A Comparison Between Three Doses of Epidural Neostigmine Versus Fentanyl as Adjuvant Analgesics in Adults

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ABSTRACT

Background: The cholinergic system has attracted new interest as a pharmacological target to accomplish effective analgesia without the limitations of opioid-induced side effects. Objective: The purpose of this prospective study was a comparison between three doses of bolus and continuous infusion of epidural neostigmine versus fentanyl as an adjuvant analgesic in adults. Patients and methods: In a prospective study of 180 adult patients undergoing lower half of the body surgeries using epidural anesthesia at Zagazig University Hospitals from May 2010 to May 2013 for comparing three doses of bolus and continuous infusion of epidural neostigmine versus fentanyl as an adjuvant analgesic. Result(s): The highest neostigmine dose used in this study 200 µg bolus or 125 µg/hour infusion showed significant better pain relief parameters than lower doses regarding duration of analgesia, postoperative VAS, number of diclofenac ampoules consumed in first postoperative 24 hours and patient satisfaction score with no significant different side effects. Neostigmine showed significant lower nausea/vomiting and no pruritis with no significant difference postoperative VAS, total number of diclofenac ampoules consumed in postoperative 24 hours and patient satisfaction score in comparison to fentanyl but fentanyl showed significant longer duration of analgesia. Conclusion(s): The highest doses of neostigmine either bolus or continuous infusion is better than lower doses and fentanyl showed longer duration of analgesia with more side effects than neostigmine doses with similar postoperative VAS, number of diclofenac ampoules consumption in first postoperative 24 hours and patient satisfaction score as highest dose neostigmine either infusion or bolus.

Key Words: epidural anesthesia, bupivacaine, neostigmine, fentanyl

INTRODUCTION

One of the methods for pain management is preemptive analgesia. A meta-analysis assessed the ability of preemptive analgesic interventions to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolong the time to first rescue analgesia. One of the most important technique for operative pain control involves the use of an epidural catheter(1).

Narcotic agents are frequently preferred analgesia; however, because of the well-known side effects of those agents such as respiratory depression, urinary retention, nausea/vomiting and pruritis. New agents are needed(2).

Neostigmine is a parasympathomimetic agent reversible anticholinesterase which inhibits breakdown of Ach. Ach is considered to be one of the major inhibitory neurotransmitters in pain modulation establish its analgesic effect by stimulating the muscarinic receptors of acetylcholine across the spinal cord, particularly in the substantia gelatinosa (lamina I, II)(3).

Epidural neostigmine provides analgesia without the severe GIT side effects (nausea/vomiting and diarrhea) consecutive to its intrathecal injection. Furthermore, neostigmine does not induce respiratory depression, hypotension, or motor blockade. Hence, the characteristics of epidural neostigmine seem to meet those requested to achieve selective analgesia (4).

PATIENTS AND METHODS

After approval of Local Ethical Committee, and taking informed consent. This prospective study was carried out on one hundred and sixty adult patients (16-65 years old), of American Society of Anaesthesiologists status I and II scheduled for elective surgery in lower half of the body (below or at level of T₁₀) under supervision of Anesthesia Department, Faculty of Medicine, Zagazig University from May 2010 to May 2013 in order to compare three bolus doses of epidural neostigmine and infusion versus fentanyl as an adjuvant analgesic. Patients with a history of back surgery, mental retardation, infection at injection sites, coagulopathy hypersensitivity to local anaesthetics or opioids were excluded form the study.

The patients were divided randomly into four main groups. All of them received epidural bupivacaine.

- Group I:
  - Ia: Epidural bolus neostigmine 100 µg.
  - Ib: Epidural bolus neostigmine 150 µg.
  - Ic: Epidural bolus neostigmine 200 µg.

PLUS

bupivacaine 10 ml 0.5%. Each subgroup contained 20 patients.

- Group II: Epidural bolus fentanyl 50 µg plus bupivacaine 10 ml 0.5%. This group contained 20 patients.

- Group III:
  - IIIa: Epidural infusion neostigmine 75 µg/hour.
  - IIIb: Epidural infusion neostigmine 100 µg/hour.
- **IIIc:** Epidural infusion neostigmine 125 µg/hour.

