Propacetamol Vs. Tramadol For Post-Operative Pain Management After Urologic Surgery

S Aghamir, M Mojtahedzadeh, F Alizadeh, H Khalili, M Sadeghi, A Najafi, K Rezaie, F Rafizadeh, F Shabani

Citation

Abstract
Paracetamol (acetaminophen) is a safe and effective analgesic that is used for relieving mild to moderate pain. Tramadol, a synthetic opioid of aminecyctohexanol group, is an analgesic with central effect and weak opioid agonistic properties. This drug is also effective on noradrenergic and serotonergic neurotransmission. The aim of this study was to compare the analgesic and side effects of Propacetamol (Prodafalgan™, UPSA, France) and Tramadol (Aburaihan Pharmaceutical, Iran) after urologic open surgeries. A total number of 40 surgical patients were prospectively randomized into two equal groups of 20 and were entered into single blinded clinical trial. Anesthesia protocol was similar for all patients. Pain intensity was measured based on a 4-point verbal rating scale (VRS). VRS was obtained before analgesic administration (T0) and at 0.5, 1.5, 3, 4.5, 6, 12, 18 and 24 hours.

Patients received either Tramadol 100 mg IV or Propacetamol 2 gr IV at T0 and then 50 mg Tramadol or 1.5 gr Propacetamol at 6, 12, 18 and 24 hours if pain was present.

Pain relief score was measured after 24 hours based on a 5 point scale. The results of this study showed that Propacetamol could be considered as a safe alternative post-operatively for pain management; however its use for severe pain management leads to inefficient pain control, necessitating supplementary analgesics.

INTRODUCTION
Paracetamol (acetaminophen) is a safe and effective analgesic that is used for relieving mild to moderate pain (\cite{1}). Oral and rectal formulations of this drug are used as adjunct parts of balanced analgesic regimens perioperatively (\cite{2,3,4}).

Propacetamol is the water–soluble prodrug of paracetamol that can be used if increased efficacy or more rapid onset of action is desired. In the blood, this drug is easily broken to paracetamol and diethylglycin under the effect of plasma esterases (\cite{5}).

Each gram of Propacetamol is there for equal to 0.5 gram of paracetamol. The latter substance then passes the blood brain barrier easily, exerting its central analgesic effect (\cite{6,7}).

The tolerability of Propacetamol is almost similar to that of paracetamol. Acetaminophen, however, is most effective for mild to moderate pain. On the other hand, the use of opioids may some times be limited because of the concern regarding their side effects, especially respiratory depression. In this situation, Tramadol could be a suitable alternative.

Tramadol, a synthetic opioid of aminecyctohexanol group, is an analgesic with central effect and weak opioid agonistic properties. This drug is also effective on noradrenergic and serotonergic neurotransmission (\cite{8}). When administered intravenously, Tramadol has a potency which is equal to pethidine and 1/10 of morphine (\cite{9}).

In patients older than 1 year it is tolerated well and has no remarkable adverse effect on hemodynamic and respiratory profiles (\cite{10}).

The aim of this study was to compare the analgesic effect and side effects of Propacetamol (Prodafalgan™, UPSA, France) and Tramadol (Aburaihan Pharmaceutical, Iran) after urologic open surgeries.

MATERIAL AND METHODS
A total number of 40 patients were prospectively...
randomized into two equal groups of 20 and were entered into this singles blinded clinical trial.

The study was approved by investigational review board at Tehran University of Medical Sciences.

All the patients were informed about the trial, however they did not know which analgesic have been prescribed for them.

Inclusion criteria were age ≥18 years, post–operative pain, uncomplicated anesthesia, ASA class I or II, consciousness which was required for co-operation and open urologic surgery with either abdominal or flank incision including open prostatectomy, RPLND, radical cystectomy, pyelolithotomy, pyeloplasty, nephrectomy and nephrolithotomy.

