**Original Contribution**

**The effect of ondansetron on analgesic efficacy of acetaminophen after hysterectomy: A randomized double blinded placebo controlled trial**

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**1. Introduction**

Control of postoperative pain and nausea-vomiting (PONV) are key components of quality of recovery after surgery [1]. Multimodal analgesia has become routine for postoperative pain. Acetaminophen is frequently added to multimodal analgesia, and its use has increased because of its effective opioid sparing resulting in reduction of opioid-related side effects [2]. Acetaminophen exerts its analgesic effects by multiple pathways including inhibition of COX-2-dependent prostaglandin E2 synthesis [3], indirectly activating cannabinoid CB1 receptors and inhibition of nitric oxide system through involvement of N-methyl-d-aspartate and substance-P [4]. The analgesic effect of acetaminophen may be primarily mediated by stimulation of descending serotoninergic pathways which inhibits nociceptive signal transmission in the spinal cord [5-8].

Serotonin 5-Hydroxytryptamine (5-HT3) receptor antagonists, such as ondansetron, are generally considered to be the first-line antiemetics due to their effectiveness in preventing PONV and rare side effects [9]. Ondansetron primarily acts at the chemoreceptor trigger zone in the medulla oblongata, but it also interacts with 5-HT3 receptors within the spinal cord which modulate transmission of pain signals [10]. Ondansetron may therefore antagonize acetaminophen because the two drugs have opposite effects on 5-HT3 pathways [11,12].

The potential interaction between 5-HT3 receptors antagonists and acetaminophen has prompted studies to evaluate the of 5-HT3 receptors antagonism on analgesic efficacy of acetaminophen. Animal work...
shows that intrathecal administration of a 5-HT3 antagonist abolishes the analgesic effect of acetaminophen [6], and that blocking 5-HT3 receptors in the dorsal horn of the spinal cord by ondansetron is non-nociceptive [13]. As might thus be expected, Arcioni et al. demonstrated that ondansetron inhibits the analgesic effects of tramadol, a central analgesic that activates descending serotonergic pathway [14]. Some human studies report that 5-HT3 antagonists decrease the analgesic efficacy of acetaminophen [7,11,12,15], while others failed to identify an association [16–18]. However, existing studies are limited by reliance on experimental pain models and relatively small sample sizes. Furthermore, existing studies mostly tested tropisetron which is not a commonly used 5-HT3 antagonist.

There is scarce data about the interaction of acetaminophen and ondansetron, although these are often co-administered. We thus postulated that ondansetron attenuates acetaminophen-induced analgesia, presumably by directing interfering with serotonin transmission in the spinal cord. We therefore tested the primary hypothesis that ondansetron administration increases pain scores in patients given acetaminophen. Our secondary hypothesis was that ondansetron administration reduces opioid postoperative requirements.

2. Materials and methods

This single-center, randomized, double-blinded study was conducted at Mustafa Kemal University Hospital. Ethics Committee approval (March 2012, Approval number 5) was obtained from the institution and written consent was obtained from participating patients. The study was registered at ClinicalTrials.gov (NCT02296333).

We enrolled 120 American Society of Anesthesiologists Physical Status I-II women 18–80 years old who were scheduled for hysterectomy with general anesthesia from May through December 2014. The study was restricted to hysterectomies with horizontal abdominal skin incision, and to patients who were able to operate a patient-controlled analgesia (PCA) device.

We excluded emergency procedures; women with pre-existing chronic pain at any site requiring opioid analgesia; women who had a history of significant Axis I psychiatric disease (major depressive disorder, bipolar disorder, schizophrenia, etc.); women with significant hepatic (ALT or AST > 2 times normal) or renal (serum creatinine > 2 mg/dl) impairment; and those reporting allergies to acetaminophen or ondansetron.

3. Protocol

Participating women were premedicated with 1–2 mg intravenous (IV) midazolam per preference of the attending anesthesiologist. Anesthesia was induced with propofol (2 mg/kg IV); intubation was facilitated by rocuronium (0.6 mg/kg IV); and anesthesia was maintained by sevoflurane in combination with nitrous oxide 50% in oxygen. Fentanyl (2 µg/kg IV) was given 3–5 min before the surgical incision.

After endotracheal intubation, patients’ lungs were mechanically ventilated to maintain the end-expiratory CO2 partial pressure between 34 and 36 mm Hg. A Pfannenstiel approach was used in each patient, with the same surgeon similarly conducting all operations. All the patients were given 1 g acetaminophen at skin closure, and an additional 1 g every 6 h for 24 h. All patients were also given tramadol HCl (0.5 mg/kg IV) at skin closure.

