Preemptive Use of Intravenous Acetaminophen, Ketamine or Their Combination in Patients Undergoing Elective Open Abdominal and Urological Surgeries: Effects on Intraoperative and Postoperative Analgesic Requirements

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Abstract

Study Objective: This study was designed to evaluate the effect of preemptive use of intravenous acetaminophen, ketamine or their combination on intraoperative and postoperative analgesic requirements in patients undergoing elective open abdominal and urological surgeries under general anesthesia.

Setting: Beni Suef University Hospital, Egypt.

Patients and Interventions: 80 ASA I-II patients undergoing elective open abdominal and urological surgeries under general anesthesia were randomly allocated into four equal sized groups:

Group I (n=20): Control group, received IV normal saline 20cc as placebo over 15 minutes IV before induction of anesthesia.

Group II (n=20): Received 1 gram acetaminophen over 15 minutes IV before induction of anesthesia.

Group III (n=20): Received IV 0.5mg/kg ketamine diluted in 20cc normal saline 15 minutes before induction of anesthesia.

Group IV (n=20): Received IV 1 gram acetaminophen and 0.5mg/kg ketamine diluted in 20cc normal saline 15 minutes before induction of anesthesia.

Measurements and Main Results: Intraoperative. Heart rate and mean arterial blood pressure: Preinduction, after induction of anesthesia every 15 minutes, intraoperative fentanyl requirements (ug).

Postoperative time to first request of analgesia (minutes), postoperative pain at rest measured at 1,8,16, and 24h postoperatively using (VAS), systolic, diastolic arterial blood pressure, heart rate at 1,8,16, and 24h and analgesic requirements of tramadol 50mg im were recorded.

Intraoperative and postoperative analgesic requirements were statistically significantly lower, and the time to first request of analgesia was statistically significantly longer in group IV than groups I,II and III.

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Postoperative pain at rest (VAS) was statistically significantly lower in group IV than groups I and II.

Postoperative heart rate, systolic and diastolic arterial blood pressure showed no clinical significant differences between the studied groups.

Conclusion: Preemptive use of intravenous combination of IV acetaminophen 1g and 0.5mg/kg ketamine decreased intraoperative and postoperative analgesic requirements and pain score more than the use of preemptive intravenous acetaminophen or ketamine alone or placebo in patients undergoing elective open abdominal and urological surgeries under general anesthesia.

Key Words: Preemptive analgesia – Acetaminophen – Ketamine.

Introduction

POSTOPERATIVE pain control has been improved due to more understanding of pain mechanisms and physiology and the development of new analgesic techniques [1].

A recent meta-analysis has documented that coadministration of non-steroidal anti-inflammatory drugs (NSAIDs) and morphine reduces opioid-related side effects [2] but NSAIDs have numerous contraindications [3]. Acetaminophen has a few contraindications and is relatively free from side effects at clinical doses [4].

Previous studies documented that the use of perioperative acetaminophen has a morphine-sparing effect [5-8], intravenous acetaminophen is used widely for postoperative pain control, very limited evidence supports it use in the preoperative period [9].

In total abdominal hysterectomy, preemptive iv acetaminophen (paracetamol) 1 g provided adequate postoperative pain control, and decreased consumption of morphine [10].
Ketamine a N-methyl-d-aspartic acid (NMDA) receptor antagonist used for perioperative analgesia although there are conflicting results about its efficacy as preemptive analgesic some studies have documented a preemptive effect [11-14] and others have not [15-19].

The aim of this study was to evaluate the effect of preemptive use of acetaminophen and ketamine or their combination compared to placebo (normal saline) on intraoperative and postoperative analgesic requirements in patients undergoing elective open abdominal and urological surgeries under general anesthesia.

**Patients and Methods**

This study was carried out at Beni Suef University Hospital from Jan. 2013 – Sep. 2013 after the approval of institutional review board and ethical committee and obtaining a written informed consent from each patient before operation.

80 patients of both sex undergoing elective open abdominal and urological surgeries under general anesthesia at Beni Suef University Hospital enrolled in this study.

**Inclusion criteria:**
- American Society of Anesthesiologist (ASA) Physical status I-II.
- Age from 18 to 60 years.

**Exclusion criteria:**
- Morbid obese patients.
- A known allergy to the one of study drugs.

**Preparation of the patients:**
The study protocol and the visual analogue scale (VAS) for pain were explained to the patients preoperatively.

