Postoperative Analgesia With Intrathecal Neostigmine; Two Different Doses Of 75 µgms And 50 µgms With Heavy Bupivacaine.

S Gupta

Abstract
This study was conducted to compare post operative analgesia and side effects of intrathecal neostigmine with two different doses of 75 µgms and 50 µgms with bupivacaine heavy 0.5 % (15mg). 90 patients of ASA grade I and II were randomly selected from a routine list of general surgery, plastic surgery, gynaecology and orthopaedic units of the hospital under spinal anaesthesia were randomly allocated to three groups of 30 patients each. 75 µgms neostigmine groups had prolonged post operative analgesia (less number of rescue analgesia and longer time to first analgesia) compared to other two groups (p<0.001). The time to first analgesia in 75 µgms groups is 236.2±1.6 min (Mean +/-SD), in 50 µgms groups is 183.9±3.36 min (Mean +/-SD), in control group is 138.5±5.1 min (Mean ±SD). Nausea and vomiting was more in 75 µgms groups (30%) compared to 50 µgms neostigmine group (16%). Bradycardia was more frequent in the 75 µgms group (26%) compared to 50 µgms neostigmine group (13%). Hypotension was also more frequent in the 75 µgms group (36%) compared to the 50 µgms neostigmine group (20%). This study concludes that though post operative analgesia is better with 75 µgms neostigmine group compared to 50 µgms neostigmine group, side effects are also more frequent in the 75 µgms neostigmine group.

METHODS
Following approval of the institutional ethics committee 90 patients of ASA CLASS І And Ѕ belonging to either sex, of age 16-55 were randomly selected from routine list of gynaecology, plastic surgery, general surgery and orthopaedics in three different groups. The following patients were excluded from study:

Emergency cases
Sepsis
H/O motion sickness
Mentally retarded and drug addicts
Any contradication to regional anaesthesia(coagulation disorders, spine deformity)

INTRODUCTION
To augment postoperative analgesia various pharmacological adjuvants such as opioids, clonidine, ketamine and midazolam were administered intrathecal with variable results. In an attempt to avoid respiratory depression and sedation associated with opiod, intrathecal neostigmine is tried as an alternative. Postoperative analgesic effect of Intrathecal neostigmine was first reported by Hood DD et al in 1995. Doses ranging from 50-200µg intrathecal neostigmine have been studied previously for postoperative pain relief. Volunteer studied the threshold dose for analgesia of approximately 50 µg. Intrathecal neostigmine inhibit metabolism of spinal released acetylcholine & produce analgesia in animals and human.

The cholinergic system plays an important inhibitory pathway for pain modulation. Cholinomimetic drugs, including cholinergic receptor agonists and acetyl cholinesterase inhibitor known to produce analgesia in various species. Experimental use of cholinesterase inhibitor have been tried for acute and chronic pain. Neostigmine is reversible acetylcholinesterase inhibitor with quaternary ammonium compound used as Cholinomimetic analgesia in human. Autoradiographic studies have revealed the presence of muscarinic binding sites in dorsal horn. (10-12-13) reported that maximum concentration of choline acetyltransferase is located in substantia gelatinosa of spinal cord.
The informed written consent was obtained from patients preoperatively as per hospital rules and regulations.

Group I – Received intrathecal injection. Bupivacaine heavy (0.5%) 3 ml.

Group II – Received intrathecal injection of Neostigmine 50 µg + injection

Bupivacaine heavy (0.5%) 3 ml.

Group III- Received intrathecal injection of Neostigmine 75 µg+ injection

Bupivacaine heavy (0.5%) 3 ml.

