A DOUBLE-BLIND COMPARISON OF THE RELATIVE EFFICACY, SIDE EFFECTS AND COST OF BUPRENORPHINE AND MORPHINE IN PATIENTS AFTER CARDIAC SURGERY

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The analgesic efficacy, side effects and cost of administration of regimens of intravenous buprenorphine and intravenous morphine were compared in a randomized double-blind trial performed during the first 24 h after cardiac surgery. Seven patients received buprenorphine by intermittent intravenous injection and six received morphine by continuous infusion. Both these regimens provided good analgesia for the entire 24 h period, with only mild pain at rest and moderate pain on vigorous coughing. Both regimens also produced mild respiratory depression but this was not of clinical importance: the mean arterial $P_{CO_2}$ in both groups was less than 45 mmHg after extubation.

The major difference between drugs in the clinical setting was the ease of administration. Buprenorphine had no narcotic code restriction and could be given by intermittent intravenous injection, whereas morphine required checking and handling as a restricted drug and administration by continuous intravenous infusion. When labour and material costs were computed, over the first 24 postoperative hours, it cost $19.76 per patient to administer morphine, but only $3.16 to administer buprenorphine. Thus the use of buprenorphine injections for the first 24 h after cardiac surgery produced pain relief and respiratory depression comparable to that produced by a morphine infusion, but with a significant cost saving in terms of labour and materials.

Key words: analgesics, anaesthesia, heart surgery, narcotic analgesics, morphinans.

Introduction

Morphine is a widely used, powerful narcotic analgesic agent. However, its convenience of use is compromised by restrictions imposed as a scheduled drug, side effects on the respiratory and cardiovascular systems$^{1-3}$ and short duration of action. The latter features make continuous intravenous infusion the preferred method of administration in postoperative patients,$^{4,5}$ especially those with an unstable circulation.$^1$ Buprenorphine is a non-scheduled, synthetic alkaloid with actions parallel to narcotic opiates,$^6$ which has been extensively used in surgical practice.$^7$ A long duration of action ($8-10$ h)$^{7,8}$ and minimal haemodynamic side effects make it effective and safe even when given by bolus intravenous injection to patients with an unstable circulation, such as those recovering from cardiac surgery.$^9$

The aim of this study was to make a prospective double-blind comparison of the analgesic efficacy and side effects of buprenorphine given by intermittent intravenous injection, and morphine given by continuous intravenous infusion in patients during the first 24 h after cardiac surgery.

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ANALGESIC PROTOCOLS

The protocols, normalized for bodyweight, are shown in Table 2. To maintain blinded conditions, all patients receiving active buprenorphine injections (supplied by Reckitt & Colman Ltd) also received a placebo infusion, and those receiving an active morphine infusion also received placebo injections. All study participants, including the principal observer (MR), remained blinded during the study. Treatment packs were prepared and held in the hospital pharmacy according to a coded randomization sequence. Double-blind conditions were maintained until completion of the analysis of results.

Table 2. Drug schedule

<table>
<thead>
<tr>
<th>Drug</th>
<th>Premedication Induction Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.3 mg i.m. 0.6 mg i.v. 0.35 mg i.v.</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg i.m. 20 mg i.v. 3 mg statim i.v. then i.v. infusion 0.5–6.0 mg/h</td>
</tr>
</tbody>
</table>

Doses shown are for a 70 kg patient.

After the doses given at induction of anaesthesia, no additional doses of the trial drugs were given during the operation. In the postoperative period, analgesic drug dosage commenced with the onset of moderate pain either at rest or on coughing. Increments of analgesic dosage were given as required, provided the patient's arterial PCO2 level was less than 50 mmHg. To preserve double-blind conditions, on each occasion the infusion rate was increased an intravenous bolus injection was given simultaneously. In any one patient, only one of these contained an active drug. All adjustments to analgesic dosage and all measurements were made by the principal observer (MR) throughout the 24 h postoperative study period.

