Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department

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ABSTRACT

Objective To compare the clinical effectiveness of intravenous paracetamol with intravenous morphine in patients with moderate to severe traumatic limb pain.

Methods This randomised, double-blind pilot study was conducted in an urban UK emergency department. Patients between 16 and 65 years old with isolated limb trauma and in moderate to severe pain (pain score of 7 or more) received either 1 g intravenous paracetamol or 10 mg intravenous morphine sulphate over 15 min. The primary outcome measure was pain score measured on a visual analogue scale at 0, 5, 15, 30 and 60 min after commencing drug administration. The requirement for rescue analgesia and the frequency of adverse reactions were also recorded.

Results 55 patients were recruited over 10 months. There was no significant difference in analgesic effect between the paracetamol and morphine groups at any time interval. There was no significant difference in the rescue analgesia administered, but there were significantly more adverse reactions in the morphine group.

Conclusion Intravenous paracetamol appears to provide a level of analgesia comparable to intravenous morphine in isolated limb trauma. Further larger studies are required.

INTRODUCTION

Pain management is one of the most important concepts in emergency care.

Traditionally, morphine has been the mainstay of treatment in patients with isolated limb trauma and moderate to severe pain. However, morphine has several undesirable side effects including sedation, nausea and respiratory depression. It is also a controlled drug which can result in a delay to administration, or limit its availability in some settings. The prospect of a non-sedating analgesic with the efficacy of an opiate, but without the constraints of a controlled drug, is therefore alluring.

Intravenous paracetamol received a UK licence in May 2004, but its use has been confined primarily to anaesthetic practice. Prior to May 2004 the prodrug propacetamol (2 g bioequivalent to 1 g of paracetamol) was available, but the use of propacetamol was limited by its local irritant side effects.

A previous study found that after wisdom tooth extraction the analgesic effect of intravenous propacetamol was indistinguishable from that of intramuscular morphine. Following orthopaedic surgery intravenous paracetamol has also been used successfully, and propacetamol has been shown to provide a similar analgesic effect to intravenous ketorolac. These results were not replicated in patients following thyroid surgery, where intravenous tramadol provided a better quality of analgesia than intravenous propacetamol. When administered with an opiate, a morphine sparing effect is seen, but this does not translate into a decrease in morphine-related adverse effects.

A single-blind emergency department study of 160 patients presenting with an isolated peripheral injury found that intravenous propacetamol, tramadol and diclofenac were all equally effective. This is the first published study to compare intravenous paracetamol with intravenous morphine for isolated limb trauma in the emergency department.

METHODS

We completed a randomised, double-blind, prospective pilot study in the emergency department of the Bristol Royal Infirmary. This UK department sees 60,000 adult patients per year.

All doctors, nurses and emergency nurse practitioners in the department were educated regarding the trial. Prior to study commencement, 60 identical phials of either 1 g of intravenous paracetamol or 10 mg of intravenous morphine sulphate were randomised at manufacture and consecutively numbered, thereby blinding both investigator and patient.

Patients with isolated limb trauma and a pain score of 7/10 or greater were identified at triage as being potentially eligible, and then underwent further assessment via a single sheet of inclusion and exclusion criteria to determine their final eligibility (see box 1).

Participants were offered verbal information about the study as well as a written information sheet. Written consent was then obtained. Patients declining to take part were administered intravenous morphine according to the emergency department’s usual practice.

After informed consent patients were administered the next consecutively numbered phial containing the study drug. The drug was infused over 15 min. Data were collected at baseline and 5, 15, 30, 45 and 60 min after the infusion was commenced. The data collected were: heart rate, blood pressure, respiratory rate, oxygen saturation (and supplemental oxygen required), Glasgow Coma Scale, pain score, local skin irritation and presence of nausea. Adverse reactions were recorded in the following situations:

- Systolic blood pressure <90 mm Hg
- Respiratory rate <10 breaths per minute
- Glasgow Coma Scale <13
Inclusion criteria
- Isolated limb trauma
- Moderate to severe pain, with initial verbal pain score of 7 or more
- Age >15 and < 66 years
- Estimated weight >50 kg

Exclusion criteria
- Chest pain
- Glasgow Coma Scale <15
- Allergy to morphine or paracetamol
- Known liver disease, or patient clinically jaundiced
- Major trauma
- Known pregnancy
- Breast feeding
- Patients requiring an immediate limb-saving procedure
- Patients in extreme distress
- Communication difficulties (foreign language, prior confusion) preventing informed consent or cooperation with pain scoring
- Oxygen saturation <95%
- Anaphylaxis

The primary outcome measure was the pain score measured using a previously validated 100 mm visual analogue scale (VAS). A reduction of 15 mm or more on VAS scoring has been shown to represent a clinically significant reduction in pain.6 Secondary outcome measures were the requirement for rescue analgesia, any adverse reaction, and patient satisfaction measured on a five-point Likert scale.

If after the initial infusion the patient’s pain relief was judged to be inadequate, intravenous morphine titrated to effect was used as ‘rescue analgesia’. If the patient complained of nausea, intravenous metoclopramide was offered as an antiemetic to those older than 21 years. This reflects the emergency department’s standard practice.

If the patient was discharged following the study they were advised to take no more than 3 g of paracetamol in the next 24 h. If admitted, an inpatient drug chart was written so that no more than 3 g of paracetamol could be administered over the next 24 h. Further intravenous morphine was prescribed as required. No further follow-up was required once the patient had left the emergency department.