**Premedication:**
The patients did not receive any premedication in either the surgical floor or the operation room.

**Monitoring:**
Electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure at 5 minutes intervals were applied.

Patients were randomly assigned into four equal size groups using a closed envelop technique as follows:

Group I (n=20): Control group, received IV normal saline 20cc as placebo over 15 minutes iv before induction of anesthesia.

Group II (n=20): Received 1 gram acetaminophen (perfalgan) over 15 minutes iv before induction of anesthesia.

Group III (n=20): Received IV 0.5mg/kg ketamine diluted in 20cc normal saline 15 minutes before induction of anesthesia.

Group IV (n=20): Received IV 1 gram acetaminophen (perfalgan) and 0.5mg/kg ketamine diluted in 20cc normal saline 15 minutes before induction of anesthesia.

**Anesthetic technique:**
General anesthesia was induced in all patients with i.v. 2-3mg/kg propofol, 2ug/kg fentanyl, 0.5mg/kg atracurium, oral cuffed endotracheal tube, anesthesia was maintained with oxygen 100%, isoflurane 1-2%, additional doses of 0.1mg/kg atracurium, mechanical ventilation with maintenance of endtidal carbon dioxide 35-40mmHg.

At the end of surgery, inhalational anesthetic was discontinued, neuromuscular blockade were reversed with neostigmin 0.04mg/kg and 0.02mg/kg atropine IV, the trachea was extubated when the patient respond to commands, all patient were transferred to PACU where they were monitored for 1 hour. Face oxygen masks were applied and their pain was assessed using the VAS If patient reported a VAS at rest of 2 or higher, tramadol 50mg im was given then 50mg im prn.

The following parameters were evaluated and recorded:
- Patients’s characteristics: Age, sex, ASA, height, weight.
- Heart rate and mean arterial blood pressure: Preinduction, after induction of anesthesia every 15 minutes intraoperative.
- Intraoperative fentanyl requirements (ug).
- Postoperative time to first request of analgesia (minutes).
- Postoperative pain at rest measured at 1,8,16, and 24h postoperatively using (VAS) where zero score corresponds to no pain and 10 to the maximum or worst pain.
- Postoperative systolic, diastolic arterial blood pressure, heart rate at 1,8,16, and 24h.
- Postoperative analgesic requirements: Tramadol 50mg im prn.

**Statistical analysis:**
Data are presented as mean and standard deviation (SD) or numbers as appropriate. Student t-
test: Was used for comparison between means of each two groups, ordinal data were analyzed by Mann-whitney U test. $p$-values $<0.05$ was considered statistically significant.

Sample size was calculated based on a previous study [20] the power of the this study is calculated and was found to be more than 95% using G *power 3.1.5 program, and the a-error level was fixed at 0.05.

**Results**

All patients completed the study. There was no statistical significant differences between the studied groups as regards to patient characteristics and operative data (Table 1).

As regards to intraoperative heart rate, no statistically significant differences between group I and group II.

It was a statistically significant higher in group I than group III from 15 to 60 minutes. It was a statistically significant higher in group I than group IV from preinduction time to75 minutes, 120 minutes and at 165 minutes (Table 2). It was a statistically significant higher in group II than group III from 15 to 60 minutes.

It was a statistically significant higher in group II than group IV from 15 to 90 minutes and at 120 and 165 minutes. It was a statistically significant higher in group III than group IV at 30,75,105,120 minutes and 165 minutes (Table 2).

As regards to intraoperative mean arterial blood pressure, there was no statistically significant differences between group I and group II except at 105 minutes intraoperative.

It was statistically significant higher in group I than group III at 15 minutes and was statistically significant higher in group I than group IV from preinduction to 105 minutes intraoperative.

It was a statistically significant higher in group II than group IV at 15,45,60,75,90,105 minutes. It was a statistically significant higher in group III than group IV at 15,60,75,105 minutes (Table 3).

There was no statistically significant differences between group I and group II as regards to intraoperative fentanyl requirements and time to first request of analgesia but postoperative tramadol requirements was statistically significantly lower in group II compared to group I.

Intraoperative and postoperative analgesic requirements were statistically significantly lower and time to first request of postoperative analgesia was statistically significantly longer in group III compared to group I.