ANAESTHESIA AND SURGERY

In addition to the trial drugs, patients received the following anaesthetic drugs: premedication, hyoscine 0.2 mg i.m.; induction, methohexitone; maintenance, nitrous oxide, oxygen and halothane and, if required, further doses of methohexitone. All patients received a long-acting muscle relaxant (pancuronium) on induction which was reversed with neostigmine and atropine when the patients returned to the cardiac intensive care unit. Postoperatively, all patients were nursed in the intensive care unit for the 24 h study period. All had a central venous catheter and a radial arterial line. On return from the operating theatre, all patients were mechanically ventilated.

ASSESSMENT OF PAIN AND DEPTH OF COUGH

The study period was the first 24 h after surgery. Observations of severity of pain were made by the principal observer every 30 min while the patients were mechanically ventilated, and 2 hourly while breathing spontaneously.

Subjective assessments of pain were made using the 'pain light' system described by Nayman. This comprised an array of five differently coloured lamps operated by a handset. Each lamp corresponded to a different degree of pain: none, mild, moderate, severe, intolerable. At each observation period, the patient was asked to indicate the severity of pain by pressing one of the buttons on the handset, which illuminated the appropriate lamp. Assessments of pain were made at rest and during coughing. Every 2 h after extubation, each patient was asked to cough as deeply as possible. An assessment was made on a four-point scale of the depth of the cough achieved and the patient was asked to indicate the level of pain during coughing. Patients cannot cough effectively while intubated, thus depth of cough cannot be assessed. Therefore, at each observation period, patients who were intubated were assigned an arbitrary score of zero for depth of cough.

On the morning of the first postoperative day, which was on average 16 h after surgery, the physiotherapist, who had no knowledge of which analgesic drug each patient was receiving, assessed and recorded on a 10 point scale the overall ability of each patient to cough, move and breathe deeply.

ASSESSMENT OF RESPIRATION

While each patient was intubated, arterial PCO2 was measured after the patient had been disconnected from the ventilator and allowed to breathe 100% oxygen. Prior to disconnection, the ventilator was adjusted to bring arterial PCO2 within the range 36–44 mmHg. Then, after 5 min of spontaneous respiration, arterial PCO2 was measured. While the intubated patient was breathing spontaneously, endtidal PCO2 was measured continuously using a Datex Model CD-102, end-tidal CO2 analyser. (Datex, Helsinki, Finland). If end-tidal PCO2 exceeded 55 mmHg at any time, an arterial blood gas sample was taken and the patient immediately reconnected to the ventilator. During these procedures, arterial PO2 remained above 150 mmHg at all times.

Patients were extubated when they fulfilled all the following criteria: stable cardiovascular system for 2 h; active gag reflex; arterial PCO2 less than 45 mmHg when breathing spontaneously for 20 min;
vital capacity greater than 10 ml/kg bodyweight; patient responding to name being spoken.

After extubation, 2 hourly measurements of arterial \( P_{CO_2} \) were made. Each measurement was preceded by a 10 min period of undisturbed rest. The following criteria were used to assess the respiratory depressant effects of both analgesic regimens: the group mean arterial \( P_{CO_2} \) at each observation time; the highest arterial \( P_{CO_2} \) value recorded in each patient after extubation; the length of time for which each patient required mechanical ventilation.

OTHER SIDE EFFECTS

Careful note was made of any instances of nausea or vomiting. Two hourly recordings were made of arterial blood pressure, heart rate and right atrial pressure. Conscious state was assessed and recorded every 2 h on the following four point scale: responding only to touch (0); very drowsy (1); drowsy (2); and fully awake (3).

COSTING OF DRUG ADMINISTRATION

The costs of administering both analgesic regimens over the 24 h observation period were estimated by an independent time-and-motion assessor from the Health Commission of Victoria. Costing encompassed the cost of the drugs and the cost of the labour and equipment involved in drug administration. The cost of each drug was calculated by multiplying the average dose of drug administered by the unit price of the drug.