Exclusion criteria were pregnancy or lactation, drug or alcohol abuse, known allergy to Tramadol or acetaminophen or any contraindications for opioids use, history of renal, hepatic or pulmonary disease, hemorrhagic disorders and taking monoamine oxidase inhibitors or discontinuation of their use within the previous 2 weeks.

Anesthesia protocol was similar for all patients consisting of metoclopramide 10 mg IV, 2) fentanyl 1 mg/kg IV, 3) atropine 0.6 mg IV as required to maintain heart rate above 50 beats/min 4) propofol 2.5 mg/kg IV 5) atracurium 0.6 mg/kg followed by 0.3 mg/kg increments as necessary 6) oxygen, nitrous oxide and isoflurane to maintain anesthesia via tracheal tube/ mechanical ventilation. Supplementary fentanyl 0.25 – 0.5 mg/kg was given intravenously as required.

Initial dose of analgesic was given as soon as patient complained of pain. Pain intensity was measured based on a 4–point verbal rating scale (VRS) that included 4 categories: 0 = no pain, 1 = slight pain, 2 = moderate pain and 3 = severe pain. VRS was obtained before analgesic administration (T) and at 0.5, 1.5, 3, 4.5, 6, 12, 18 and 24 hours.

Patients received either Tramadol 100 mg IV or Propacetamol 2 gr IV at T and then 50 mg Tramadol or 1.5 gr Propacetamol at 6, 12, 18 and 24 hours if pain was present. The maximum total dose for Propacetamol and Tramadol were 8 g/d and 300 mg/d, respectively.

Additional pain was managed with the supplemental morphine 5mg IV, repeated as required, not exceeding 0.2 mg/kg.

Pain relief score was measured after 24 hours based on a 5 point scale: 0 = no pain relief, 1 = unsatisfactory pain relief, 2 = fair, satisfactory pain relief, 3 = good pain relief and 4 = complete pain relief.

Laboratory data Including CBC, BUN, Cr, Na, K, PT, PTT, Alb, ALT, AST and FBS were obtained pre and 24 hours post-operatively. Venous blood gas (VBG) was also analyzed just before and 15 minutes after the first dose to detect the possible adverse effect the drug on ventilation (PvCO₂).

Tramadol was administered as IV injection of 2 ml of drug during 2-3 minutes and Propacetamol was dissolved in 100 ml of normal saline and infused ever 15 minutes. All the patients in either group received an injection of 2ml of distilled water and / or infusion of 100 ml of normal saline for the study blindness.

Demographic characteristics were compared across treatment groups using two-sided Student’s t-test. The use of rescue medication was compared using a two-sided Fisher exact test. P< 0.05 was considered statistically significant.

Results are presented as the number of patients (%) or mean (SD) when appropriated.

**RESULTS**

There were no significant differences between the two groups in term of their age distribution, weight, ASA score and physical status (table 1). The mean duration of surgery was similar for both groups.

**Figure 1**

Table 1: This table show demographic variables of the two groups of patients. ASA: American Society of Anesthesiologists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tramadol</th>
<th>Propacetamol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.7 ± 21.6</td>
<td>43.3 ± 23.7</td>
<td>P&gt; 0.05</td>
</tr>
<tr>
<td>Weight</td>
<td>64.1 ± 7.2</td>
<td>66.6 ± 8.3</td>
<td>P&gt; 0.05</td>
</tr>
<tr>
<td>ASA (III) score</td>
<td>19/1</td>
<td>17/2</td>
<td>P&gt; 0.05</td>
</tr>
</tbody>
</table>

Pain intensity scores were comparable at any time (table2) but patients in the Propacetamol (P) group needed significantly more morphine than the Tramadol (T) group to relieve their pain (8.50 ± 5.15 vs. 4.75 ± 4.9; P=0.025).

After the first dose of analgesic, 3 patients (15 %) in the T group and 10 patients (50%) in the P group needed a rescue medication; the difference was significant (P= 0.041)

Neither one of the patients were over sedated in either group.
Two patients in the P group and 9 patients in the T group developed an emetic event (nausea and / or vomiting); which the difference was significant (p=0.035).