Intraoperative and postoperative analgesic requirements were statistically significantly lower and time to first request of postoperative analgesia was statistically significantly longer in group IV compared to group I (Table 4).

Intraoperative and postoperative analgesic requirements were statistically significantly higher and time to first request of analgesia was statistically significantly shorter in group II compared to group IV.

Intraoperative and postoperative analgesic requirements were statistically significantly higher and time to first request of analgesia was statistically significantly shorter in group III compared to group IV (Table 4).

As regards to postoperative Visual Analogue Scale, it was statistically significantly lower in group II compared to group I except at 16 hours postoperative and was statistically significant lower in group III and group VI compared to group I, and was statistically significant higher in group II compared to group IV, no statistical significance between group III and group IV (Table 5).

There was no statistically significant differences in postoperative heart rate between group I and both group II and III, and there was statistically significant differences between group I and group IV at 8 and 16 hours postoperative, Table (6) and there was a statistically significant differences between group II and group IV at 16 hours, and between group III and group IV at 8 and 16 hours.

There was no statistically significant differences in postoperative systolic arterial blood pressure between group I and group II.

But it was statistically significant lower in group III and group IV compared to group I from 8 to 24 hours postoperative, and was statistically significant higher in group II than group IV at 8 and 16 hours, no statistically significant differences between group III and group IV (Table 7).

There was no statistically significant differences in postoperative diastolic arterial blood pressure between group I and group II, but it was statistically significant lower in group III and group VI compared to group I at 16 hours postoperative and was statistically significant lower in group IV compared to group II and III at 16 hours (Table 8).
### Table 1: Patient characteristics and operative data in the studied groups. Data presented as Mean ±SD, numbers.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=20)</th>
<th>Group II (n=20)</th>
<th>Group III (n=20)</th>
<th>Group IV (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.0±13.6</td>
<td>40.2±13.0</td>
<td>41.3±10.8</td>
<td>43.3±11.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.5±4.6</td>
<td>162.0±5.5</td>
<td>160.2±5.8</td>
<td>160.3±5.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9±11.0</td>
<td>80.8±10.0</td>
<td>75.0±11.9</td>
<td>76.3±11.1</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>7/13</td>
<td>6/14</td>
<td>6/14</td>
<td>8/12</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>8/12</td>
<td>7/11/2</td>
<td>7/13</td>
<td>5/15</td>
</tr>
<tr>
<td>Operation (stone kidney/cholecystectomy/simple nephrectomy)</td>
<td>8/120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>123.75±25.69</td>
<td>124.00±19.7</td>
<td>120.00±19.46</td>
<td>119.25±20.34</td>
</tr>
</tbody>
</table>

Group I: Control group.
Group II: 1 gram acetaminophen IV.
Group III: Ketamine IV 0.5 mg/kg.
Group IV: 1 gram acetaminophen and 0.5 mg/kg ketamine.

No statistically significant differences between the studied groups, *p*-values >0.05.

### Table 2: Intraoperative heart rate (Bpm). Data presented as Mean±SD.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group I (n=20)</th>
<th>Group II (n=20)</th>
<th>Group III (n=20)</th>
<th>Group IV (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinduction</td>
<td>83.1±8.8</td>
<td>86.7±8.9</td>
<td>88.3±7.5</td>
<td>90.4±8.0*</td>
</tr>
<tr>
<td>15 min</td>
<td>89.3±8.6</td>
<td>89.9±5.3†</td>
<td>83.2±5.4*</td>
<td>80.0±6.6‡</td>
</tr>
<tr>
<td>30 min</td>
<td>86.0±6.2</td>
<td>87.2±8.9†</td>
<td>81.3±7.0*</td>
<td>76.2±7.2*‡</td>
</tr>
<tr>
<td>45 min</td>
<td>87.7±8.0</td>
<td>85.1±6.1†</td>
<td>81.0±6.3*</td>
<td>77.6±8.6†</td>
</tr>
<tr>
<td>60 min</td>
<td>85.0±8.6</td>
<td>83.8±7.6†</td>
<td>78.6±6.6*</td>
<td>78.2±8.0*‡</td>
</tr>
<tr>
<td>75 min</td>
<td>84.1±5.5</td>
<td>83.8±8.2</td>
<td>80.7±5.5</td>
<td>74.0±8.1*‡</td>
</tr>
<tr>
<td>90 min</td>
<td>83.1±6.5</td>
<td>82.6±6.9</td>
<td>79.8±6.4</td>
<td>76.4±7.2‡</td>
</tr>
<tr>
<td>105 min</td>
<td>81.3±8.3</td>
<td>81.5±6.8</td>
<td>82.4±6.4</td>
<td>76.7±7.7†</td>
</tr>
<tr>
<td>120 min</td>
<td>81.5±8.4</td>
<td>82.8±7.6</td>
<td>82.7±7.9</td>
<td>74.6±5.6*‡</td>
</tr>
<tr>
<td>135 min</td>
<td>82.7±6.9</td>
<td>73.8±21.9</td>
<td>82.0±3.1</td>
<td>75.3±6.6</td>
</tr>
<tr>
<td>150 min</td>
<td>82.2±6.8</td>
<td>82.5±7.9</td>
<td>83.0±2.6</td>
<td>77.5±10.6</td>
</tr>
<tr>
<td>165 min</td>
<td>79.5±6.4</td>
<td>76.3±5.5</td>
<td>82.0±0.0</td>
<td>64.0±0.0**‡</td>
</tr>
</tbody>
</table>