For morphine, equipment costed included a flask of intravenous fluid, an intravenous giving set, a burette, and a precision drip regulator (Dial-a-flow; Sorenson Manufacturing Company, USA). For buprenorphine, only needles and syringes were costed. Labour costs were estimated by multiplying the salary cost per minute of a trained nursing sister by the total time taken over the 24 h postoperative period to set up, refill and regulate a morphine infusion, or the time taken to draw up and administer intravenous injections of buprenorphine.

STATISTICAL METHODS

Results are expressed as the mean ± standard error of the mean. Statistical analyses were performed using the analysis of variance for a split-unit design[10] for pain scores and \( P_{CO_2} \) and the \( t \)-test for duration of intubation.

Results

ANALGESIA

Both protocols met the clinical needs of patients for analgesia. There was no instance of severe pain requiring non-blinded analgesic supplement. Over the 24 h study period, patients in the buprenorphine group received a mean of 0.56 ± 0.16 mg of buprenorphine; that is, an average of 1.7 injections. Patients in the morphine group received a mean of 54.2 ± 5.3 mg of morphine. Figure 1 shows the mean pain scores at rest and on coughing for both groups over the 24 h observation period. Pain at rest was only mild on average in both groups, with no significant between-group difference (\( F = 1.1; P > 0.25 \)). The mean resting pain score over the whole 24 h period was 0.53 ± 0.16, in the buprenorphine group and 0.78 ± 0.18 in the morphine group.

Pain on coughing was moderate on average in both groups, with no significant between-group difference (\( F = 0.10; P > 0.5 \)). The mean pain score on coughing over the 24 h period was 1.7 ± 0.23 in the buprenorphine group and 1.8 ± 0.20 in the morphine group.

Figure 2 shows the assessments of the patients' ability to cough. The mean depth of cough improved steadily in both groups over the 24 h observation period with no significant between-group difference (\( F = 0.52; P < 0.5 \)). The mean depth of cough over the whole 24 h period was 1.5 ± 0.36 in the buprenorphine group and 1.3 ± 0.13 in the morphine group. The physiotherapist's assessment of each patient's overall ability to cough, move and breathe deeply on the morning of the first postoperative day also did not show any difference between the two groups.

![Figure 1](image-url)
Time after operation

Fig. 2 Mean depth of cough (± s.e.m.). Buprenorphine (O---O); morphine (●--●).

RESPIRATION

Figure 3 shows the mean values for arterial \( P_{\text{CO}_2} \) for both groups over the 24 h observation period. Initially, without ventilatory assistance, both groups had high mean arterial \( P_{\text{CO}_2} \) levels. However, after the sixth postoperative hour, the mean arterial \( P_{\text{CO}_2} \) in both groups was below 45 mmHg with no significant between-group difference \( (F = 2.07; P < 0.2) \). The mean arterial \( P_{\text{CO}_2} \) over the whole 24 h period was 45.0 ± 0.41 mmHg in the buprenorphine group and 42.8 ± 1.44 mmHg in the morphine group. After extubation, an arterial \( P_{\text{CO}_2} \) of 50 mmHg or more was recorded in three patients in each group. The highest \( P_{\text{CO}_2} \) of 56 mmHg was observed in a patient in the morphine group.

The time requirement for intubation and mechanical ventilation was similar in both groups (Fig. 3). There was no significant difference between the mean duration of intubation in the buprenorphine group, 5.8 ± 0.97 h, and the morphine group, 4.7 ± 0.40 h, \( (r = 0.966; P > 0.4) \).

OTHER SIDE EFFECTS

Nausea was experienced by four patients in each group. Four patients in the buprenorphine group vomited, in one instance repetitively. No patient in the morphine group vomited. Hypotension requiring inotropic drug support occurred in two patients in the morphine group. No cardiovascular side effects were observed in the buprenorphine group.

Immediately after return from the operating theatre patients in both groups were assessed on average as 'very drowsy'. Over the 24 h observation period conscious state improved steadily in both groups. At 24 h, all patients were assessed as 'awake'. There was no significant difference between the mean conscious state score in the buprenorphine group, 2.2 ± 0.21, and the morphine group, 2.3 ± 0.15 \( (F = 0.17; P > 0.25) \).