Randomization 1:1 without stratification was web-based using computer-generated codes. The system was accessed shortly before induction of anesthesia to mask allocation until the last practical moment. Drugs were covered by opaque plastic to keep the surgical team and anesthesiologists blinded to treatment. Patients assigned to ondansetron were given ondansetron HCl (8 mg, 2 ml IV) at closure of the skin incision. Patients assigned to placebo were given 2 ml saline IV, also at skin closure.

After return of spontaneous ventilation and tracheal extubation, patients were transferred to the post anesthesia care unit (PACU). Patients were connected to a patient-controlled analgesia (PCA) device and postoperative analgesia was provided by 20-mg intravenous bolus injections of tramadol HCl at a lockout interval of 15 min and with a maximum 4-h limit of 150 mg. The PCA device was discontinued when patients made no demands for the opioid analgesic in the preceding 4-h interval or at a maximum of 24 h after surgery.

When pain exceeded 4 cm on a visual analogue scale (VAS), a rescue dose of 75 mg diclofenac sodium was given intramuscularly. If systolic arterial pressure (SAP) decreased to <90 mm Hg or mean arterial pressure to <50 mm Hg, ephedrine HCl (5 mg IV) was given. If the heart rate decreased to <50 beats/min, atropine sulfate (0.5 mg IV) was given. When patients sustained nausea or vomiting lasting longer than 5 min, metoclopramide HCl (10 mg IV) was given.

4. Measurements

All postoperative measurements were conducted by a research assistant who was blinded to group allocation. All patients were educated preoperatively at anesthesia clinic about how to use VAS tool consisting of a 10-cm-long ruler and a marker that the patient moved to a point indicating their intensity; 0 cm was designated no pain, and 10 cm as the worst imaginable pain. Postoperative pain was recorded separately with patients (who remained blinded to treatment) resting in bed and while sitting upon arrival at PACU and 1, 2, 4, 8, 12, 16, 20, and 24 thereafter.

Sedation was assessed using the Ramsay sedation scale [19]. Heart rate, blood pressure, oxygen saturation (SpO2), respiratory rate, pain, sedation, opioid usage, cumulative analgesic consumption, and antiemetic use were assessed upon arrival in the PACU, and then 1, 4, 8, 12, 16, 20, and 24 h thereafter while awake. After the 4th postoperative hour, postoperative pain management was additionally assessed as 1 = unsatisfied, 2 = slightly satisfied, 3 = mostly satisfied, 4 = completely satisfied [20]. Hospital anxiety and depression surveys [21] were evaluated before discharge from the hospital.

Postoperative side effects including nausea-vomiting, bradycardia (heart rate lower than 50 beats per minute), hypotension (decrease in systolic arterial pressure of >10 mm Hg from baseline), itching, headache, and respiratory depression (respiratory rate <10) were recorded at intervals specified above. We recorded time to first flatus, initial ambulation, and first oral intake of solid food. The total amounts of opioid (tramadol) administration, rescue analgesics, antiemetics for 24 h were recorded.

5. Statistical analysis

The two randomized groups were compared for balance on demographics and baseline characteristics using standard summary statistics and the absolute standardized difference (ASD), defined as the absolute difference in means or proportions divided by the pooled standard deviation. Any variable with an ASD >0.20 was considered imbalanced, and was adjusted for in all analyses.

The analgesic effect of acetaminophen with ondansetron or placebo on the VAS pain scores while resting in bed and while sitting was evaluated using separate multivariable regression models. The overall mean difference between the two randomized groups in the pain scores while resting in bed was not evaluated (treatment-by-time interaction P < 0.001) but in the VAS while sitting was evaluated (treatment-by-time interaction P = 0.59) using a mixed effect model with repeated measurements. The corresponding confidence interval was appropriately adjusted for multiple comparisons with a Bonferroni correction.

We assessed the analgesic effect of acetaminophen with ondansetron on total opioid consumption (after logarithm transformation) during the first 24 h after arrival at PACU, using a multivariable
ences of 0.66 and 0.70, respectively (Table 1). We thus adjusted for anesthesia and duration of surgery, with absolute standardized difference.

Results

Coadministration of ondansetron and acetaminophen increased acute pain scores while patients rested supine by about 1.7 cm (on a 10-cm scale) upon arrival to the PACU, and pain scores remained about 1.3 cm greater after the initial hour of recovery. Differences while sitting were smaller, only 0.6 cm, and restricted to PACU arrival. After the first hour of recovery, there were no further significant differences in pain scores either resting in bed or sitting. That the inhibitory effect of ondansetron was restricted to one postoperative hour thereafter. The estimated mean difference was 1.7 (99.7% CI: 0.8, 2.6) cm upon arrival in the PACU and 1.3 (0.5, 2.1) cm 1 h later. Thereafter, pain score remained greater in patients given ondansetron, but not significantly so. The analgesic effect of acetaminophen plus ondansetron on VAS pain scores while resting in bed depended on the measurement time (treatment-by-time interaction \( P < 0.001 \)). Thus, the overall mean difference between the two randomized groups was not evaluated.

