Transdermal nitroglycerin as an adjuvant to intrathecal neostigmine and bupivacaine for prolongation of postoperative pain relief

Safiya I. Shaikh1, Marutheesh Mallappa2, Vikas Joshi3, Roopa Sachidananda4

ABSTRACT

Objectives: Transdermal nitroglycerin patch is being used as an adjuvant to neostigmine for postoperative analgesia, besides its vasodilator effects on cardiovascular system. We aimed to evaluate the transdermal nitroglycerin for its capability to enhance analgesia when used as an adjuvant to intrathecal neostigmine and bupivacaine in elective lower abdominal surgeries.

Methodology: We enrolled 60 adult ASA-1 and 2 patients undergoing lower abdominal surgeries under spinal anesthesia. In this double blind randomized study, patients were assigned into two groups, Group NT received transdermal nitroglycerin patch (5 mg/24 h) and Group NE received placebo patch along with 5 µg of neostigmine and 15 mg of 0.5% hyperbaric bupivacaine. Spinal anesthesia was performed at L3-L4 level, with 25 gauge spinal needle and 3.5 ml of the drug solution was injected intrathecally per the group allocation. Sensory block was checked using pin prick method and motor block was assessed by modified Bromage scale. Pulse rate, blood pressure and SpO2 were monitored. Intra-operative complications were noted. Sample size was calculated to be 60 with a total of two groups with alpha of 0.05 and a power of 90 %. Test for analysis among two groups was done by ANOVA for quantitative and Chi-square test for qualitative data. A p < 0.05 was considered as significant.

Results: The characteristics of intraoperative block were comparable among two groups. The mean duration of analgesia in Group NT was significantly longer (p < 0.001) than in Group NE (476.9 ± 17.3 vs. 386.9 ± 17.2 min respectively). Group NE had higher VAS scores and the number of rescue analgesic requirement was significantly more in Group NE as compared to Group NT. Hemodynamic changes remained insignificant in both groups. Incidence of side effects were not significant in both the groups.

Conclusion: We conclude that the transdermal nitroglycerin used as an adjuvant to intrathecal neostigmine and bupivacaine prolongs postoperative analgesia.

Key words: Transdermal; Nitroglycerin; Neostigmine; Postop analgesia

INTRODUCTION

Pain has been a major concern of humankind since medieval times and it has been the subject of ubiquitous efforts to understand and to control it. Spinal subarachnoid block is one of the most versatile regional anesthesia techniques available today as it is very economical and easy to administer with...
the advantage of providing surgical anesthesia. Hyperbaric bupivacaine 0.5% is the most commonly used drug for spinal anesthesia. Prolongation of pain relief by various adjuvants, for example opioids (morphine, fentanyl), ketamine, clonidine, and neostigmine, have been investigated by various investigators.

Spinal administration of neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia, hence it is an alternative non-opioid additive to local anaesthetics. Several researches stated that nitroglycerin (NTG) patch application in addition to neuraxial S (+)-ketamine, neostigmine, or sufentanil, enhances postoperative analgesia and reduces the need for other analgesic medication.

This study was undertaken to evaluate efficacy and potency of transdermal nitroglycerin patch with regard to its analgesic enhancing effects, when used as an adjuvant to intrathecal neostigmine and bupivacaine.

**METHODOLOGY**

The study was conducted at Karnataka Institute of Medical Sciences, Hubballi. After obtaining ethical committee approval, 60 adult patients between 18–60 years of age belonging to American Society of Anesthesiologists (ASA) physical status I or II, of either sex, who were admitted for elective lower abdominal surgeries were recruited for the study. Patients with previous spinal surgeries, spinal deformities, hemorrhagic disorders and cardio respiratory co-morbidities were excluded from the study.

All the patients received tablet diazepam 10 mg and tablet ranitidine 150 mg orally on the night before surgery. All of them were familiarized with 0–10 verbal analogue scale (VAS) for pain and instructed to inform whenever they felt pain at the operated site in the postoperative ward. The patients were randomized into two groups of 30 each. Group NE received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 5 µg of neostigmine diluted to 0.5 ml with 0.9% normal saline to make a total volume of 3.5 ml + transdermal placebo patch. Group NT received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 5 µg of neostigmine diluted to 0.5 ml with 0.9% normal saline and transdermal nitroglycerin (tNTG) patch (5 mg/24 h). Each group received a total volume of 3.5 ml.

In the preanesthesia room, patients were premedicated with midazolam 0.05 mg/kg IV and preloaded with crystalloid 10 ml/kg. In the operation theatre, lumbar puncture was performed at L3-L4 level, with 25 gauge spinal needle and 3.5 ml of the drug solution was injected intrathecally over 30 sec as per the group allocation.

