June 2009

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Comparison of analgesic effect of tramadol alone and a combination of tramadol and paracetamol in day-care laparoscopic surgery

Mohammad Ali and Fauzia A. Khan

**Background and objective** To compare the analgesic efficacy of tramadol alone (1.5 mg kg\(^{-1}\)) with a tramadol (1 mg kg\(^{-1}\)) and paracetamol combination in day-care laparoscopic patients.

**Methods** The analgesic efficacy of intravenous tramadol alone (1.5 mg kg\(^{-1}\)) (group T) was compared with a combination of intravenous tramadol (1 mg kg\(^{-1}\)) and oral paracetamol 1 g (group TP) in 60 day-care laparoscopic patients in a prospective randomized double-blind clinical trial in a tertiary care hospital. Intraoperative haemodynamic responses and postoperative visual analogue scores were used to assess the analgesic efficacy.

**Results** Only one patient (in group T) received a single dose of rescue analgesia intraoperatively. The highest pain scores were recorded at 30 min postoperatively in both groups, and rescue analgesia was needed in eight patients in group T and in 13 patients in group TP (P = 0.08). The incidence of moderate-to-severe nausea was high in group T (P = 0.001).

**Conclusion** We conclude that reducing the dose of tramadol to 1 mg kg\(^{-1}\) and combining it with paracetamol 1 g orally decreased the incidence of side effects of tramadol without reducing analgesic efficacy. *Eur J Anaesthesiol* 26:475–479 © 2009 European Society of Anaesthesiology.

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Laparoscopy and dye test is a common day-care surgical procedure. It is associated with pain of moderate intensity. Narcotic analgesics when used for providing analgesia have multiple side effects (nausea, vomiting, constipation, respiratory depression and delayed recovery), which make these drugs less suitable for day-care patients [1].

Tramadol is a cyclohexanol derivative with weak mu agonist, opioid-like activity. It also inhibits the reuptake of norepinephrine and promotes the release of serotonin. The synergy of monoaminergic and opioid activity achieves analgesic effects. It is indicated for moderate-to-severe pain. Its advantages over other narcotic drugs are that it causes less respiratory depression than morphine and codeine and does not share the propensity of nonsteroidal anti-inflammatory drugs (NSAIDs) to provoke asthma, gastrointestinal mucosal damage and renal impairment [2–4]. Common side effects of tramadol are nausea, vomiting, dizziness, drowsiness and dry mouth.

Paracetamol is a metabolite of phenacetin, which has also been used for mild-to-moderate pain. It is a cyclooxygenase inhibitor resulting in the inhibition of prostaglandin synthesis predominantly in the central nervous system rather than in peripheral tissues. In general, it is free of side effects in dosages used for acute pain management, but a mild increase in hepatic enzymes is seen occasionally, which is reversible [5]. Tramadol alone or in combination with paracetamol may be considered as an alternative analgesic for day-care laparoscopic surgeries. Combining analgesics may provide greater analgesia than can be achieved by increasing doses of individual components. At the same time, the combination may improve tolerability by using lower doses of each medication. Combinations are most effective when individual agents act synergistically, and data from animal studies suggest that tramadol and paracetamol have synergistic activity [6]. If paracetamol is combined with lower doses of tramadol and the same or even better analgesia may be achieved as with tramadol alone because of synergism, this may also decrease the incidence of side effects of tramadol. The objective of this study was to compare the analgesic efficacy of tramadol alone (1.5 mg kg\(^{-1}\)) with a tramadol (1 mg kg\(^{-1}\)) and paracetamol (1 g) combination in day-care laparoscopic patients.

**Methods** After approval from the ethics review committee and written informed consent, 60 ASA I or II women of child-bearing age (18–40 years), presenting for laparoscopy and...
dye test, were recruited in the study. The methodology used for recruitment was convenience sampling.

Patients with a history of allergy or hypersensitivity to tramadol or paracetamol or both, history of epilepsy, chronic usage of analgesic drugs or monoamine oxidase inhibitors were excluded. The sample size of 56 patients was based on detecting a difference of one unit on the visual analogue scale (VAS), keeping \( \alpha \) error at 0.05 and \( \beta \) error at 0.2. Sixty patients were enrolled. They were divided into two groups, ‘T’ and ‘TP’, of 30 patients each. Patients were randomized for treatment allocation. Sixty slips of paper were taken, and 30 were labelled as ‘group T’ and the remainder as ‘group TP’. These slips were mixed and were placed in opaque envelopes and were picked randomly by an assistant anaesthetist who was not involved in taking observations during the study.

