Rectal paracetamol has a significant morphine-sparing effect after hysterectomy

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We have evaluated the morphine-sparing effect of rectal paracetamol during the first 24 h after abdominal hysterectomy in a placebo-controlled, double-blind study. We studied 72 patients receiving patient-controlled analgesia (PCA) with i.v. morphine after a standardized anaesthetic, allocated randomly to receive rectal paracetamol 1.3 g, diclofenac 50 mg or placebo, after wound closure and at 8 and 16 h. Suppositories were blinded by the hospital pharmacy. Study violations excluded data from seven patients. Patient data, morphine doses during anaesthesia and recovery, and sedation and nausea scores were comparable. Mean morphine consumption during PCA was 35.0 (SD 20.4) mg, 32.7 (27.4) mg and 54.9 (28.3) mg in the paracetamol (n=24), diclofenac (n=20) and placebo (n=21) groups, respectively (P<0.05). Morphine sparing during PCA for paracetamol and diclofenac (36% vs 40% over 24 h) was significant from 4 h. Global scores of average pain over 24 h were lower after diclofenac compared with paracetamol (P<0.01) and placebo (P=0.08). We conclude that rectal paracetamol was an efficacious adjuvant analgesic after regular dosing.

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Addition of a non-steroidal anti-inflammatory drug (NSAID) to an opioid for treating moderate and severe pain after surgery can improve the quality of analgesia, reduce postoperative opioid consumption by more than 30% and may be associated with a reduction in opioid side effects.1–5 However, there are contraindications and risks associated with the use of NSAID during the perioperative period.6 This may limit the options for pain management and reduce the quality of pain relief in many patients.

Paracetamol is an alternative analgesic recommended for routine use in postoperative pain management. It can be given to almost all patients, irrespective of age and underlying disease.6 Oral paracetamol has significant efficacy and reduces opioid requirements when treating postoperative pain.7,8 Rectal preparations of paracetamol are also available for use when oral delivery is inappropriate. However, paracetamol is commonly considered to be a weak analgesic by medical and nursing staff. For this reason it is likely to be underused in adult postoperative pain management and reserved for the oral treatment of mild pain. Further, the lack of published evidence of efficacy after rectal delivery for managing moderate and severe postoperative pain in adults may exacerbate this situation. This contrasts with the well-documented efficacy and opioid-sparing effect of NSAID after surgery. We performed a prospective, double-blind, randomized study to evaluate the morphine-sparing effect of rectal paracetamol in patients at risk of moderate and severe postoperative pain.

Patients and methods

After obtaining approval from the Hospital Ethics Committee and written informed consent, we studied 72 patients, ASA I or II, aged 25–60 yr, weighing 40–100 kg, undergoing elective abdominal hysterectomy. Exclusion criteria included a history of allergy or contraindications to the use of paracetamol or NSAID, concurrent use of either opioids or NSAID during the week before surgery, and inability to use the apparatus for patient-controlled analgesia (PCA). Each patient was instructed before surgery on the use of the PCA, the 100-mm visual analogue scales (VAS) for reporting pain and the verbal rating scales (VRS 0–10) for reporting pain relief and nausea.

All patients received a standardized anaesthetic. Anaesthesia was induced with propofol 2–3 mg kg⁻¹, tracheal intubation was performed after administration of atracurium 0.5 mg kg⁻¹ and the lungs were ventilated mechanically with isoflurane and 70% nitrous oxide in oxygen. Analgesia comprised morphine 0.15 mg kg⁻¹. Increments of morphine and atracurium were given as required. Cyclizine 50 mg
i.v. was given at the time of wound closure and neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

Patients were allocated randomly to one of three equal groups to receive rectal paracetamol 1.3 g, diclofenac 50 mg or placebo suppositories given after wound closure (time = 0) and at 8 and 16 h. Paracetamol suppositories were manufactured by the hospital pharmacy using paracetamol 1.3 g in Witepsol H15 in a 4-g mould. Placebo suppositories were manufactured to look identical to the diclofenac and paracetamol suppositories. The contents were known only to the research pharmacist (who had no direct involvement in the study) and were revealed to other staff after data collection.