Pain scores while sitting were significantly greater in ondansetron patients than those given placebo upon arrival in PACU. The estimated mean difference was 0.6 (99.7% CI: 0.1, 1.0). There was no difference between the two groups at any other measurement times thereafter. The overall mean difference between the two randomized groups was 0.3 (97.5% CI: −0.3, 1.0) for ondansetron minus placebo, \( P = 0.55 \) (Table 2) (Fig. 1).

6.2. Secondary analysis

Median total opioid (tramadol) consumption was 441 [Q1, Q3: 280, 578] mg in the ondansetron group and 412 [309, 574] mg in the placebo group. No difference was observed between the two groups; the estimated ratio of median total opioids consumption was 0.99 (95% CI: 0.81, 1.11) for ondansetron vs. placebo, \( P = 0.95 \). The two groups did not differ on heart rate, blood pressure, oxygen saturation, or respiratory rate during the first 24 h in the PACU (Table 3). Ramsey sedation scores differed significantly, but not by clinically meaningful amounts. The ondansetron group was more likely to receive rescue analgesics, but less likely to experience complications, receive antiemetics, or experience PONV (Table 3).

7. Discussion

The ondansetron group had significantly higher pain scores than the placebo group while resting in bed upon arrival in PACU and 1 h

### Table 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ondansetron (N = 60)</th>
<th>Placebo (N = 60)</th>
<th>ASD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 [46, 54]</td>
<td>49 [44, 57]</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4 [25.8, 31.3]</td>
<td>29.4 [26.8, 33.2]</td>
<td>0.18</td>
</tr>
<tr>
<td>ASA Physical Status II (vs. I, no.)</td>
<td>52 (87)</td>
<td>48 (80)</td>
<td>0.18</td>
</tr>
<tr>
<td>Anesthesia duration, hours</td>
<td>1.7 [1.4, 2.3]</td>
<td>2.2 [1.9, 2.6]</td>
<td>0.66</td>
</tr>
<tr>
<td>Surgery duration, hours</td>
<td>1.4 [1.1, 2.0]</td>
<td>1.9 [1.7, 2.3]</td>
<td>0.70</td>
</tr>
</tbody>
</table>
| ASA = American Society of Anesthesiologists; ASD = absolute standardized difference. * Absolute difference in means or proportions divided by the pooled standard deviation. Any variable with an ASD > 0.20 was considered imbalanced, and was adjusted for in all analyses.