All patients were premedicated with oral midazolam (7.5 mg) 1 h preoperatively and received a further oral tablet which was either placebo (group T) or paracetamol (1 g) (group TP) 30 min before induction. The calculated dose of tramadol for each group was prepared in a 5 ml syringe, and the total volume was made up to 5 ml by adding distilled water by a person unconnected to the methodology and then at 10, 30 and 60 min intervals. The last reading was taken at 4 h from induction of anaesthesia (on the day-care unit). Pethidine (10 mg) was administered intravenously as rescue analgesia if the patient complained of moderate-to-severe pain (score of 4 or above on VAS of 1–10). Postoperative analgesia was administered by nursing staff blinded to treatment groups, and the number of doses received was noted.

Nausea was assessed by verbal descriptive scale (no nausea, mild, moderate and severe nausea), and the episodes of both nausea and vomiting were noted. Metoclopramide (10 mg) was given intravenously if a patient complained of moderate or severe nausea or had vomiting. Other side effects such as dizziness, sweating, headache and dry mouth were also noted. All patients were observed for a total of 4 h starting from the time of induction.

### Statistics

Data were entered on Statistical Package for Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, Illinois, USA). VAS scores for pain and haemodynamic responses were analysed using repeated-measures analysis of variance. The independent samples \( t \)-test was used for comparing means of age and weight of patients and duration of anaesthesia. A \( P \) value of less than 0.05 was considered significant. The chi-squared test was used to compare the number of patients in each group who received rescue analgesia and to compare the incidence of side effects.

### Results

Patients’ characteristics and duration of anaesthesia are given in Table 1. A decrease in HR compared with the baseline was observed in both groups. The maximum

<table>
<thead>
<tr>
<th>Group T (n = 30)</th>
<th>Group TP (n = 30)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>30.9 ± 5.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.0 ± 6.1</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>57.4 ± 12.7</td>
</tr>
</tbody>
</table>

Values are means ± SD. * \( P = 0.03 \).
decline in group T was 14% at 20 min after incision and 10% at 40 min after incision in group TP. HR was comparable in both groups at comparable time intervals with no statistically significant difference (Fig. 1).

Fluctuations in systolic BP were within 15% of baseline in both groups. Mean systolic BP was comparable in groups T and TP at comparable time intervals except before incision and 1 min after incision (Fig. 2). Changes in diastolic BP as compared with baseline were within 20% in both groups. Mean diastolic BP was comparable in groups T and TP in most readings except at 1 min and 20 min after incision (Fig. 2). Only one patient in group T received a single dose of rescue analgesia intraoperatively. None of the patients in group TP required rescue analgesia intraoperatively.

Eight patients in group T and 13 patients in group TP had pain scores of more than 3, that is, VAS score 4–6 (\(P = 0.08\)), and they all received rescue analgesia (Table 2). Postoperatively, none of the patients had severe pain (VAS score >6).

The highest pain scores were recorded at 30 min postoperatively in the recovery room in both groups (Table 2). In group T, mean pain score was 2.43 (SD ± 1.77), and, in group TP, 3.13 (SD ± 1.25) at 30 min. Mean pain scores were comparable at different time intervals in both groups except at 4 h, group T, 0.33; group TP, 0.80 (\(P = 0.03\)) (Table 3).

Moderate-to-severe nausea in the recovery room was present in 30% (\(n = 9\)) of patients in group T compared with no patients in group TP (\(P = 0.001\)). Other side effects such as vomiting, dry mouth and dizziness were more frequent in group T, but the difference was not statistically significant (Table 4).

### Discussion

Although laparoscopic surgery results in substantially less severe discomfort than the corresponding open procedure, pain associated with laparoscopy can be considerable. Prevention and treatment of pain relies on local anaesthesia, NSAIDs and opioid analgesics, often used in combination. Caudal block [7], inguinal block [8], local analgesic effect of tramadol and paracetamol Ali and Khan 477 Analgesic effect of tramadol and paracetamol Ali and Khan 477

<table>
<thead>
<tr>
<th>Time intervals</th>
<th>Group T ((n = 30))</th>
<th>Group TP ((n = 30))</th>
</tr>
</thead>
<tbody>
<tr>
<td>On arrival in recovery room</td>
<td>0.30 ± 0.7</td>
<td>0.43 ± 1.0</td>
</tr>
<tr>
<td>At 10 min</td>
<td>1.60 ± 1.0</td>
<td>1.50 ± 1.0</td>
</tr>
<tr>
<td>At 30 min</td>
<td>2.43 ± 1.7</td>
<td>3.13 ± 1.2</td>
</tr>
<tr>
<td>At 60 min</td>
<td>1.87 ± 1.2</td>
<td>2.23 ± 1.0</td>
</tr>
<tr>
<td>At 4 h</td>
<td>0.33 ± 0.6</td>
<td>0.80 ± 0.9*</td>
</tr>
</tbody>
</table>

Values are means ± SD. *\(P < 0.05\).
intensity, tramadol was used in a dose of 1.5 mg kg\(^{-1}\) in various procedures, depending upon the expected severity of pain [12,15]. As pain associated with laparoscopy and dye test is expected to be moderate in young women undergoing laparoscopic surgery, who generally have a higher incidence of nausea and vomiting than other population groups [22]. Another contributory factor may be the use of pethidine as rescue analgesia (five patients who had moderate or severe nausea or vomiting had received rescue analgesia). A statistically significant difference between the two groups emerged regarding their body weight despite randomization (\(P=0.03\)), but we administered tramadol according to per kilogram body weight, therefore this difference is less likely to affect the efficacy of the drug.