After 24 hours, the mean pain relief score was 2.70 ± 1.30 and 2.30 ± 1.34 for T and P group, respectively (P=0.345); 14 Patients (70 %) in the T group and 10 patients (50 %) in the P group had good / complete pain relief (P= 0.731).

None of the laboratory parameters showed any significant changes 24 hours post-operatively. Only one patient in the P group showed a less than 3 times rise in ALT and AST which was normalized shortly after discontinuation of the drug without any permanent sequelae. In neither group PaCO₂ had changed significantly 15 minutes after the first dose; this value was also comparable between the two groups 15 minutes after the first dose (table 3).

**Table 2:** This table shows pain intensity score after operation. The values represented as Mean±SD. T represent Time and subscript show hours after surgery.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tramadol</th>
<th>Propacetamol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>2.20±0.83*</td>
<td>2.00±0.97*</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₁₀</td>
<td>0.8±1.15</td>
<td>1.50±1.23</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₁₅</td>
<td>1.7±0.81</td>
<td>1.80±0.83</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₂₀</td>
<td>1.4±0.68</td>
<td>1.60±0.88</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₂₅</td>
<td>1.3±0.85</td>
<td>1.40±0.68</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₃₀</td>
<td>1.15±0.58</td>
<td>1.25±0.63</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₄₀</td>
<td>1.00±0.72</td>
<td>1.2±0.69</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₅₀</td>
<td>0.95±0.75</td>
<td>1.10±0.718</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>T₆₀</td>
<td>0.80±0.83</td>
<td>1.05±0.99</td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

*Mean±SD

**Table 3:** This table shows PaCO₂ changes after drug administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>45.92±6.057</td>
<td>49.21±12.3</td>
<td>0.085</td>
</tr>
<tr>
<td>Propacetamol</td>
<td>46.30±8.544</td>
<td>47.75±9.000</td>
<td>0.264</td>
</tr>
<tr>
<td>P value</td>
<td>0.896</td>
<td>0.667</td>
<td></td>
</tr>
</tbody>
</table>

*Mean±SD

**DISCUSSION**

The emotional distress by a surgical experience is aggravated by the severity of post–operative pain.

Pain management after operation is one of the most important challenges which not only provides certain comfort for the patient, but facilitates early mobilization. Post–operative pain is a classic indication for systemic analgesics use (11). Opioids are the primary treatment for patients with moderate to severe pain but these drugs are not always easily tolerated and are associated with dose dependent side effects.

Propacetamol (Pro-dafalgan) is the water-soluble formulation of paracetamol with negligible side effects that its efficacy for treating post–operative pain has been investigated in several studies.

Ranucci et al compared the effect of Tramadol, Propacetamol and ketorolac after cardiac surgery. Patients received either 60 mg of ketorolac, 2gr of Propacetamol or 200 mg of Tramadol after early extubation. Pain assessment with verbal rating scale (VRS) showed less pain intensity in those who were treated with ketorolac compared with that of Propacetamol. Patients treated with Tramadol did not differ significantly with the other two groups. Patients with severe pain according to VRS were more in the Propacetamol group than the other two groups. In the Tramadol group PaCO₂ was significantly higher than the other two groups, although this difference was clinically unimportant. They concluded that Tramadol and ketorolac were better choices for pain management in these patients (12).

Oral acetaminophen plus IV Propacetamol and oral plus IV Tramadol were also compared for pain management after tonsillectomy by Pendiville et al. They had treated patients with either 30 mg/kg of Propacetamol or 3 mg/kg of Tramadol before induction of anesthesia and acetaminophen suppository (15 mg/kg) or Tramadol drops (2.5 mg/kg) afterwards and at home. Although side effects of nausea and vomiting were comparable between the two groups, pain relief was considerably higher in the Tramadol group (13).

