Intravenous Patient Controlled Analgesia After Elective Orthopedic Surgeries under general anesthesia: Tramadol / Ondansetron versus Morphine/ Ondansetron; A Comparative study

Doaa Rashwan MD*

*Anesthesia Department, faculty of medicine, BeniSuefUniversity, Egypt.

Background and objectives:
This study was designed to evaluate the effects of addition of ondansetron to intravenous patient controlled analgesia, tramadol versus morphine on analgesic requirements and adverse events after elective orthopedic surgeries under general anesthesia.

METHODS: 120 adult male and female patients ASA I and II undergoing elective orthopedic surgeries undergeneral anesthesia were randomly allocated into two groups:
Group TO (n=60): ondansetron 4 mg was administered at the end of surgery and 24 mg was added to PCA pump which was programmed to deliver tramadol boluses of 10 mg, lockout interval 15 minutes, no background infusion, maximum doses per hour 40 mg.
Group MO (n=60): ondansetron 4 mg was administered at the end of surgery and 24 mg was added to PCA pump which was programmed to deliver morphine boluses of 1 mg, lockout interval 15 minutes, no background infusion, maximum doses per hour 4 mg.
Postoperative volume of tramadol and morphine (mg) consumed, severity of postoperative pain at rest using VAS, postoperative systolic arterial blood pressure and heart rate in 24 h, patient satisfaction, adverse effects (nausea, vomiting, sedation, hypotension, respiratory depression) were recorded, number of patients required rescue analgesia with diclofenac sodium.
Results: no statistical significant differences in the severity of postoperative 24 hours pain at rest, adverse events between the two groups or in the postoperative systolic, diastolic arterial blood pressure and heart rate

Key words: tramadol, morphine,PCA, ondansetron, PONV

Introduction:
Post operative pain needs to be controlled without causing adverse effects as respiratory or cardiovascular depression, gastrointestinal disorder. The choice of analgesic agent should offer the best analgesic effect and improve patient’s satisfaction and safety (1).

Tramadol is a weak opioid, used for post operative pain relief (2). Intravenous patient-controlled analgesia with tramadol is an accepted method to deliver postoperative analgesia (3), but there is a risk of PONV with tramadol (4), which are major adverse events during postoperative anesthesia period, affecting length of hospital stay, and costs. (4)

Serotonin is an important neurotransmitter of the descending pathways that down-modulate spinal nociception, ondansetron, a selective 5-HT3 receptor antagonist (5) is used for prophylaxis against PONV (6-8). tramadol which is a central analgesic dependent on enhanced serotoninergic transmission (9), it is associated with frequent incidence of PONV, which may lead to discontinuation of PCA (9)

Morphine is the gold standard for postoperative pain control (10), but it has a high risk of side-effects eg. respiratory depression, nausea, vomiting, pruritus, urinary retention (11).

Previous studies showed conflicting results about the efficacy of tramadol and ondansetron when co-administered due to their opposing serotoninergic effects (6), it was reported that tramadol-induced analgesia is partially antagonized by ondansetron (12), and that it reduced the analgesic effect of tramadol PCA but not morphine PCA (13).

Objectives: was to evaluate the effects of addition of ondansetron to tramadol versus morphine IV PCA on postoperative analgesic consumption, and adverse events after elective orthopedic surgeries under general anesthesia.

Patients and Methods:
After approval of the review board in Al Razi orthopedic Hospital- Kuwait, a written informed consent was obtained from 120 ASA I and II male and female patients aged 20-50 years old, planned for elective orthopedic surgeries (lumbar discectomy, fixation and fixation of fracture pelvis) under general anesthesia from January 2009 to December 2010.

Those with history of use of antidepressant drugs, epilepsy, history of PONV, allergic reaction to the drugs used in the study or having mental or psychiatric disorders preventing the use of PCA device were excluded from the study.

The study protocol and the visual analogue scale (VAS) for pain, the use of PCA device were explained to each patient during the preoperative visit.

In the operating room, intravenous cannula was inserted, ringer solution was started. Electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure at 5 minutes intervals were applied.