Postoperatively, patients mostly from the combination group complained of either mild or moderate pain, but the difference was not statistically significant. None of the patients experienced severe pain in either group.

By combining drugs with different mechanisms of action and pharmacokinetic profiles, one can enhance efficacy even though lower doses of individual drugs are used [17]. Various studies have suggested enhanced analgesic efficacy using multimodal analgesic strategies compared with unimodal analgesic treatment so that one can limit side effects, reduce postoperative pain and analgesic requirements and facilitate an earlier return to normal activities. Many studies have confirmed the efficacy and tolerability of a combination of paracetamol and tramadol in both acute and chronic pain [18–20].

Combinations of tramadol and paracetamol have demonstrated genuine synergy in animal studies [6]; therefore, in our present study, we reduced the dose of tramadol to 1 mg kg\(^{-1}\) in combination with 1 g of paracetamol. Intraoperatively, none of the patients required rescue analgesia in the combination group (TP). Postoperatively, none of the patients had severe pain (VAS score \(>6\)). This again confirms its analgesic efficacy.

The only side effect that had a significantly higher incidence in group T was moderate-to-severe nausea. Safety data for tramadol have recently been summarized by Coissmann et al. [21]. The following side effects have been observed after the use of tramadol. The most frequent adverse events were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness or fatigue (2.3%), sweating (1.9%), vomiting (1.7%) and dry mouth (1.6%). Adverse events that occurred in less than 1% but more than 0.1% of patients were somnolence, hypotension, flushing, upset stomach, constipation, nausea and vomiting, sedation, sleep disorder, pruritus, abdominal pain, diarrhoea, tachycardia and local irritation. The frequency of nausea and vomiting was higher in our study than that reported with the use of tramadol. The higher frequency may be due to the fact that the patients in our study were young women undergoing laparoscopic surgery, who generally have a higher incidence of nausea and vomiting than other population groups [22]. Another contributory factor may be the use of pethidine as rescue analgesia (five patients who had moderate or severe nausea or vomiting had received rescue analgesia). A statistically significant difference between the two groups emerged regarding their body weight despite randomization (\(P=0.03\)), but we administered tramadol according to per kilogram body weight, therefore this difference is less likely to affect the efficacy of the drug.

### Table 4 Comparison of side effects between groups T and TP

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group T (n = 30)</th>
<th>Group TP (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-to-severe nausea</td>
<td>9</td>
<td>0*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Shivering</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sweating</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are number of patients experiencing side effects. *\(P=0.001\).
There is no single well accepted and widely applicable method of measuring intraoperative pain. In our study, intraoperative pain was assessed by haemodynamic responses. Profound physiological changes often accompany pain, for example sympathetic response resulting in increase in HR and BP, but studies indicate that these physiological and endocrine events occurring concurrently with pain may be a general response to stress and not unique to pain [23]. Both our study groups were comparable in attenuating the haemodynamic responses.

We assessed postoperative pain with a VAS, which is a valid tool for measurement of pain but has certain limitations [24]. A VAS measures pain as a unidimensional experience. It quantifies only the intensity of pain and not the quality of pain. Patients may be very random in how they place their mark on the scale. The VAS is not easily administered to patients who have perceptual–motor problems.

Mean pain scores were comparable between the two groups at almost all time intervals. None of the patients had a score of more than 6. More patients in group TP (43%) than in group T (27%) had a pain score more than 3 (VAS score 4–6), but this difference is statistically insignificant (P = 0.08).

In conclusion, tramadol alone (1.5 mg kg⁻¹) and the tramadol (1 mg kg⁻¹) with paracetamol (1 g) combination provided adequate intraoperative and postoperative analgesia with haemodynamic stability in day-care gynaecological laparoscopic patients. Reducing the dose of tramadol to 1 mg kg⁻¹ and combining it with paracetamol (1 g) orally decreased the incidence of side effects of tramadol without reducing analgesic efficacy.

Acknowledgement
The authors acknowledge Mr Salman Sabir and Mr Iqbal Azam (statisticians) for their help in statistical aspects of this study.

References
23 Christensen P, Brandt MR, Rem J. Influence of extradural morphine on the physiological and endocrine events occurring concurrently with pain may be a general response to stress and not unique to pain [23]. Both our study groups were comparable in attenuating the haemodynamic responses.