**PLUS**

Bupivacaine loading dose 10 ml 0.5% then 10 ml 0.25% / hour, mixed with neostigmine infusion and started after complete motor block. Each subgroup contained 20 patients.

- **Group IV:** Epidural infusion fentanyl 50 µg/hour plus bupivacaine same as group III. This group contained 20 patients.

Preoperative evaluation of VAS (5) to all patients for pain assessment and no patient received sedation or opioid premedication before arrival at operating room. In operating room, after intravenous access preloading with 10 ml/kg intravenous infusion ringer lactate and application of monitors, epidural catheterization was performed under strict aseptic condition at L₂-L₃ or L₃-L₄ interspace in sitting position. A test dose of 3 ml injection of lignocaine (2%) containing 1:200,000 epinephrine was given through epidural catheter to confirm proper placement. Then, after 15 minutes, lumbar epidural bolus or loading doses were given and the somatosensory blockade was evaluated by pinprick test.

**Preoperative measurement:**

The onset time of sensory blockade with maximal cephalad spread was assessed by bilateral pinprick method along the mid-clavicular line. It was defined as the time form epidural injection to the occurrence of sensory block at dermatome level T₁₀. The motor blockade was assessed using a modified Bromage scale (0-3) (6), the time of complete motor blockade was defined as the time from epidural injection to achieve bromage scale 3. The surgical anesthesia was considered effective when T₁₀ dermatome was anesthetized. Preoperative assessment of HR, BP, RR and SpO₂ was done.

**Intraoperative measurement:**

1. **Haemodynamic changes:** Hypotension, bradycardia and decrease SpO₂.
2. **Sedation score** according to Ramsay sedation scale (7).
3. **Two-segment regression time.**
4. **First dose failure** in different types of surgery.
5. **Side effects:** nausea/vomiting or pruritis.

**Postoperative measurements:**

1. Postoperative VAS by 10 cm scale (0 cm = no pain to 10 cm = the worst possible pain) of over all 24h patient’s impression.
2. **Time before first call for diclophenac as systemic analgesic.**
3. **Total numbers of diclophenac ampoules consumed during first postoperative 24 hours.**
4. **Overall postoperative 24h patient satisfaction using a 1-3 verbal scale(8).**

5. **Side effects:** ileus and urine retention.

**Statistical analysis:**

At the end of study, all data were checked, entered and analyzed by using Special Package for Social Science (SPSS) version 17. Data were expressed as mean ± standard deviation for quantitative continuous variables.

Number and percentage for categorical variables, chi-square (X²), Fisher exact test, ANOVA (F) test, paired t test were used when appropriate, post hoc test for comparison in between the groups.

p < 0.05 was considered statistically significant.

**RESULTS**

There were no significant difference regarding patient age, sex, weight, height, type of surgery, duration of surgery and preoperative VAS between groups of epidural bolus doses (groups I and II) and also between groups of epidural infusion doses (groups III and IV).

There were no significant difference across the three bolus doses of neostigmine (groups Ia, Ib and Ic) relative to sensory block onset time and time to complete motor block, but there were significant correlations between fentanyl group (II) and rapid onset of analgesia and time to complete motor block (table 1).

In our study, there were no significant differences between the groups regarding hypotension and bradycardia, (table 1).

In our study, we found that there was a significant sedation with increasing the dose of neostigmine (dose dependent) and with fentanyl dose. There was no significant difference between the group Ic and group II regarding patient sedation (table 1).

The current study established that addition of epidural neostigmine 100 µg, 150 µg and 200 µg to bupivacaine increases the duration of analgesia in dose-dependent manner through prolonged duration for first call for diclophenac. Also, there was a significant prolonged duration before first call for diclophenac with fentanyl group in comparison with neostigmine group. There were no significant differences between the highest dose neostigmine (group Ic) and fentanyl dose regarding postoperative VAS, total number of diclophenac ampoule consumption in first 24 hours and patient satisfaction score (table 1).