Group I: Control group.
Group II: 1 gram acetaminophen IV.
Group III: Ketamine IV 0.5mg/kg.
Group IV: IV 1 gram acetaminophen and 0.5mg/kg ketamine.

*p*-values <0.05 is statistically significant.
† Statistically significant differences compared to group I.
‡ Statistically significant differences compared to group II.
§ Statistically significant differences compared to group III.

Bpm = Beat per minute.

### Table 4: Intraoperative and Postoperative analgesic requirements, TFA. Data presented as Mean±SD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=20)</th>
<th>Group II (n=20)</th>
<th>Group III (n=20)</th>
<th>Group IV (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl (ug)</td>
<td>200.0±16.2</td>
<td>185.0±23.5‡</td>
<td>150.0±42.9*</td>
<td>122.5±38.0*§</td>
</tr>
<tr>
<td>TFA (min)</td>
<td>19.5±13.2</td>
<td>19.3±7.7§</td>
<td>27.3±10.1*</td>
<td>43.5±7.6§‡</td>
</tr>
<tr>
<td>Tramadol (mg)</td>
<td>160.0±26.2</td>
<td>125.0±30.3*</td>
<td>122.5±30.2*</td>
<td>82.5±33.5*§</td>
</tr>
</tbody>
</table>

Group I: Control group.
Group II: 1 gram acetaminophen.
Group III: Ketamine IV 0.5mg/kg.
Group IV: IV 1 gram acetaminophen and 0.5mg/kg ketamine.

*p*-values <0.05 is statistically significant.
† Statistically significant differences compared to group I.
‡ Statistically significant differences compared to group II.
§ Statistically significant differences compared to group III.

### Table 5: Postoperative visual analogue scale, data presented as Mean±SD.

<table>
<thead>
<tr>
<th>VAS</th>
<th>Group I (n=20)</th>
<th>Group II (n=20)</th>
<th>Group III (n=20)</th>
<th>Group IV (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h</td>
<td>4.8±1.1</td>
<td>4.1±0.8*</td>
<td>3.5±0.9*</td>
<td>3.0±0.9*‡</td>
</tr>
<tr>
<td>8h</td>
<td>3.6±0.5</td>
<td>2.9±0.6*</td>
<td>2.5±0.5*</td>
<td>2.4±0.7*§</td>
</tr>
<tr>
<td>16h</td>
<td>2.7±0.5</td>
<td>2.3±0.7§</td>
<td>2.0±0.8*</td>
<td>1.6±0.7*§</td>
</tr>
<tr>
<td>24h</td>
<td>2.6±0.7</td>
<td>2.2±0.7§</td>
<td>1.3±0.4*</td>
<td>1.2±0.4*§</td>
</tr>
</tbody>
</table>

Group I: Control group.
Group II: 1 gram acetaminophen.
Group III: Ketamine IV 0.5mg/kg.
Group IV: IV 1 gram acetaminophen and 0.5mg/kg ketamine.