### Table 2

<table>
<thead>
<tr>
<th>VAS pain score</th>
<th>Ondansetron (N = 60)</th>
<th>Placebo (N = 60)</th>
<th>Mean difference (99.7% CI)* (groups 1–2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting in the bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival in the PACU</td>
<td>5.6 ± 1.7</td>
<td>3.8 ± 1.6</td>
<td>1.07 (0.75, 2.59)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>1 h thereafter</td>
<td>5.1 ± 1.6</td>
<td>3.7 ± 1.2</td>
<td>1.31 (0.50, 2.11)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>4 h thereafter</td>
<td>3.7 ± 1.2</td>
<td>3.0 ± 1.3</td>
<td>0.65 (−0.07, 1.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>8 h thereafter</td>
<td>3.2 ± 1.2</td>
<td>2.5 ± 1.1</td>
<td>0.63 (−0.05, 1.31)</td>
<td>0.01</td>
</tr>
<tr>
<td>12 h thereafter</td>
<td>2.7 ± 1.0</td>
<td>2.2 ± 1.0</td>
<td>0.46 (−0.10, 1.02)</td>
<td>0.01</td>
</tr>
<tr>
<td>16 h thereafter</td>
<td>2.0 ± 0.9</td>
<td>1.8 ± 1.0</td>
<td>0.13 (−0.40, 0.66)</td>
<td>0.46</td>
</tr>
<tr>
<td>20 h thereafter</td>
<td>1.6 ± 1.0</td>
<td>1.1 ± 1.0</td>
<td>0.48 (−0.11, 1.07)</td>
<td>0.02</td>
</tr>
<tr>
<td>24 h thereafter</td>
<td>0.8 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>0.34 (−0.10, 0.77)</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall effectd</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>While sitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival in the PACU</td>
<td>9.8 ± 0.6</td>
<td>9.1 ± 0.9</td>
<td>0.57 (0.14, 1.00)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>1 h thereafter</td>
<td>8.8 ± 1.1</td>
<td>8.6 ± 1.0</td>
<td>0.07 (−0.52, 0.66)</td>
<td>0.71</td>
</tr>
<tr>
<td>4 h thereafter</td>
<td>7.5 ± 1.4</td>
<td>7.5 ± 1.4</td>
<td>−0.03 (−0.84, 0.78)</td>
<td>0.91</td>
</tr>
<tr>
<td>8 h thereafter</td>
<td>6.3 ± 1.6</td>
<td>6.1 ± 1.8</td>
<td>0.11 (−0.87, 1.08)</td>
<td>0.74</td>
</tr>
<tr>
<td>12 h thereafter</td>
<td>5.4 ± 1.7</td>
<td>5.1 ± 1.7</td>
<td>0.14 (−0.84, 1.11)</td>
<td>0.67</td>
</tr>
<tr>
<td>16 h thereafter</td>
<td>4.1 ± 1.6</td>
<td>4.2 ± 2.0</td>
<td>−0.27 (−1.28, 0.73)</td>
<td>0.41</td>
</tr>
<tr>
<td>20 h thereafter</td>
<td>3.2 ± 1.5</td>
<td>3.1 ± 1.7</td>
<td>0.05 (−0.88, 0.97)</td>
<td>0.88</td>
</tr>
<tr>
<td>24 h thereafter</td>
<td>2.0 ± 1.3</td>
<td>1.7 ± 1.2</td>
<td>0.32 (−0.40, 1.04)</td>
<td>0.18</td>
</tr>
<tr>
<td>Overall effectd</td>
<td>−</td>
<td>−</td>
<td>0.34 (97.5% CI: −0.32, 1.00)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*a* The overall mean difference between the two randomized groups in the VAS resting in bed was not evaluated (treatment-by-time interaction \( P = 0.001 \)) but in the VAS while sitting was evaluated (treatment-by-time interaction \( P = 0.59 \)).

*b* The corresponding confidence interval was adjusted for multiple comparisons appropriately by Bonferroni correction; the 97.5% CI was reported for the overall effect and 99.7% CI was reported at each assessment time (i.e., 0.025/8).

*d* Statistically significant.
presumably resulted from single-dose administration of a drug with a half-life of 3–4 h and unknown central nervous system clearance [22]. Our findings are also supported by several animal [23–25] and human studies [12,15,26]. Ramirez et al. examined coadministration of ondansetron and acetaminophen in pediatric patients having tonsillectomies. Children given acetaminophen were nearly three times as likely to require morphine (57% vs 21%) to achieve similar PACU pain scores [15]. In pediatrics, opioid consumption was been suggested as a more accurate indicator of pain level [27,28].

Pickering and colleagues compared the efficacy of acetaminophen analgesia in patients having ear surgery who were given tropisetron or placebo [17]. Postoperative pain scores were 30% greater in the tropisetron patients which is consistent with our hypothesis. However, the difference was not statistically significant because inter-individual variability was greater than the investigators anticipated. Their result should thus be considered under-powered rather than truly negative. A further consideration is that while tropisetron is similar to ondansetron, 5-HT3 antagonists differ their anti-serotonergic potential [29,30]. The same authors in a different study used an electrical stimulus as pain model to evaluate pain in healthy volunteers and reported that 5-HT3 antagonists (tropisetron and granisetron) decrease the analgesia of acetaminophen when coadministered [7]. However, our results contrast with several other clinical studies that evaluated similar drug interactions [16,17]. Jokela et al., for example, reported that a single dose of ondansetron did not reduce the analgesic efficacy of acetaminophen in patients recovering from laparoscopic hysterectomy [16]. A plausible explanation relates to their selection of surgical model and methodology. Postoperative pain after laparoscopic procedures is usually short-lived and mild. It is reasonable to assume that acetaminophen, even with its efficacy reduced by ondansetron, nonetheless provided adequate analgesia for the typically mild pain after laparoscopic surgery, thus minimizing possible difference. Another explanation might be the timing of acetaminophen administration and the dose of ondansetron used. In contrast to our study, acetaminophen was given at induction and ondansetron was given at the end of surgery; furthermore, most of their hysterectomies lasted longer than 2 h. The time between acetaminophen and ondansetron might also have been excessive, allowing substantial elimination of acetaminophen before ondansetron was given and thus limiting the drug-drug interaction [16]. This explanation seems consistent with the short-lived effect we observed. And finally, Jokela et al. gave 4 mg ondansetron which is presumably less effective at blocking 5-HT3 receptors than the 8 mg dose we used.