In our study, we found significant lower nausea/vomiting with neostigmine groups in comparison to fentanyl group. There were no significant ileus side effect difference between the groups. Also, neostigmine groups showed no pruritis or urine retention side effects (table 2).
In our study, we found that first dose failure was significant with lower neostigmine doses. Orthopedic and vascular surgeries showed significant high first dose failure with the groups of lower neostigmine doses than highest dose neostigmin (group Ic) or fentanyl group (group II) (table 3).

In our study, we found no significant difference between the groups of epidural infusion regarding hypotension or bradycardia. Cases of bradypnea or hypoxemia were not reported in our study (table 4).

In our study, there were a significant sedation with the highest dose of neostigmine infusion (group IIIc) and fentanyl group (group IV). There were no significant difference between the other two groups (groups IIIa and IIIb) and also no significant difference between highest dose of neostigmin (group IIIc) and fentanyl (group IV) regarding sedation (table 4).

In our study, the neostigmine infusion groups showed a significant short duration to two-segment regression in comparison to fentanyl and we found also that there was a significant correlation between the lowest dose of neostigmine and short duration to two-segment regression (table 4).

Table (1): Assessment of epidural bolus doses.

<table>
<thead>
<tr>
<th></th>
<th>Group Ia (n=20)</th>
<th>Group Ib (n=20)</th>
<th>Group Ic (n=20)</th>
<th>Group II (n=20)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of onset of sensory block (minutes)</td>
<td>27.2 ±4.9**</td>
<td>26.8±2.1**</td>
<td>25.2±2.3**</td>
<td>18.4 ± 3.2</td>
<td>20.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Time of complete motor block (minutes)</td>
<td>37.5 ±4.8**</td>
<td>38 ± 4.8**</td>
<td>36 ±3.3**</td>
<td>25.6 ± 3.8</td>
<td>37.2</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Intraoperative assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamic changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5(25.0)</td>
<td>4 (20.0)</td>
<td>3 (15.0)</td>
<td>4(20.0)</td>
<td>X^2 = 0.62</td>
<td>0.89</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1(5.0)</td>
<td>2 (10.0)</td>
<td>3(15.0)</td>
<td>3(15.0)</td>
<td>X^2 = 0.78</td>
<td>0.86</td>
</tr>
<tr>
<td>Bradypnea</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>X^2 = 0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased saturation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>X^2 = 0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation score</td>
<td>2.6 ± 0.5**</td>
<td>2.8± 0.5**</td>
<td>3.5 ±0.5</td>
<td>3.6 ± 0.5</td>
<td>18.48</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Postoperative assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First call for diclophenac from complete block (minutes)</td>
<td>88.8±8.8**</td>
<td>107.5±8.4**</td>
<td>145.6±25.4</td>
<td>212.8±32.7</td>
<td>70.0</td>
<td>0.00*</td>
</tr>
<tr>
<td>Postoperative VAS</td>
<td>3.6±0.5**</td>
<td>2±0.7**</td>
<td>1.6±0.7</td>
<td>1.4 ± 0.5</td>
<td>23.0</td>
<td>0.000*</td>
</tr>
<tr>
<td>Total number of diclophenac in 24 hours</td>
<td>2.8±0.5*</td>
<td>1.2±0.8</td>
<td>1.2±0.4</td>
<td>1.2 ± 0.3</td>
<td>11.29</td>
<td>0.000*</td>
</tr>
<tr>
<td>Patient satisfaction score</td>
<td>1.1±0.3**</td>
<td>1.2±0.4**</td>
<td>2.2±0.6</td>
<td>2.6±0.5</td>
<td>27.56</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
Ftest=(ANOVA=analysis of variance).
*significant (p<0.05)
**post hoc test in comparison between groups.
Table (2): Side effects of epidural bolus doses

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Group Ia (n=20)</th>
<th>Group Ib (n=20)</th>
<th>Group Ic (n=20)</th>
<th>Group II (n=20)</th>
<th>x²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>2(10%)*</td>
<td>1(5%)*</td>
<td>1(5%)*</td>
<td>6(30%)*</td>
<td>9.59</td>
<td>0.02*</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0%)*</td>
<td>0(0%)*</td>
<td>0(0%)*</td>
<td>3(15%)*</td>
<td>9.23</td>
<td>0.026*</td>
</tr>
<tr>
<td>Illeus</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>2(10%)*</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Urine Retention</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are expressed as number(percentage).
X²= chi squer test.
*significant (p<0.05).