Sensory block was checked using pin prick method and motor block was assessed by modified Bromage scale, 0: No motor block, 1: Inability to raise extended leg; able to move knees and feet, 2: Inability to raise extended leg and move knee; able to move feet, 3: Complete block of motor limb. Oxygen was administered by Hudson mask at the rate of 5 L/min. The transdermal patch (placebo or nitroglycerin) was applied on the thorax (ventral, T2-T4), in a non-anesthetized area, 20 min after spinal puncture. Total nitroglycerin content of transdermal nitroglycerin patch was 25 mg; total drug releasing area was 10 cm². It delivered nitroglycerin at the rate of 20-25 µg/cm²/h or 5 mg/24 h.

Pulse rate, blood pressure and SpO₂ were monitored till the end of surgery. Intra-operative complications like hypotension, respiratory depression, nausea, vomiting, shivering were noted and treated as required. Hypotension greater than 15% below the baseline value was treated by the incremental dose of mephenteramine 6 mg IV. Any fall in the heart rate below 60 beats per minute was treated with incremental doses of atropine 0.3 mg. Intra-operative nausea was treated with ondansetron 4 mg IV, Shivering was treated with 100% oxygen, warm fluids and adequate covering. No other sedation or analgesic drug was given to the patients. Time from subarachnoid injection to administration of first rescue analgesic was taken as total duration of analgesia.

Pain was assessed with the help of VAS at 15 min, 30 min and the at hourly intervals upto 12 hours. The Table 1: Demographic profile in the groups

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Group NE</th>
<th>Group NT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male</td>
<td>14/16</td>
<td>16/14</td>
<td>0.606</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.7</td>
<td>41.37</td>
<td>0.833</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.2</td>
<td>58.1</td>
<td>0.476</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.4</td>
<td>162.7</td>
<td>0.643</td>
</tr>
<tr>
<td>BMI</td>
<td>22.1</td>
<td>21.9</td>
<td>0.666</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>23/7</td>
<td>23/7</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean duration of surgery (min)</td>
<td>86.0</td>
<td>82.0</td>
<td>0.238</td>
</tr>
</tbody>
</table>

Table 2: Intraoperative parameters

<table>
<thead>
<tr>
<th>Intra-operative parameters</th>
<th>Group NE</th>
<th>Group NT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory onset in min at T10 level</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.5</td>
<td>0.800</td>
</tr>
<tr>
<td>Motor onset in min (Bromage scale)</td>
<td>6.4 ± 1.0</td>
<td>5.9 ± 0.8</td>
<td>0.057</td>
</tr>
</tbody>
</table>
last reading was taken at 24 h post spinal. Any patient with VAS score of four and more qualified for rescue analgesic (inj diclofenac 1.5 mg/kg IM).

Statistical analysis

Considering a 10% increase in the duration of analgesia and a similar percentage of hemodynamic variations due to tNTG as an adjuvant to intrathecal neostigmine was compared with the previous studies (Ahmed et al.) calculated the sample size to be 60 with a total of two groups with alpha of 0.05 and a power of 90%. Test for analysis among two groups was done by ANOVA for quantitative and Chi-square test for qualitative data. A p < 0.05 was considered as significant.

RESULTS

There was no significant difference among the two study groups in respect of age, sex, height, weight, BMI, ASA and duration of surgery (Table 1).

The onset of sensory block was 2.5 ± 0.6 and 2.5 ± 0.5 min in Group NE and NT respectively and there was no significant difference in two groups with regards to time to achieve grade 3 motor block 6.4 ± 1 and 5.9 ± 0.8 min in Group NE and NT respectively (Table 2).

Table 3 shows the comparative hemodynamic parameters i.e. mean arterial pressure (MAP), pulse rate (PR) in two groups during the perioperative period. The differences in duration of two segment regression of sensory block and total duration of motor blockade in the groups were statistically insignificant. Duration of analgesia was significantly longer in Group NT in comparison to Group NE (476.9 ± 17.3 vs. 386.9 ± 17.2 min) which was clinically and statistically highly significant (p < 0.001). The mean consumption of rescue analgesic per patient was 2.20 ± 0.7 (NE) and 1.83 ± 0.8 (NT). This difference was statistically significant (p < 0.05) (Table 4). VAS scores in Group NE were persistently greater than that of Group NT (Table 5), but the difference were statistically not significant.

Regarding complications, there was no significant difference among the groups in the frequency of nausea, vomiting and shivering. Although statistically significant differences were seen in average MAP readings, all these differences were clinically insignificant (Table 6).