### Table 3
Summary of hemodynamics and complications during the first 24 h of PACU.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ondansetron (N = 60)</th>
<th>Placebo (N = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average of heart rate, beats/min</td>
<td>81 ± 8</td>
<td>83 ± 5</td>
<td>0.12</td>
</tr>
<tr>
<td>Average of systolic BP, mm Hg</td>
<td>128 ± 15</td>
<td>125 ± 14</td>
<td>0.23</td>
</tr>
<tr>
<td>Average of diastolic BP, mm Hg</td>
<td>75 ± 7</td>
<td>74 ± 4</td>
<td>0.19</td>
</tr>
<tr>
<td>Average of MAP, mm Hg</td>
<td>93 ± 9</td>
<td>91 ± 7</td>
<td>0.13</td>
</tr>
<tr>
<td>Average of oxygen saturation, %</td>
<td>98 ± 2</td>
<td>99 ± 2</td>
<td>0.24</td>
</tr>
<tr>
<td>Average of respiratory rate</td>
<td>16 ± 2</td>
<td>16 ± 2</td>
<td>0.67</td>
</tr>
<tr>
<td>Average of Ramsey sedation scale</td>
<td>1.87 ± 0.12</td>
<td>1.93 ± 0.10</td>
<td>0.005</td>
</tr>
<tr>
<td>Number of rescue analgesics, no. (%)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (5)</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (12)</td>
<td>27 (45)</td>
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</tr>
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<td>2</td>
<td>18 (30)</td>
<td>11 (18)</td>
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<tr>
<td>3</td>
<td>14 (23)</td>
<td>5 (8)</td>
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<td>4</td>
<td>10 (17)</td>
<td>6 (10)</td>
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<tr>
<td>5</td>
<td>8 (13)</td>
<td>3 (5)</td>
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</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Number of complications, no. (%)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>51 (85)</td>
<td>31 (52)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (12)</td>
<td>22 (37)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (3)</td>
<td>5 (8)</td>
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<td>3</td>
<td>0 (0)</td>
<td>1 (2)</td>
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</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Number of antiemetics, no. (%)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45 (75)</td>
<td>26 (43)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (18)</td>
<td>24 (40)</td>
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<td>2</td>
<td>3 (5)</td>
<td>7 (12)</td>
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<td>3</td>
<td>0 (0)</td>
<td>2 (3)</td>
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</tr>
<tr>
<td>4</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>PONV, no (%)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>45 (75)</td>
<td>26 (43)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11 (18)</td>
<td>21 (35)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (3)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (3)</td>
<td>8 (13)</td>
<td></td>
</tr>
</tbody>
</table>

Student t or Fisher’s exact Chi-square tests were used.

![Fig. 1. Boxplots of (A) VAS resting in bed and (B) VAS while sitting over the first 24 h in the PACU (N = 120). The first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.](image)
A natural consequence of evaluating hysterectomies is that we enrolled only women. Although sex differences in pharmacokinetics and pharmacodynamics might affect the interaction of ondansetron and acetaminophen [31], it seems likely that our results will largely apply to men. Bandschapp et al. previously showed that coadministration of acetaminophen and tropisetron led to lower plasma concentration of acetaminophen, suggesting a potential pharmacokinetic interaction as both drugs are primarily metabolized by the liver [12]. However, we did not measure the plasma concentrations of our drugs and thus cannot rule out a pharmacokinetic effect rather than the drug interaction we postulate.

In summary, ondansetron significantly decreased the analgesic effect of acetaminophen in the initial postoperative period. Our results thus confirm that acetaminophen analgesia is partially mediated by serotonin receptors. However, the reduction was of marginal clinical importance and short-lived. Clinicians can thus use the combination without anticipating much analgesic impairment.

Author contributions

1. Onur Koyuncu, MD
   - Role: This author helped design the study, conduct the study, and write the manuscript
   - Attestation: This author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

2. Steve Leung, MD
   - Role: This author helped conduct the study, and write the manuscript
   - Attestation: This author reviewed the analysis of the data and approved the final manuscript

3. Jing You, MS
   - Role: This author helped analyze the data and write the manuscript
   - Attestation: This author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

4. Menekse Oksar
   - Role: This author helped conduct the study, and write the manuscript
   - Attestation: This author reviewed the analysis of the data and approved the final manuscript

5. Selim Turhanoglu
   - Role: This author helped conduct the study, and write the manuscript
   - Attestation: This author reviewed the analysis of the data and approved the final manuscript

6. Cagla Akkurt
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   - Attestation: This author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

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