Table (3): Relation between types of surgery and epidural first bolus dose failure

<table>
<thead>
<tr>
<th></th>
<th>Group Ia (n=20)</th>
<th>Group Ib (n=20)</th>
<th>Group Ic (n=20)</th>
<th>Group II (n=20)</th>
<th>x²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic</td>
<td>5 (25%)*</td>
<td>3(15%)*</td>
<td>1(5%)</td>
<td>1(5%)</td>
<td>10.2</td>
<td>0.016*</td>
</tr>
<tr>
<td>Urology</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5</td>
<td>0.18</td>
</tr>
<tr>
<td>Vascular</td>
<td>5 (25%)*</td>
<td>3(15%)*</td>
<td>2(10%)</td>
<td>1(5%)</td>
<td>9.6</td>
<td>0.019*</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5</td>
<td>0.18</td>
</tr>
<tr>
<td>First dose failure</td>
<td>12 (60%)*</td>
<td>8 (40%)*</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td>8.6</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Data are expressed as number (percentage).
X² = chi squer test.
*significant (p<0.05).

Table (4): Assessment of epidural infusion doses

<table>
<thead>
<tr>
<th></th>
<th>Group Ia (n=20)</th>
<th>Group Ib (n=20)</th>
<th>Group Ic (n=20)</th>
<th>Group II (n=20)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative assessment</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamic changes</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2(10.0)</td>
<td>3(15.0)</td>
<td>2(10.0)</td>
<td>6(30.0)</td>
<td>X²  = 3.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1(5.0)</td>
<td>3(15.0)</td>
<td>3(15.0)</td>
<td>4(20.0)</td>
<td>X²  = 1.98</td>
<td>0.58</td>
</tr>
<tr>
<td>Bradypnea</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>X²  = 0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased saturation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>X²  = 0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation score</td>
<td>2.3 ± 0.5**</td>
<td>2.4 ± 0.5**</td>
<td>3.1 ± 0.6</td>
<td>3.2 ± 0.6</td>
<td>18.48</td>
<td>0.000*</td>
</tr>
<tr>
<td>Time to two-segment regression from complete block in minutes</td>
<td>90 ± 4.7*</td>
<td>100 ± 4.2**</td>
<td>100 ± 5.5**</td>
<td>120 ± 6.1</td>
<td>118.17</td>
<td>0.000*</td>
</tr>
<tr>
<td>Postoperative assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First call for diclofenac from complete block (minutes)</td>
<td>131.3±8.5**</td>
<td>131.1±7.8**</td>
<td>140±8.2</td>
<td>170±12.0</td>
<td>31.06</td>
<td>0.000*</td>
</tr>
<tr>
<td>Postoperative VAS</td>
<td>3±0**</td>
<td>2.6 ±0.4***</td>
<td>1.7±0.5</td>
<td>1.5±0.6</td>
<td>9.80</td>
<td>0.000*</td>
</tr>
<tr>
<td>Total number of diclofenac ampules in 24 hours</td>
<td>2.3±0.5**</td>
<td>2.4±0.5***</td>
<td>1.8±0.5</td>
<td>1.7±0.6</td>
<td>4.05</td>
<td>0.015*</td>
</tr>
<tr>
<td>Patient satisfaction score</td>
<td>1.8±1.0**</td>
<td>1.8±0.7**</td>
<td>2.6±0.5</td>
<td>2.5±0.6</td>
<td>4.22</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, number(percentage).
F test (ANOVA=analysis of variance).
X²= chi squer test.
*significant (p<0.05)
**post hoc test in comparison between groups.
DISCUSSION

Epidural anesthesia is a safe and inexpensive technique with the advantage of providing surgical anesthesia and postoperative pain relief. Neostigmine is an acetylcholinesterase inhibitor used as adjuvant analgesia epidurally (9).

In this study, we found that no significant difference across the three bolus doses of neostigmine (groups Ia, Ib and Ic) relative to sensory block onset time and time to complete motor block, but there were correlations between fentanyl group and rapid onset of analgesia and time to complete motor block.