Nursing staff in the recovery ward treated pain with increments of i.v. morphine titrated to patient comfort. PCA (Graseby PCAS) delivering morphine 1 mg with a 5-min lockout and no background infusion was then started. Nausea and vomiting were treated with prochlorperazine 12.5 mg i.m. as required. If alternative analgesia or other treatment was required, a study violation was recorded and the patient was withdrawn from the study. Nursing staff recorded pain (100 mm VAS) and level of sedation (four-point categorical scale: none, mild, moderate or severe) at 8 and 16 h after the first suppository had been given. All patients were visited by one of the authors at 24 h and asked to assess their worst and average pain (using global 24 h scores, VRS 0–10). Morphine consumption during anaesthesia, in the recovery ward and during PCA, and incidence of vomiting were also recorded.

A sample size of 72 patients (three groups of 24) was calculated to be required to detect a 30% reduction in PCA morphine consumption (the primary outcome measure) at α=0.05 with a power of 0.8 based on previous relevant clinical data from our hospital. Data were analysed using ANOVA, chi-square or Kruskal–Wallis tests as appropriate. Paired comparisons were made using the Student’s t and Mann–Whitney U tests if overall differences were significant at the 5% level; P<0.05 was considered statistically significant.

Results

Data from seven patients were excluded from analysis because of study violations: one returned to theatre with haemorrhage (placebo), two requested withdrawal because of inadequate analgesia (placebo) and pruritus (diclofenac), and four had missing data (one placebo, three diclofenac). Table 1 shows patient characteristics and clinical data for the remaining 65 patients. Groups were comparable in patient data and morphine consumption during anaesthesia and in the recovery ward.

Patients who received paracetamol and diclofenac used significantly less morphine during PCA than those who received placebo (mean 24 h dose 35 (SD 20.4) mg vs 32.7 (27.4) mg vs placebo; P<0.05). Mean morphine sparing during PCA for paracetamol and diclofenac was 36% and 40%, respectively. Figure 1 shows cumulative PCA morphine consumption. Patients who received paracetamol and diclofenac used less morphine than those who received placebo, from 2 h after starting PCA.

There were no significant differences in pain or sedation scores at 8 and 16 h, or global 24 h scores for worst pain, average pain relief and average nausea. Global 24 h average pain scores were significantly different overall (P=0.015) and lower in patients who received diclofenac compared with the other groups (P=0.008 vs paracetamol; P=0.08 vs placebo).

Table 1  Patient and clinical data (mean (SD or range), median [range] or number) in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol (n = 24)</th>
<th>Diclofenac (n = 20)</th>
<th>Placebo (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43.7 (28–57)</td>
<td>40.3 (29–47)</td>
<td>42.4 (33–52)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.1 (12.4)</td>
<td>69.6 (9.8)</td>
<td>68.8 (13.2)</td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During anaesthesia</td>
<td>10.8 (2.3)</td>
<td>10.9 (3)</td>
<td>9.6 (3.6)</td>
</tr>
<tr>
<td>In recovery ward</td>
<td>10 (6.6)</td>
<td>9.6 (8)</td>
<td>11.1 (8.4)</td>
</tr>
<tr>
<td>From PCA (0–24 h)</td>
<td>35 (20.4)</td>
<td>32.7 (27.4)</td>
<td>54.9 (28.3)</td>
</tr>
<tr>
<td>Pain VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 h</td>
<td>25 [1–96]</td>
<td>25 [0–69]</td>
<td>32 [92–69]</td>
</tr>
<tr>
<td>16 h</td>
<td>22 [8–94]</td>
<td>30 [0–84]</td>
<td>35 [6–99]</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pain relief</td>
<td>80 [40–100]</td>
<td>80 [30–100]</td>
<td>70 [40–100]</td>
</tr>
<tr>
<td>VRS over 24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average nausea VRS over 24 h</td>
<td>28 [0–90]</td>
<td>20 [0–90]</td>
<td>40 [0–100]</td>
</tr>
<tr>
<td>Vomiting (n %)</td>
<td>5 (21)</td>
<td>2 (10)</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

Fig 1 Cumulative morphine consumption (mean, SD) during patient-controlled analgesia. Significantly different from placebo: *P<0.05, **P<0.01 for paracetamol and †P<0.05 for diclofenac.
Discussion

We have demonstrated that rectal paracetamol given regularly had significant analgesic efficacy in the management of pain during the first 24 h after major surgery in a group of female patients. The magnitude of the morphine-sparing effect was comparable with that of diclofenac. As oral paracetamol also has demonstrable efficacy for treating moderate and severe postoperative pain (greater than oral paracetamol also has demonstrable efficacy for treating effect was comparable with that of diclofenac. As oral opioids such as codeine phosphate 60 mg and tramadol 100 mg), it has an undeserved reputation as a weak analgesic for postoperative pain management.