Dejonckheere et al also assessed the efficacy of Tramadol and Propacetamol for pain after thyroidectomy and found that although both needed equal supplementary morphine, pain relief in the Tramadol group was better than that of the other group and although more patients in the Tramadol group experienced nausea and vomiting during the first 2 hours after operation, the difference during the whole time of the study was not significant (14).

Hoogewijs et al, on the other hand, had found no difference between Propacetamol, petidine, Tramadol and diclofenac in terms of pain control after single peripheral injuries (15).

In our study, although pain intensity score was comparable between the two groups at any time, patients in the Propacetamol group needed considerably higher dose of
morphine for pain control (8.50 ± 5.15 vs. 4.75 ± 4.9; P = 0.025) than Tramadol group. It seems that equal pain control in the Propacetamol group was achieved at the expense of more morphine consumption. Need for rescue medication was also more in the Propacetamol group, as 10 patients (50%) in this group needed additional morphine compared to 3 patients (15%) in the Tramadol group (P= 0.041).

Side effects of nausea and vomiting were comparable in Hoogewijs’, Pendeville’s and Dejonckheere’s studies between Tramadol and Propacetamol groups.

In this study, we observed significantly higher rate of emetic events in the Tramadol group (9 (45 %) vs. 2(10 %) patients; P = 0.035).

Verchere et al compared the analgesic efficacy of Propacetamol, Propacetamol plus Tramadol and Propacetamol plus nalbuphine after craniotomy and because of ineffectiveness of analgesia in the Propacetamol group, inclusions was terminated after the eighth patient (16).

One concern regarding the use of opioids is respiratory depression. In the Hoogewijs’ study, patients had considerably higher PaCO$_2$ in the Tramadol compared to the Propacetamol group (48 ± 6 mmHg vs. 42.2 ± 3.4 mmHg) (16). In our study PvCO$_2$ 15 min after administration of the first dose did not differ significantly with that of the baseline in neither of the groups (P= 0.085 and 0.244 for the Tramadol and Propacetamol groups, respectively).

PvCO$_2$ was also comparable between the two groups after the first dose (P = 0.667).

Although the mean pain relief score after 24 hours was similar in both groups (2.7 ± 1.3 and 2.30 ± 1.34 for Tramadol and Propacetamol groups, respectively; P = 0.345); the higher dose of morphine consumption in the Propacetamol group should be kept in mind when considering this similarity.

Hepatic damage, a concern with the use of paracetamol, was not encountered with doses of Propacetamol up to 8 grams per day.

**CONCLUSION**

Propacetamol could be considered as a safe alternative post-operatively for pain management; however its use for severe pain management leads to inefficient pain control, necessitating supplementary analgesics.

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**CORRESPONDENCE TO**

Hossein Khalili, Department of Pharmacotherapy, Tehran University of Medical Sciences, Tehran, IRAN E-mail: khalilil@tums.ac.ir Fax and phone: 098-021-66959090

**References**


Author Information

S. K. Aghamir, M.D.
Assistant Professor, Department of Urology, SINA Hospital, Tehran University of Medical Sciences

M. Mojtahedzadeh, Pharm D, BCPS
Associated Professor, Department of Pharmacotherapy, SINA Hospital, Tehran University of Medical Sciences

F. Alizadeh, M.D.
Department of Urology, SINA Hospital, Tehran University of Medical Sciences

H. Khalili, Pharm D
Department of Pharmacotherapy, Faculty of Pharmacy, Tehran University of Medical Sciences

M. Sadeghi, M.D.
Department of Anesthesiology, SINA Hospital, Tehran University of Medical Sciences

A. Najafi, M.D.
Department of Anesthesiology, SINA Hospital, Tehran University of Medical Sciences

K. Rezaie
Intensive Care Nurse, SINA Hospital, Tehran University of Medical Sciences

F. Rafizadeh
Intensive Care Nurse, SINA Hospital, Tehran University of Medical Sciences

F. Shabani
Intensive Care Nurse, SINA Hospital, Tehran University of Medical Sciences