**Taspinar et al. (10)** found that 4 µg/kg or 8 µg/kg epidural bolus neostigmine shows no significant difference across two groups relative to sensory block onset time and time to complete block in comparison to each other.

**Tekin et al. (11)** compared bupivacaine plus neostigmine 4 µg/kg and bupivacaine plus 1 µg/kg fentanyl using Patient-Controlled Epidural Analgesia (PCEA) and reported that analgesia begins faster and lasts longer in patient receiving low doses of local anesthetic and opioid in patients after abdominal hysterectomy.

In this study, there were no significant differences between the bolus groups regarding hypotension and bradycardia.

**Harjai et al. (12)** reported that mean arterial blood pressure and heart rate showed no significant changes between groups after injection of epidural neostigmine 100 µg and 200 µg in patients undergoing lower extremity surgery.

**Tawfik et al. (13)** found no significant difference between neostigmine 50 µg and fentanyl after intrathecal injection as regard changes in mean blood pressure or heart rate.

In our study, there were no significant differences among the bolus dose groups regard bradypnea or decreased oxyhemoglobin saturation (SpO₂) (these complications were not recorded in our study at all).

**Taspinar et al. (10)** found that no difference between group received 4 µg/kg or group 8 µg/kg epidural neostigmine for lower extremity surgery as regard intraoperative oxyhemoglobin saturation changes.

**Bajwa et al. (14)** did not observe a single case of respiratory depression when comparing group of ropivacaine 0.75% plus fentanyl 75 µg and group of ropivacaine plus 75 µg clonidine group and they explained that probably due to smaller dose of fentanyl given in their study.

These results were matched with our findings as low absorption of epidural neostigmine and low dose of used fentanyl.

In our study, we found that there was a significant sedation with increasing the dose of bolus neostigmine (dose dependent) and with fentanyl dose. There was no significant difference between the highest dose of neostigmine and fentanyl dose regarding patient sedation.

**Harjai et al. (12)** reported that the addition of epidural neostigmine produced mild sedation in both neostigmine group (100 µg and 200 µg), but sedation was statistically significant with high dose of neostigmine (200 µg) (dose-dependent). This matches with our study.

**Bajwa et al. (14)** found that there were a significant sedation with the group receiving ropivacaine plus fentanyl 75 µg alone than the group receiving ropivacaine-clonidine or ropivacaine-clonidine-fentanyl in epidural anesthesia for lower abdominal surgery.

In our study, we found that there were significant lower nausea/vomiting with neostigmine groups in comparison to fentanyl group.

Nausea/vomiting is seen less frequently in epidural neostigmine studies of (15) (16).

**Kawai et al. (17)** concluded that patient-controlled epidural analgesia with ropivacaine alone resulted in a significantly lower incidence of nausea and vomiting than ropivacaine-fentanyl group.

**Tawfik et al. (13)** concluded that sedation and nausea were the causes of delayed discharge in the neostigmine group while pruritis and respiratory monitoring were the main concern in fentanyl group.

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**Table (5): Side effects of epidural infusion doses**

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Group IIIa (n=20)</th>
<th>Group IIIb (n=20)</th>
<th>Group IIIc (n=20)</th>
<th>Group IV (n=20)</th>
<th>X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>1 (5%)*</td>
<td>1(5%)*</td>
<td>2(10%)*</td>
<td>8(40%)*</td>
<td>13.33</td>
<td>0.004*</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0%)*</td>
<td>0(0%)*</td>
<td>0 (0%)*</td>
<td>3(15%)*</td>
<td>9.23</td>
<td>0.026*</td>
</tr>
<tr>
<td>Ileus</td>
<td>0(0%)</td>
<td>1 (5%)</td>
<td>1(5%)</td>
<td>2 (10%)</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Urine Retention</td>
<td>0 (0%)</td>
<td>0(0%)</td>
<td>0 (0%)</td>
<td>1(5%)</td>
<td>4.16</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Data are expressed as number(percentage).

*significant (p<0.05).