A recent placebo-controlled study evaluating the analgesic effect of paracetamol and ibuprofen for hysterectomy found no analgesic- or opioid-sparing effect with either drug. However, in this study single oral doses were used, given 1 h before operation. As these analgesics have relatively short plasma elimination half-lives, this study design may not have been appropriate for demonstrating significant postoperative analgesic effects.

Although our previous clinical experience had suggested that rectal paracetamol was a useful adjuvant analgesic in adult patients after surgery, we were surprised by the magnitude of the morphine-sparing effect. A study using the i.v. formulation of paracetamol (propacetamol, licensed in France) demonstrating an opioid-sparing effect of 37% when given regularly during the first 24 h of PCA after orthopaedic surgery. However, the absolute bioavailability of rectal paracetamol may be as low as 30–40% in healthy volunteers and 80% of that of oral tablets. There is evidence of a dose-related analgesic effect in adult volunteers using i.v. paracetamol and a relationship between plasma paracetamol concentration and analgesic response in children. Further, rectal paracetamol doses of 40 mg kg⁻¹ may be necessary in children to achieve ‘therapeutic’ plasma concentrations, considered to be 10–20 μg ml⁻¹ for an antipyretic effect. Therefore, rectal paracetamol in conventional doses may be expected to have a relatively poor analgesic- and opioid-sparing effect. This assumption may be one reason why rectal paracetamol is not used commonly in adults after surgery and trauma.

However, our study implies that plasma concentrations after regular rectal paracetamol 1.3 g were sufficient to achieve opioid sparing comparable with that of i.v. paracetamol and NSAID such as diclofenac. This suggests that opioid sparing may not be related directly to the magnitude of plasma concentrations or may have a ceiling at low concentrations after paracetamol. A lack of published data on paracetamol kinetics and analgesic effects in postoperative pain management, particularly after rectal delivery in adult patients, points to a need for further research. This knowledge may be used to optimize the rectal delivery of paracetamol in this patient population.

Our study also indicates that a single rectal dose of 1.3 g has important efficacy, as morphine use in the paracetamol group was less than that in the placebo group at 2 h after starting PCA (P<0.05). This corresponded to a time approximately 3–4 h after the first dose of paracetamol. I.v. paracetamol has been shown previously to have significant opioid-sparing activity after 4 h and data from a human volunteer study recorded the peak analgesic effect of i.v. paracetamol at approximately 2.5 h. Therefore, giving rectal paracetamol as early as possible after induction of anaesthesia may maximize its analgesic effect in the immediate postoperative period.

We noted that rectal diclofenac may have been associated with better analgesia than paracetamol (and placebo). It is difficult to interpret this observation as our study sample size was calculated to detect differences in morphine consumption between treatment and placebo, not differences between the two treatment groups or other variables. Whereas the analgesic properties of paracetamol are likely to result solely from a central effect, diclofenac, previously classified as a peripherally acting analgesic, also has central activity. This may explain differences in the quality of analgesia with each drug. However, we measured only pain intensity and not other attributes of pain. It is also possible that the low bioavailability of rectal paracetamol, although sufficient to produce significant opioid sparing, may have reduced overall analgesic efficacy compared with diclofenac, which has rapid rectal absorption. The analgesic efficacy of rectal paracetamol in adults may be improved by using higher doses, as recommended in children.

Our results suggest that rectal paracetamol should be considered an analgesic adjuvant with comparable opioid-sparing activity to NSAID. As paracetamol can be given to almost all patients, we recommend that rectal paracetamol be considered for routine use in all patients at risk of moderate and severe pain during the perioperative period and after trauma when oral delivery is inappropriate. Although the i.v. preparation is not widely licensed or available for perioperative use, it may also have a role in patients where both oral and rectal routes are inappropriate. The probable additive analgesic effect when given with an NSAID such as diclofenac suggests that a combination of both drugs should also be considered routinely for acute pain management. This requires further evaluation in adults.

References

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