The patient’s vital data including temperature, pulse rate, blood pressure, and respiratory rate were noted. All routine investigations were received and recorded in all the cases. Visual Analogue Scale (VAS) was shown to the patient and the procedure of postoperative measurement was explained in detail. Patients were carefully questioned regarding duration of pain free period, type and severity of pain if occurred and amount of analgesia required and the data was recorded. The severity of postoperative pain was measured using a 10–cm visual analogue scale (VAS) (0=no pain, 10=the worst possible pain) during cough or movement at 2-hr intervals or whenever the patient requested analgesia. Postoperative analgesia was provided by intramuscular diclofenac sodium 75 mg. if necessary (if the VAS score was ≥4). All patients received inj. Ranitidine 100mg and inj. Atropine 4µg/kg (0.2mg) i.v., inj phenergan 0.5 mg/kg i.m 30 minutes before anaesthesia as a premedication. Recording of vital data was done 15 minutes before and after premedication and just before giving spinal anaesthesia. Postoperative analgesia was provided by intramuscular diclofenac sodium 75 mg. if necessary (if the VAS score was ≥4). All patients received inj. Ranitidine 100mg and inj. Atropine 4µg/kg (0.2mg) i.v., inj phenergan 0.5 mg/kg i.m 30 minutes before anaesthesia as a premedication. Recording of vital data was done 15 minutes before and after premedication and just before giving spinal anaesthesia. Postoperative analgesia was provided by intramuscular diclofenac sodium 75 mg. if necessary (if the VAS score was ≥4). All patients received inj. Ranitidine 100mg and inj. Atropine 4µg/kg (0.2mg) i.v., inj phenergan 0.5 mg/kg i.m 30 minutes before anaesthesia as a premedication. Recording of vital data was done 15 minutes before and after premedication and just before giving spinal anaesthesia. After preloading with ringer lactate solution 10ml/kg, subarachnoid puncture was performed at L3-L4 inters pace with 25G spinal needle with patients in sitting or lateral position under all strict aseptic and antiseptic precautions. After clear and free flow of CSF, chosen study solution was injected slowly after CSF aspiration.

The rostral dermatome level of sensory anaesthesia to pinprick was determined and motor blockade using Modified Bromage Scale was recorded, viz.

0 - Ability to raise extended legs, no blockade

1 - Inability to raise extended leg and knee flexion is decreased, but full flexion of

2 - Inability to raise legs or flex knee, flexion of ankle and feet is present, Partial

Blockade 66%

3 - Inability to raise leg, flex knee or ankle or move toes. Complete paralysis.

Patients in whom sensory blockade did not reach T6 were excluded from the study. Hypotension, defined as systolic blood pressure ≤ 90 mm Hg or less than 70% of pre-anaesthetic value, was treated with ephedrine (5-10mg) intravenously. Bradycardia (≤ 50beats/mins) was treated with intravenous atropine (0.5 mg). Nausea and vomiting were treated with intravenous metoclopramide (10 mg).

Sedation score also calculated from

Sedation score, Chernik et al.14

Awake 0

Sleeping comfortably, easily arousable 1

Deep sleep but arousable 2

Deep sleep but not arousable 3

Temperature, pulse, blood pressure, respiratory rate, oxygen saturation, ECG were monitored and measured immediately before spinal anaesthesia, 15 minutes after spinal blockade and then at 15 minutes interval till 60 minutes.

Pulse rate, BP, respiratory rate, SPO2 were measured at 30min, 60 min, 90min, 120min, 3 hour, 6 hours, 9 hours, and 12 hours.

The level of sensory and motor block during the postoperative period was assessed every 15 minutes until sensory block reached L5 dermatome and the Bromage scale reached grade 0 for residual anaesthesia effect.

The regression of two segments of spinal level was taken as “0” hours. Postoperatively when patients were shifted to ward, vital data were recorded at 3hour, 6hour, 9 hour and at 12 hours and analgesic requirement during first twenty four post operative hours was recorded. Patients were also observed for side effects like nausea, vomiting, bradycardia, tachycardia, hypotension, drowsiness, and headache.

Patients were carefully questioned regarding duration of pain.

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of analgesia required and the data was recorded. The severity
of postoperative pain was measured using a 10-cm visual
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with intravenous atropine (0.5 mg). Nausea and vomiting
were treated with intravenous metoclopramide (10 mg). The
time to first analgesia (TFA) and any postoperative side
effects were noted with special reference to nausea and
vomiting.

All data are expressed as number or mean±S.D or
S.E. Continuously distributed variables were analyzed using
one-way analysis of variance with SPSS15. P<0.05 was
considered statistically significant.