$X^2$= chi square.
The current study established that addition of epidural neostigmine 100 µg, 150 µg and 200 µg to bupivacaine increases the duration of analgesia in dose-dependent manner through prolonged duration for first call for diclofenac. Also, there was a significant short duration before first call for diclofenac with neostigmine groups in comparison to fentanyl group.

Nakayama et al. (18) concluded that 10 µg/kg of epidural neostigmine in bupivacaine provides a longer duration of analgesia than bupivacaine alone or with 5 µg/kg of neostigmine after abdominal hysterectomy.

Tekin et al. (11) reported that analgesia begins faster and lasts longer in patients receiving low doses of local anesthetics and opioids in comparing analgesic activity of neostigmine 4 µg/kg to fentanyl 1 µg/kg using patient-controlled epidural analgesia.

Tawfik et al. (13) found that spinal neostigmine was as effective as fentanyl and significantly prolonged the time to the first analgesic administration compared to the saline group. Both neostigmine and fentanyl groups differed significantly from the saline group (p = 0.05 and p< 0.001 respectively).

In this study, there was a significant correlation between high-bolus neostigmine dose and low postoperative VAS (dose dependent) and also there were significant correlations between high VAS with neostigmine groups in comparison to fentanyl group.

Göktug et al. (19) concluded that 300 µg and 450 µg epidural neostigmine administered before anesthesia provides effective postoperative pain relief than saline and 150 µg epidural neostigmine after open cholecystectomy reducing intra- and post-operative opioid requirement.

Tekin et al. (11) stated that that visual analog scale scores were lower in the group receiving bupivacaine plus fentanyl significantly than the other groups receiving bupivacaine plus neostigmine or bupivacaine alone.

In our study, there were a significant correlation between the lowest dose of neostigmine (100 µg) and the high total number of diclofenac ampules received during first postoperative 24 hours, but no significant difference between the other two doses of neostigmine (150 µg and 200 µg) or fentanyl dose (50 µg) groups.

Taspinar et al. (10) has shown lower analgesic consumption at 12 and 24 hours in the 8 µg/kg neostigmine group than 4 µg/kg neostigmine and saline group.

Tekin et al. (11) found that during the following 24 hours, total analgesic consumption was significantly lower in the group receiving bupivacaine plus fentanyl than the other groups receiving bupivacaine plus neostigmine or bupivacaine alone.

In this study, there were a significant correlation between the highest dose of neostigmine (200 µg) and high patient satisfaction score and also a significant correlation between fentanyl group and high patient satisfaction score.

Tekin et al. (11) recorded that there was a significant decrease in group bupivacaine according to the comparison of satisfaction scores of other fentanyl or neostigmine groups at the end of 24 hours.

In our study, we found that first bolus dose failure was significant with lower neostigmine doses, orthopedic and vascular surgeries showed significant high first dose failure with the groups of lower doses of neostigmine than the highest dose of neostigmine or fentany group.

Taspinar et al. (10) reported that the number of delivered bolus doses was lower in the 8 µg/kg neostigmine group compared to the saline and 4 µg/kg neostigmine group.

There is discrepancy about the effective dose of epidural neostigmine which may partly be explained by the type of surgery, the dose being larger for more extensive and painful surgical procedure than for minor ones (15).

However, in patient who underwent abdominal hysterectomy, coadministration of epidural neostigmine 5 µg/kg neostigmine plus bupivacaine did not produce effective analgesia postoperatively, whereas coadministration of epidural neostigmine 10 µg/kg neostigmine plus bupivacaine provided effective analgesia (18).

In our study, we found no significant difference between the infusion dose groups regarding hypotension and bradycardia, matched with (20)(8).

In this study, there were a significant sedation with the highest dose of neostigmine infusion and fentanyl infusion groups. There were no significant difference between the other two doses of neostigmine and also no significant difference between the highest dose of neostigmine and fentanyl regarding patient sedation.

Ross et al. (8) observed an increase in incidence of sedation when neostigmine infusion was added to bupivacaine and also the sedative effect of low dose of epidural neostigmine infusion to be very minimal if any.