General anesthesia was induced in all patients with i.v. propofol 2-3 mg/kg, fentanyl 2 ug/kg.
cisatracurium 0.15mg/kg, oral cuffed endotracheal tube, anesthesia was maintained with oxygen 50%, nitrous oxide 50%, sevofothane, additional doses of cisatracurium and mechanical ventilation, tramadol 2mg/kg was given to patients in group TO and morphine 0.1mg/kg to patients in group MO for intraoperative analgesia

At the end of surgery neuromuscular blockade was reversed with neostigmin 0.04mg/kg and atropine 0.02mg/kg IV, the trachea was extubated when the patient respond to commands, all patient were transferred to PACU where they were monitored for 1 hour. The postoperative pain at rest was assessed using Visual Analogue Scale (VAS), where zero score corresponds to no pain and 10 to the maximum or worst pain. Patients were then instructed to start using patient-controlled the PCA pump (CADD-Legacy® PCA, model 6300 Ambulatory infusion pump; Deltec, Inc. St Paul, MN 55112 USA, 40-3920-51B)

Patients were randomly allocated into two equal sized groups using a closed envelop technique: Group TO (n=60); ondansetron 4 mg (Zofran®), Ondansetron hydrochloride dihydrate 4mg/2ml GlaxoSmithKline) was administered at the end of surgery and 24 mg was added to PCA pump. The PCA reservoir bag was filled with 1000mg of tramadol diluted in normal saline (10 mg/ml), the PCA pump was programmed to deliver tramadol boluses of 10 mg, lockout interval 15 minutes, no background infusion, maximum doses per hour 40 mg.

Group M O (n=60); ondansetron 4 mg was administered at the end of surgery and 24 mg was added to PCA pump. The PCA reservoir bag was filled with 100mg of morphine diluted in normal saline (1mg/ml) the PCA pump was programmed to deliver morphine boluses of 1 mg, lockout interval 15 minutes, no background infusion, maximum doses per hour 4 mg.

The following parameters were evaluated and recorded: data of the patients since discharge from operation theatre were collected by acute pain management team of the hospital (an anesthetist and anesthesia technician) and recorded in the PCA sheets: Patient characteristics. The severity of postoperative pain at rest measured at 1, 8, 16, and 24 h postoperatively using (VAS). Postoperative systolic, diastolic arterial blood pressure, heart rate at 1, 8, 16, and 24 h, hypotension was considered if BP systolic pressure was less than 90 mmHg. Volume of tramadol and morphine consumed (mg) in 24 hours

Number of patients required rescue analgesia; diclofenac sodium 75 mg i.m. Number of patients had PONV Respiratory depression (RR less than 8) Urine retention, pruritus, constipation

Sedation: was assessed with a five-point scoring scale (0 = fully awake; 1 = drowsy, closed eyes; 2 = asleep, easily aroused with light tactile stimulation or a simple verbal command; 3 = asleep, arousable only by strong physical stimulation; and 4 = unarousable). (5)

Grade of Patients' satisfaction (good/fair/unsatisfactory).

Statistical analysis: data are presented as mean (SD) or median (range), number and percentage as appropriate. Data were computerized and statistically analyzed using SPSS version 19 (IBM, 2010). Chi-squared and Fisher exact tests were used for categorical qualitative variables. Comparison between group means was carried out using student t-test. The significance level was considered at P value < 0.05.

Results:
All patients completed the study, patient's characteristics showed no statistical significant difference between the two studied groups, table (1).

No statistical significant difference in the severity of postoperative 24 hours pain at rest, adverse events between the two groups, tables (2),(3). No statistical significant difference in the postoperative systolic, diastolic arterial blood pressure and heart rate tables (4),(5),(6).

Discussion:
The present study demonstrated that addition of ondansetron to tramadol and morphine intravenous patient controlled analgesia after elective orthopedic surgeries did not increase the analgesic requirements or adverse events. Neele R Lautersand his colleagues (3) on their study on patients recovering from major surgery concluded that co-administration of ondansetron and tramadol neither increased postoperative analgesic consumption nor the frequency of vomiting.

Arcioni R and his colleagues (5) showed that patients received IV tramadol PCA (bolus = 30 mg; lockout interval = 10 min) and ondansetron 1 mg/ ml/h required significantly larger doses of tramadol and higher incidence of vomiting but their tramadol doses were higher than the dose we used in this study.

Cubukçu Z et al (13) concluded that ondansetron 0.1 mg/kg after induction of anesthesia increased the analgesic consumption significantly in patients received tramadol PCA than those received morphine PCA.

Another study showed that a single 4mg dose of ondansetron given at the induction of anesthesia decreases the analgesic efficacy of tramadol and does not reduce the 24-h incidence of PONV (16)

The involvement of both drugs in the serotonin (5-HT) pathway may be the possible reason, tramadol inhibits 5-HT reuptake so it increase the concentration of this neurotransmitter within the synaptic cleft and ondansetron blocks 5-HT effects at its specific receptors. This might partially antagonize tramadol induced analgesia mediated via serotonin (16).

Other studies showed no difference in tramadol consumption (17,18) but animal studies showed conflicting results. Ethan et al (20) did not find an ondansetron related decrease of tramadol’s
analgesic effectiveness in mice, in contrast, Du Restler et al (23) demonstrated the presence of a functional antagonism.