*p*-values <0.05 is statistically significant.
Preemptive analgesia is a strategy for administration of analgesics before the surgical stimulus to attenuate postoperative pain [21].

Acetaminophen (Paracetamol) is a non-opioid agent, it acts on the central nervous system by inhibition of central cyclooxygenase, It also suggested to inhibit both isoforms of cyclooxygenase enzymes, it also has an indirect effect on the serotonergic system [10].

Previous studies showed conflicting results about the efficacy of IV acetaminophen as a preemptive analgesic agent. Its effective for relief of somatic pain as in orthopedic surgeries more than the visceral pain of abdominal surgeries which can be explained by the fact that large component of visceral pain consists of afferent fibers that are normally unresponsive to stimuli and become activated only in the presence of inflammation but it has less pronounced anti-inflammatory effects [9].

A study done by Arici et al., [10] showed that iv acetaminophen 1g given 30 minutes before induction of anesthesia provided adequate postoperative analgesia in patients undergoing total abdominal hysterectomy.

It was reported that preemptive IV acetaminophen 15mg/kg given half an hour preoperatively in adult patients undergoing lower limb surgery under spinal anesthesia, reduced postoperative 24 hours meperidine consumption and resulted in a lower pain scores than in patients given preventive IV acetaminophen 15mg/kg and 100mL of IV normal saline before skin closure and longer time to initial analgesic requirement in the preemptive and preventive acetaminophen groups than the control group who received 100mL of intravenous normal saline as a placebo [22].

In contrast, preemptive use of 1 g intravenous paracetamol 30 minutes before incision in abdominal surgery does not reduce the analgesic consumption or postoperative pain intensity [23], also in patients underwent lumbar disc surgeries the administration of 1g i.v. paracetamol 15 minutes
before the induction or 15 minutes before the end of operation has no preemptive analgesic effect [24].

Noxious inputs may cause N-methyl-D-aspartate (NMDA) glutamate receptor activation and central sensitization, analgesic intervention before the noxious stimulus may attenuate sensitization and acute pain [25].

In laparoscopic gynecologic surgery, preoperative IV ketamine (0.15mg/kg) has a preemptive analgesic effect [11].

Preemptive ketamine 0.5mg/kg ketamine followed by a ketamine infusion (10 micrograms.kg-1.min-1) decreased postoperative analgesic consumption in patients underwent abdominal surgery [14].

While in patients underwent total mastectomy preoperative ketamine 0.15mg/kg has no preemptive analgesic effect [16].

It was reported that IV ketamine 0.4mg/kg failed to demonstrate a preemptive analgesic effects in patients underwent abdominal hysterectomy [17]. Also preoperatively 1mg/kg ketamine did not reduce postoperative pain compared to 1mg/kg dose of ketamine given at the end of surgery [18] and preoperative ketamine 0.5mg/kg in patients underwent cesarean section had no preemptive analgesic effect [26].

In contrast, a subanesthetic dose of intravenous ketamine bolus of (0.25-0.5mg/kg) followed by an infusion of (0.125-0.25mg/kg per h) reduced mechanical hyperalgesia and improved postoperative analgesia in patients scheduled for rectal adenocarcinoma surgery under combined epidural/general anesthesia [27], also intravenous ketamine 0.15mg/kg, 30 minute before surgery followed by ketamine 2mcg/kg/min infusion decreased postoperative pain and morphine consumption after open renal surgery [28] It was reported that intravenous ketamine 0.5mg/kg before incision followed by 24-h infusion (2 microg xkg (-1) x min(-1)) reduced postoperative morphine consumption after total hip arthroplasty [29].

A study in patients undergoing laparoscopic cholecystectomy showed that the combination of low-dose ketamine 0.15-mg/kg plus diclofenac sodium 1mg/kg diluted in 100-mL isotonic saline i.v. 20 minutes before the induction of anesthesia had a significantly lower pain score and longer time to postoperative analgesic request compared with patients receiving placebo and ketamine 0.15mg/kg alone [20].

**Conclusion:**

Preemptive use of intravenous combination of iv acetaminophen 1g and 0.5mg/kg ketamine decreased intraoperative and postoperative analgesic requirements and pain score more than the use of preemptive intravenous acetaminophen or ketamine alone or palcebo in patients undergoing elective open abdominal and urological surgeries under general anesthesia.

**References**