Tan et al. (21) reported that epidural opioid can be associated with dose-dependent adverse effects for sedation, pruritis, nausea and respiratory depression.
In our study, the neostigmine infusion groups showed a significant short duration to two-segment regression in comparison to fentanyl and we found also that there was a significant correlation between the lowest dose of neostigmine and short duration to two-segment regression.

Bhat et al. (22) found that the time of two-segment regression was statistically significantly different among group A receiving bupivacaine alone, group B receiving bupivacaine plus 50 µg neostigmine and group C receiving bupivacaine plus 150 µg neostigmine with group C more prolonged time than the other two groups in spinal anesthesia for lower abdominal and lower limb surgery.

Bajwa et al. (14) reported that the regression of block height was slightly prolonged in ropivacaine plus fentanyl group than the group of ropivacaine-clonidine and the group of ropivacaine-clonidine-fentanyl in epidural anesthesia for lower abdominal surgery.

In our study, we found that there were significant lower nausea-vomiting with neostigmine infusion groups in comparison to fentanyl group.

Chia et al. (20) stated that thoracic infusion of epidural neostigmine was not associated with an increased incidence of postoperative nausea and vomiting.

Eisenach (23) noted that neostigmine does not produce respiratory depression or pruritis in comparison to fentanyl during epidural infusions.

In our study, we found that there were significant correlation between the lower neostigmine doses (group IIIa, IIIb) regarding short duration for first call for diclophenac(durataion of analgesia), high total number of diclophenac ampoules consumption in postoperative 24 hours, high postoperative VAS and low patient satisfaction score in comparison to the highest dose neostigmine(IIIc) and fentanyl dose(IV).

there were significant prolonged duration of analgesia in group IIIc compared to the other groups of neostigmine reflected by prolonged duration before 1st call for diclophenac, but fentanyl group still has upper hand in prolonged duration of analgesia in comparison to the highest dose of neostigmine significantly. No significant difference between highest neostigmine group and fentanyl group was found regarding total number of diclophenac in first postoperative 24h., postoperative VAS and patient satisfaction score.

Chia et al. (20) concluded that continuous thoracic epidural neostigmine started before anesthesia provided preemptive, preventive analgesia and analgesic-sparing effect that improved postoperative analgesia for these patients and that 125 µg/hour continuous epidural neostigmine infusion was effective for thoracotomy which is one of extensive and painful surgical procedures.

Ross et al. (8) concluded that adding neostigmine (4 µg/ml) instead of opioids can improve the quality of epidural pain relief for women in labor while decreasing the hourly bupivacaine requirement by 19%-23% and produced maternal satisfaction with analgesia.

Roelants et al. (24) concluded that epidural combination of neostigmine 500 micrograms (6-7 micrograms/kilogram) with sufentanil 10 micrograms provides similar duration of analgesia as epidural-sufentanil 20 micrograms allowing effective and selective analgesia devoid of side effects.

CONCLUSION
The highest doses of epidural bolus or infusion neostigmine used in this study showed significant better analgesic effects than lower doses with no significant different side effects. Fentanyl drug showed significant longer duration of analgesia than neostigmine drug with similar postoperative VAS, number of diclophenac ampoules consumed in first postoperative 24 hours, and patient satisfaction score but more significant side effects than neostigmine drug.

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A Comparison Between Three Doses of


أجريت هذه الدراسة بمساهمات كلية الطب البشري جامعة الزقازيق على 16 مريض تراوح فئتهن ما بين 16 عام واً 65 عام في خضوع لتجذير معمل الجزء الموسيقي من الجسم في الفترة ما بين مارس 2010 إلى مايو 2012. 

تهدف هذه الدراسة إلى المقارنة بين إعطاء ثلاث جرعات من النيوستجمين بالضغط أو التنقيط في أمراض الأعصاب الجزء الخلفي (100 ميكروجرام/مليتر)، عند المرضى بجرعة 5 ميكروجرام/مليتر بكميات 20 مريض لكل جرعة.