DISCUSSION

“The aim of the wise is not to secure pleasure, but to avoid pain” - Aristotle. Postoperative pain management is essential for early ambulation and recovery of the patient. Various methods of

<table>
<thead>
<tr>
<th>Postoperative parameters</th>
<th>Group NE</th>
<th>Group NT</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for 2 segment regression (min)</td>
<td>77.8 ± 2.6</td>
<td>79.0 ± 2.4</td>
<td>0.078</td>
</tr>
<tr>
<td>Duration of motor blockade (min)</td>
<td>175.7 ± 6.2</td>
<td>176.1 ± 6.0</td>
<td>0.834</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>386.9 ± 17.2</td>
<td>476.9 ± 17.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of analgesics required in 24 h</td>
<td>2.20 ± 0.7</td>
<td>1.83 ± 0.8</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 6: Comparison of the side effects of two groups

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group NE N (%)</th>
<th>Group NT N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>0 (10.0%)</td>
<td>6 (10.0%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2 (3.3%)</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>3 (5.0%)</td>
<td>4 (6.7%)</td>
</tr>
</tbody>
</table>
Transdermal nitroglycerin as spinal adjuvant

Postoperative pain relief are available.

Intrathecal neostigmine causes dose dependent postoperative analgesia by inhibiting breakdown of acetylcholine in dorsal horn and spinal meninges. Acetylcholine causes analgesia through direct action on spinal cholinergic muscarinic receptors m1 and m3.

Transdermal nitroglycerin patch has been related to nitric oxide (NO) formation during degradation of organic nitrates and there is evidence that endogenous NO is necessary to inhibit nociceptive transmission. The enhancement of analgesic effect of transdermal nitroglycerin would be secondary to NO action at primary afferent and at the 2nd order neuron.

Almost all the researchers have identified that there is no prolongation of surgical anesthesia in patients receiving tNTG as an adjuvant to intrathecal neostigmine in different doses. In our study also the prolongation of two segment regressions and duration of motor blockade was not statistically significant.

As per Ahmed et al. and Patel et al. we used doses of 5 µg of intrathecal neostigmine and transdermal nitroglycerin patch (5 mg/day). A higher dose of neostigmine have been shown to produce many untoward side effects such as nausea, vomiting. Hence, as to reduce the dose of neostigmine and potentiate its analgesic property, other adjuvants such as clonidine, opioids, and transdermal nitroglycerin (tNTG) patch have been added along with it.

In our study the duration of analgesia was significantly higher with tNTG group which goes along with other studies. Addition of 5 mg/day of tNTG to intrathecal neostigmine has increased the duration of analgesia.

To other studies showed there was no statistically significant difference in hemodynamic disturbances which is similar to our study.

The verbal analogue scale (VAS) is a simple and often used method for evaluating variations in pain intensity. Rescue analgesia was provided by intramuscular injection of diclofenac 75 mg, when patient complains of pain or VAS 4 and above. In our results, we found that during initial 300 min, i.e. from baseline to 300 min, the difference was statistically insignificant (p > 0.05). Difference in VAS scores of two groups NE and NT becomes statistically significant at 360th to 480th min with p values < 0.05. VAS score was higher in neostigmine group requiring rescue analgesia at 300 min and maximum VAS scores at 360th-420th min, where as in nitroglycerin group VAS score started to increase only after 420th min and maximum scores of VAS was seen at 480th-540th min. Nitroglycerin group had lower scores of VAS even at 12th and 24th hours. Our results were similar to study conducted by Rameez et al. which showed average VAS scores of combination (tNTG and neostigmine) group were significantly lower than neostigmine group.

From above discussed results it can be clearly stated that transdermal nitroglycerin as an adjuvant to intrathecal neostigmine and bupivacaine prolongs duration of analgesia compared to intrathecal neostigmine or bupivacaine alone.

**Limitations**

Limitation of our study is that, tNTG is a newer mode of peri-operative analgesic use, and there are only few studies supporting its use for analgesia, more studies are needed to establish the safety and efficacy of this drug and further scope will be to design the study with different doses of neostigmine and nitroglycerin.

**Conclusion**

We conclude that transdermal nitroglycerin patch (5 mg/day) safely prolongs the duration of postoperative analgesia when it is used as an adjuvant to intrathecal low dose neostigmine 5 µg and bupivacaine 15 mg in patients undergoing below umbilical surgeries.

Conflict of interest: None declared by the authors

Authors’ contribution:

SS & MM: Concept, conduc of the study work, literature search, statistical analysis and manuscript editing.

VJ & RS: conduct of study and manuscript editing.
REFERENCES