RESULTS
The mean age, weight, heights, duration of surgery or ASA
status were comparable in all three groups. There was no
significant difference in onset of sensory or motor blockade
in all groups. All patients had adequate spinal level of T6
and intraoperative hemodynamics was stable and
comparable in all three groups. [TABLE: 1]

Figure 1
Table 1 Demographic data

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.55</td>
<td>16.55</td>
<td>17.50</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>84.27±10.47</td>
<td>84.70±10.80</td>
<td>85.13±10.74</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180.33±8.42</td>
<td>157.30±9.00</td>
<td>153.64±6.72</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>161.67±24.99</td>
<td>90.83±21.62</td>
<td>87.16±41.94</td>
</tr>
<tr>
<td>Ratio: Male:Female</td>
<td>8:7</td>
<td>8:7</td>
<td>8:7</td>
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</tbody>
</table>

The onset of sensory blockade in seconds as judged by loss
of pinprick sensation, bilaterally at shin of tibia in Group I
was 145.8±0.5 second, Group II was 216±0.6 seconds, Group
III was 216±0.6 seconds. [TABLE: 2]

Figure 2
Table 2 Results

The duration of sensory blockade in Group I was
155.6±26, Group II 211.2 ±31.7, Group III 233.4±34.7. The duration of
motor blockade in Group I was 153±16.8, Group II was
169.3 ±20.7, and Group III was 193.9±24.

The time to first analgesia in Group I was 138.5±5.1, Group
II was 183 ±3.3 and Group III was 236.2 ±1.6. The total
doses of rescue analgesia required for Group III was low as
compared to Group I and Group II.

Patients in groups II and III demonstrated a highly
significant increase in the incidence of nausea, vomiting,
bradycardia and hypotension.

Before premedication mean pulse rate in all patients was
84.93 ± 8.30 (mean ± S.D.) minutes in group I, 83.87 ± 6.96
(mean ± S.D.) per minute in group II and 85.67±5.63 (mean
± S.D.) per min in group III which was statistically non
significant (P>0.05). After pre medication in all the patients,
mean pulse rate increased in all the three groups. There were
instances of decrease in pulse rate marked in group III
intraoperatively at around 45, 60, 75, 90 mins. There was no
bradycardia (i.e. pulse rate <60/min).[GRAPH 1 AND
GRAPH 2]
Postoperative Analgesia With Intrathecal Neostigmine; Two Different Doses Of 75 µgms And 50 µgms With Heavy Bupivacaine.

**Figure 3**
Fig: 1 showing changes in heart rate

**Figure 4**
Fig: 2 showing changes in mean arterial pressure

After premedication there is slight increase in M.A.P, followed by decrease in M.A.P. The M.A.P is lowest in group III, The M.A.P in group I&II was almost comparable.

This table shows incidence of side effects in preoperative period in all three groups. In group I, 1(3.33%) patients had nausea and vomiting, 2(6.66%) and hypotension. There was no bradycardia, tachycardia and sedation in group I. In group II, 2 patients had nausea and vomiting, 2 patients had bradycardia, 5 patients had developed hypotension while none had tachycardia, sedation. In group III, 9 patients had nausea & vomiting, 8 had bradycardia and 10 had hypotension. [Table:3]

**DISCUSSION**

Intrathecal administration of cholinergic receptor agonist or cholinesterase inhibitors produces antinociceptive effect which is mediated by spinal muscarinic receptors in animals and human beings. Intrathecal administration of neostigmine inhibits the metabolism of spinally released acetylcholine that produces analgesia without neurotoxicity in animals and humans, and enhanced the onset of sensory block. However, we didn’t observe any enhancement of onset of sensory block. In our study, two segment regression of block was prolonged in the 75µg neostigmine group as compared to control group and the 50µg neostigmine group.

The duration of motor block was statistically significantly prolonged in 75 µg which indicates that motor block could be dose dependant (P<0.01). The threshold dose for post operative analgesia found to be approximately 50µg. We found that greatly enhanced analgesia in 75µg dose as
22. Klamt JG, Schillitell A et al, post operative effect of intrathecal neostigmine and its influence on spinal analgesia,
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