As regards to morphine, Boonmak Pet al (24) showed that 4 mg ondansetron plus 0.2 mg mL-1 given with PCA morphine can reduce nausea and vomiting and improved patient satisfaction. Jellish WS and his coworkers (22) concluded that addition of 30 mg of ondansetron to PCA morphine in patients undergoing abdominal surgery, resulted in less PONV. Conclusion: the addition of ondansetron to tramadol and morphine intravenous patient controlled analgesia after elective orthopedic surgeries did not increase the analgesic requirements or adverse events.’

References:
Agrawal JK, Pradhan W:Tramadol in patient controlled analgesia for postoperative management. PMJN, Postgraduate Medical Journal of NAMS, Volume 9, Number 2, July-Dec 2009


Jan L, De Witte, Bart Schoenmaekers, Daniel I. Sessler, Thierry Delooof: The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron, AnesthAnalg 2001;92:1319–21


Table (1) Patient characteristics. Data presented as mean ±SD or number
No statistical significant differences between the studied groups.

Group TO: PCA tramadol +ondansetron
Group MO: PCA morphine + ondansetron

Table (2): Postoperative Visual Analogue Scale (VAS) Data presented as median and range.

<table>
<thead>
<tr>
<th>VAS</th>
<th>Group TO (n=60)</th>
<th>Group MO (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hours</td>
<td>4 (2-5)</td>
<td>4 (2-4)</td>
</tr>
<tr>
<td>8 hours</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>16 hour</td>
<td>2 (1-3)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>24 hour</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>

Group TO: PCA tramadol +ondansetron
Group MO: PCA morphine + ondansetron

Table (3): Postoperative tramadol or morphine analgesics, data presented as mean ±SD or number consumed (mg/24h), adverse events, sedation scores, patient satisfaction, patients needed for rescue analgesics, data presented as number and (%).

<table>
<thead>
<tr>
<th></th>
<th>Group TO (n=60)</th>
<th>Group MO (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol or morphine consumed in 24h (mg)</td>
<td>331±32.17</td>
<td>32.04±3.98</td>
</tr>
<tr>
<td>Nausea n (%)</td>
<td>5 (8.3)</td>
<td>7 (11.6)</td>
</tr>
<tr>
<td>Vomiting n (%)</td>
<td>2 (3.3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Respiratory rate &lt;8 n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypotension n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritis n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urine retention n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation n (%)</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Sedation score (0/1/2/3/4)</td>
<td>(47/13/0/0/0)</td>
<td>(45/15/0/0/0)</td>
</tr>
<tr>
<td>Patient satisfaction: (good/fair/unsatisfactory)</td>
<td>(42/16/2)</td>
<td>(44/15/1)</td>
</tr>
<tr>
<td>Need for rescue analgesics n (%)</td>
<td>2 (3.3)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

Group TO: PCA tramadol +ondansetron
Group MO: PCA morphine + ondansetron

Table (4): Postoperative systolic arterial blood pressure (mmHg), data presented as mean ± SD.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Group TO (n=60)</th>
<th>Group MO (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>141.00±3.6</td>
<td>140.54±3.8</td>
</tr>
<tr>
<td>8 hours</td>
<td>135.45±2.4</td>
<td>134.73±5.6</td>
</tr>
<tr>
<td>16 hour</td>
<td>132.79±7.69</td>
<td>133.66±8.48</td>
</tr>
</tbody>
</table>
No statistical significant differences between the studied groups

**Table (5) Postoperative diastolic arterial blood pressure (mmHg), data presented as mean± SD**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Group TO (n=60)</th>
<th>Group MO (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>74.34±6.48</td>
<td>75.28±5.12</td>
</tr>
<tr>
<td>8 hours</td>
<td>73.34±6.48</td>
<td>72.28±5.12</td>
</tr>
<tr>
<td>16 hour</td>
<td>73.55±5.10</td>
<td>71.59±5.63</td>
</tr>
<tr>
<td>24 hour</td>
<td>72.20±3.22</td>
<td>71.60±2.00</td>
</tr>
</tbody>
</table>

No statistical significant differences between the studied groups

**Table (6) Postoperative heart rate (Bpm), data presented as mean± SD**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Group TO (n=60)</th>
<th>Group MO (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>71.45±2.31</td>
<td>70.51±3.67</td>
</tr>
<tr>
<td>8 hours</td>
<td>70.00±2.31</td>
<td>69.50±6.30</td>
</tr>
<tr>
<td>16 hour</td>
<td>68.00±4.58</td>
<td>68.37±2.00</td>
</tr>
<tr>
<td>24 hour</td>
<td>69.78±2.54</td>
<td>68.24±2.47</td>
</tr>
</tbody>
</table>

No statistical significant differences between the studied groups

Group TO : PCA tramadol + ondansetron
Group MO : PCA morphine + ondansetron