COST COMPARISON

The results of costing the two analgesic regimens are shown in Table 3. The cost of the drugs themselves was a small proportion of total costs and similar for both regimens. For buprenorphine the average drug purchase cost per patient was $2.02 and for morphine $1.19. However, the consumables needed to administer a morphine infusion, namely a container of intravenous fluid, an intravenous giving set and a precision drip regulator, cost $12.29 per patient. In contrast, the syringes and needles required for the administration of buprenorphine cost $0.29 per patient. The labour involved in setting up, refilling and monitoring a morphine infusion over the 24 h study period cost $6.28 per patient. In contrast, the labour involved in administering injections of buprenorphine cost $0.85 per patient.

Table 3. Mean cost per patient ($) of administering buprenorphine or morphine over the 24 h postoperative period

<table>
<thead>
<tr>
<th>Item</th>
<th>Buprenorphine</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>2.02</td>
<td>1.19</td>
</tr>
<tr>
<td>Equipment</td>
<td>0.29</td>
<td>12.29</td>
</tr>
<tr>
<td>Labour</td>
<td>0.85</td>
<td>6.28</td>
</tr>
<tr>
<td>Total</td>
<td>3.16</td>
<td>19.76</td>
</tr>
</tbody>
</table>

Thus, for the 24 h postoperative period it cost a total of $19.76 to administer a morphine infusion to each patient compared with $3.16 to administer buprenorphine by injection to each patient.
Discussion

This double-blind comparison of buprenorphine and morphine in patients immediately after major surgery showed that both drugs gave good pain relief at rest and moderate pain relief on coughing. Both drugs caused slight respiratory depression. Other mild side effects observed were hypotension in the case of morphine, nausea and vomiting for buprenorphine and sedation by both drugs.

The aim of this study was to produce sufficient analgesia to enable patients to cough freely without raising arterial P\textsubscript{CO}\textsubscript{2} above 50 mmHg. Maximum tolerable limits for arterial P\textsubscript{CO}\textsubscript{2} of 50 mmHg\textsuperscript{11} and 55 mmHg\textsuperscript{12} have been used in studies of respiratory function after cardiac surgery. In the present study, three patients in each group transiently developed an arterial P\textsubscript{CO}\textsubscript{2} greater than 50 mmHg. The highest recorded value being 56 mmHg in one patient in the morphine group. No adverse effects attributable to hypercapnia were observed in any patient and patients were extubated on average 5.3 h after surgery.

Morphine by infusion is generally accepted as the safest and most effective regimen of analgesia\textsuperscript{4,3} and as the standard against which other strong analgesics should be compared. In the present study of patients with potentially unstable cardiovascular and respiratory systems, we found that buprenorphine given by intravenous bolus was as effective and safe as morphine given by continuous infusion.

The possibility exists that there was a small but definite difference between the two groups, but that the number of patients in this trial was insufficient for this difference to reach statistical significance (type II error). Therefore, the 95\% confidence limits were calculated for the mean between-group differences in pain score and arterial P\textsubscript{CO}\textsubscript{2}. This showed that the present authors had excluded, with 95\% confidence, a difference between the two analgesics of 0.9 pain units at rest and on coughing, and a difference of 6 mmHg in mean arterial P\textsubscript{CO}\textsubscript{2}. To detect a smaller difference in respiratory depression and in the incidence of other side effects would require a trial involving a substantially greater number of patients.

Although the two drugs were similar in their pharmacological effects, buprenorphine had a clear advantage over morphine in terms of cost and ease of administration. These considerations assume increasing importance in times of cost containment and shortage of trained nurses. Over the first 24 h after surgery buprenorphine provided the same analgesia as morphine at one-sixth of the cost.

The present authors conclude, on the basis of these results, that further evaluation of buprenorphine in cardiac surgical patients and other high-risk groups is justified.

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References
