of postoperative analgesia. The more satisfactory analgesia has been achieved in Group II, Group IV and Group V as compare favourably with control (Group I).

In Group III neostigmine does not cause any antinociceptive effect as it did not prolong the duration of analgesia than control (Group I).

Conclusion

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

The neostigmine 50 mgm epiduraly is less effective in prolonging the duration of analgesia than 50 mgm intrathecal neostigmine.

The neostigmine in a dose of 100 mgm as an additive to epidural lignocaine proved to be best in prolonging the duration of analgesia.

The increased dose, 150 mgm of neostigmine prolongs the duration of postoperative analgesia but at the cost of increased incidence of side effects.

References