1. المجموعة الأولى: تم إعطاء جرعة تقليفية من النيوستجمين على الأسنان الاتفاقية للعود الفيروز (50 ميكروجرام/مليتر مع المرضى بكميات 10 ميكروجرام/مليتر بكميات 20 مريض لكل جرعة).  
2. المجموعة الثانية: تم إعطاء جرعة تنقية من النيوستجمين بكميات 5 ميكروجرام/مليتر لكل حال.  
3. المجموعة الثالثة: تم إعطاء جرعة تنقيطية من النيوستجمين على الأسنان الاتفاقية للعود الفيروز (75 ميكروجرام لكل حال) مع المرضى بكميات 5 ميكروجرام/مليتر لكل حال.

1. المراجعات الناتجة عن الأحجام والطعوم والألعاب أو مضاعفات أخرى: 
2. الطب البشري لم يكن بكرك ديكراك. 
3. الدماغ المبتكر لسيكلك فابك. 
4. الدماغ المبتكر لسيكلك فابك.

1. المقارن بين إعادة ثلاث جرعات من النيوستجمين بالضغط أو التنقيط على الأسنان الاتفاقية للعود الفيروز وفترات للعصب الرئيسي كمسكن مساعد.  
2. عمومًا أظهرت هذه الدراسة أن الاستخدام الفعال في الآفات الفيروزية في 남ع العلمي ومسكن المضاعفات الناتجة عن (مع النيوستجمين).

3. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين والإنداد الحسي أو أكتمال الإحساس.

4. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين وفترات للعصب الرئيسي.

5. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين وفترات للعصب الرئيسي بالعصب الرئيسي بين المرضى.  
6. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين وفترات للعصب الرئيسي بين المرضى.

8. أظهرت هذه الدراسة بعد الراحة مستويات من 0.600 هرتز.  

2. عمومًا أظهرت هذه الدراسة بين إعطاء ثلاث جرعات من النيوستجمين بالضغط أو التنقيط على الأسنان الاتفاقية للعود الفيروز وفترات للعصب الرئيسي كمسكن مساعد.  
3. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين وفترات للعصب الرئيسي.

6. وجدنا علاقة ذات دلالة إحصائية بين الجرعات المستخدمة من عقار النيوستجمين وفترات للعصب الرئيسي بين المرضى.
3. لم يكن هناك اختلاف ذات دالة إحصائية بين عقار الفنتايل وعقار النيوستجين فيما يخص شدة الألم بعد الجراحة بالقياس البصرى وعدد أمبولات المسكن خلال 24 ساعة بعد الجراحة ودرجة إرضاء المريض بعد الجراحة (مع الجرعات الإضافية وال التنفيذية).

4. لم يكن هناك اختلاف ذات دالة إحصائية بين نجاح الجراحة بالجرعة الأولية الإضافية بين عقار النيوستجين والفنتايل. ومما يمكنا قبول استخدام الجرعات الأعلى المستخدمة في هذه الدراسة سواء الجرعة الإضافية أو الجرعة التنفيذية كبدائل لعقار الفنتايل.

3. عوامل تميز استعمال عقار الفنتايل بعقار النيوستجين:
1. وجد أن هناك علاقة ذات دالة إحصائية بين عقار الفنتايل وبداية الانسداد الحسي أو اكتمال الانسداد الحركي مقارنة بعقار النيوستجين (مع الجرعات الإضافية).
2. وجد أن هناك علاقة ذات دالة إحصائية بين عقار الفنتايل وطول المدة قبل طلب المسكن مقارنة بعقار النيوستجين (مع الجرعات الإضافية والتنفيذية).
3. وجدنا علاقة ذات دالة إحصائية بين عقار الفنتايل وطول المدة قبل الارتداد الحسي بنسبة دون العصب الصدري العاشر (مع الجرعات التنفيذية).

ومما يمكنا قبول أن عقار الفنتايل ما زال له ميزات وذالك نوصي برداس أخرى لاستخدام عقار النيوستجين بجرعات أعلى نظراً لفاعليته التأثبي وقلة المضاعفات الناتجة عن استخدام أعلى الأم الجاوية للعمود الفقري سواء بالتنفيذية أو الإضافية على الرغم من وجود تطور كبير في مجال التخدير بأنهنا ما زالتنا نحاول أن نصل لأفضل وتحدى أن نحاول وإن لم نستطيع الوصول إلى أفضل العقارات وأفلا ضراً على المرضى.