Sample size
As noted above, the minimum clinically significant difference on a 100 mm VAS has been shown to be 15 mm.9 Assuming a SD of 15 mm and using a two-group, two-sided t-test (setting a at 0.05 and β at 0.8), 21 patients per group are required to detect a difference of 15 mm between groups. Allowing for dropouts and incomplete data collection we aimed to recruit 30 patients per group.

Statistical analysis
Descriptive analysis was undertaken using the functions of the Excel computer program. Pain scores in the two groups were compared using simple parametric statistics (t-tests); other outcome measures were compared using \( \chi^2 \) tests.

RESULTS
Fifty-five patients were recruited to the study over a 10-month period. Table 1 shows the baseline characteristics of the two randomisation groups and table 2 shows the pain score in each group at all time intervals. No significant difference in analgesic effect was seen between the paracetamol and morphine groups at any time point.

Eight patients in each group required rescue analgesia (\( p=0.95 \) on \( \chi^2 \) testing: no significant difference), but there were significantly more adverse reactions in the morphine group (eight patients) compared to the paracetamol group (two patients; \( p=0.03 \) on \( \chi^2 \) testing).

Patient satisfaction is shown in table 3. No significant difference was found between the two groups (\( p=0.44 \) on \( \chi^2 \) testing).

DISCUSSION
We have shown that the analgesic properties of intravenous paracetamol are similar to those of intravenous morphine in acute traumatic limb pain. A larger multicentre emergency department trial is warranted.

Our results are compatible with previous research indicating the potential effectiveness of intravenous paracetamol when used postoperatively.4–6 The one previous trial of intravenous paracetamol in the emergency department showed it to be equivalent to non-steroidal anti-inflammatory drugs given intravenously,4 which have in turn been demonstrated to be superior to intravenous opioids (pethidine) when given for renal colic in an emergency department setting.10 On this basis we felt that it was justified to use intravenous morphine as the comparison treatment, and because this is the current ‘gold standard’ for acute pain management in the emergency department.

The age restrictions applied to the study group were calculated deliberately. It could be argued that the elderly would benefit more from a non-sedating analgesic, but we were concerned that the standard comparison of 10 mg of morphine over 15 min would have an unacceptably high rate of adverse events in older adults. However, even with this selected group, significantly more adverse events occurred in the morphine arm.

Table 1 Baseline characteristics of the two randomisation groups

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol group</th>
<th>Morphine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>38 (16 to 64)</td>
<td>35 (16 to 62)</td>
</tr>
<tr>
<td>Median</td>
<td>36 years</td>
<td>34 years</td>
</tr>
<tr>
<td>Site of injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Lower limb</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Paracetamol group (n = 28) Mean (SD) VAS score</th>
<th>Morphine group (n = 27) Mean (SD) VAS score</th>
<th>p Value on Student t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76.4 (15.0)</td>
<td>70.1 (9.9)</td>
<td>0.16 (NSD)</td>
</tr>
<tr>
<td>15</td>
<td>69.9 (17.8)</td>
<td>61.6 (19.8)</td>
<td>0.13 (NSD)</td>
</tr>
<tr>
<td>30</td>
<td>63.5 (22.3)</td>
<td>55.0 (29.7)</td>
<td>0.19 (NSD)</td>
</tr>
<tr>
<td>45</td>
<td>59.7 (23.5)</td>
<td>49.7 (26.9)</td>
<td>0.14 (NSD)</td>
</tr>
<tr>
<td>60</td>
<td>52.9 (27.4)</td>
<td>44.0 (22.6)</td>
<td>0.28 (NSD)</td>
</tr>
</tbody>
</table>

VAS, visual analogue scale; NSD, no significant difference.
It could be argued that morphine is better titrated to effect, and indeed this is our usual practice, but it was clearly impractical to adopt this approach within the trial design. Titration is also time-consuming, and one of the potential advantages of intravenous paracetamol is the use of a standard adult dose with limited side effects and none of the restrictions of a controlled drug.

The results for patient satisfaction show a trend towards improved satisfaction with morphine when compared to paracetamol. However, this was not statistically significant and a larger study would be needed to definitively answer this question. Morphine is an anxiolytic as well as an analgesic, and satisfaction with morphine may therefore be related to effects beyond analgesia alone.

Perfalgan (a readily available 1 g intravenous paracetamol solution made by Bristol-Myers Squibb) costs £1.59 a phial, while proprietary morphine sulphate 10 mg/ml costs only £0.19. This difference in price needs to be taken into account, but may be offset by the reduced side effects of intravenous paracetamol and easier administration.

While the results from this research are promising, it is only a small and single-centre pilot study. It also took longer to complete than initially anticipated, but we do not believe this significantly undermines the results. The trial stopped recruiting at 55 rather than 60 patients due to the expiry date on the trial drugs.

**CONCLUSION**

Intravenous paracetamol appears to provide a level of analgesia comparable to intravenous morphine in isolated limb trauma, while causing less side effects than morphine. A larger multi-centre trial is necessary to definitively establish the role of intravenous paracetamol within the analgesic ladder for this patient group.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the NHS ethics committee. RED reference number 07/H0106/118.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**REFERENCES**


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