Balanced pre-emptive analgesia: does it work? A double-blind, controlled study in bilaterally symmetrical oral surgery

W. I. CAMPBELL, R. W. KENDRICK AND J. P. H. FEE

Summary
We studied 32 patients undergoing bilateral symmetrical lower third molar surgery under general anaesthesia to determine if the combined effects of pre-emptive local anaesthetic block using 0.5% bupivacaine, together with i.v. tenoxicam and alfentanil had any benefits over postoperative administration. Patients acted as their own controls and were allocated randomly to have surgery start on one side, the second side always being the pre-emptive side. Difference in pain intensity between the two sides was determined using visual analogue scales completed by each individual at 6 h, and at 1, 3 and 6 days after operation. A long-form McGill pain questionnaire was also used to assess difference in pain intensity between the two sides on the morning after surgery. There was no significant difference in pain intensity at any time after surgery. Our findings indicate that the combined use of pre-emptive analgesia from 0.5% bupivacaine, tenoxicam and alfentanil did not reduce postoperative pain intensity in patients undergoing molar exodontia. (Br. J. Anaesth. 1998; 81: 727–730).

Keywords: analgesia, pre-emptive; non-steroidal anti-inflammatory drugs; anaesthetics local, bupivacaine; analgesics opioid, alfentanil; pain, postoperative; surgery, dental

Postoperative pain may be controlled by the use of local anaesthetic block, opioids, non-steroidal anti-inflammatory drugs; or a combination of these. It has been proposed that by administering analgesia before noceception, it may be possible to prevent central sensitization. Animal work, together with clinical observations in acute and chronic pain states, appear to confirm this hypothesis.

Initially, the results of controlled clinical studies appeared to favour the theory that pre-emptive analgesia was of value in clinical practice. Other studies have not shown any benefit of administration of analgesia in a pre-emptive manner. Previous studies by us have not illustrated a pre-emptive analgesic effect with the use of local anaesthesia, despite relatively large numbers of subjects either acting as their own controls or in two separate groups. The pre-emptive use of a non-steroidal anti-inflammatory drug before surgery may be more beneficial than its action starting after surgical incision. In addition, opioids have been shown to have a beneficial effect if given before rather than after surgical incision.

In this study, we determined if there was any benefit in using pre-emptive balanced analgesia. To do this, a bilateral symmetrical surgical model was used to allow patients to act as their own controls and minimize confounding factors, thus increasing the power of the study. Each patient received a non-steroidal anti-inflammatory drug, local anaesthetic block and opioids before incision on one side, and after surgery on the other side.

Patients and methods
The study was approved by the local Ethics Committee. We studied 32 ASA I and II patients, aged 18 yr or more, undergoing removal of both lower third molar teeth, provided that the teeth were bilaterally symmetrical on radiological examination. If upper third molars were to be removed, patients were included only if all four third molars were removed. Patients who gave a history of asthma or aspirin intolerance were excluded. Informed written consent was obtained in each case.

Before surgery, patients were shown how to complete a pain questionnaire, which they retained and completed after surgery. Pain assessment was carried out using two 10-cm vertical visual analogue scales (VAS), one for each operation side, at each of the following times: 6 h after surgery, and on the mornings of days 1, 3 and 6 after surgery. Anchor points were 0 = no pain, 100 = worst pain possible. A long-form McGill pain questionnaire was also completed on the morning after surgery. Patients were asked to complete the VAS on the left side of the page for their left-sided pain and the VAS on the right side of the page for their right-sided pain. They then completed a single McGill pain questionnaire by placing the letters L (left), R (right) or R+L (both sides) beside the words which described the sensation which they experienced on the morning after surgery. All pain questionnaires were completed independently by the patients and posted back to the author.

The procedure was carried out under general anaesthesia. Anaesthesia was induced with propofol and maintenance with 1.5% halothane and 60% oxygen. Patients and methods...
nitrous oxide in oxygen via a nasal tracheal tube. Restricted randomization was used to allocate patients to one of two groups. Two bundles of 16 small cards detailing which side to start the operation on were placed in sealed envelopes, shuffled and numbered sequentially. Immediately after induction of anaesthesia, the surgeon opened one of the randomization envelopes. Group A received an inferior alveolar and a long buccal nerve block, using 0.5% plain bupivacaine 2 ml at each nerve, on the left side only. If the upper third molars were also to be removed, buccal infiltration with 0.5% plain bupivacaine 1 ml was administered on the left side. Surgery then commenced on the right (contralateral) side and when this was complete local anaesthetic was injected as above on this side.

Immediately after removal of the first lower tooth, but before wound closure, the surgeon indicated that he was going to operate on the opposite side. Tenoxicam 20 mg, alfentanil 2 mg, atropine 0.3 mg and ondansetron 8 mg were then administered i.v. If heart rate was less than 50 beat min\(^{-1}\) and when this was complete local anaesthetic was then commenced on the right (contralateral) side and when this was complete local anaesthetic was injected as above on this side.

The purpose of the above procedure was to establish two groups, each of 16 patients: one with surgery commencing on the right and the other with surgery starting on the left. Regardless of grouping, the first side operated on was always the side which was blocked by local anaesthetic after exodontia. Surgery did not start on the second side until at least 10 min had elapsed after neuronal block with bupivacaine and at least 5 min before pretreatment with alfentanil and tenoxicam. The anaesthetist and patient were both unaware of the pretreatment sides. If surgery was more difficult on one side or the patient was not bilaterally numb and pain free, they were excluded and their randomization envelope reallocated to the next available patient who met the entry criteria for the study. Surgical difficulty was rated by the surgeon after operation as: (i) simple tooth elevation; (ii) bone removal or tooth division; (iii) bone removal and tooth division; or (iv) as (iii) but very difficult. Analgesia was available after operation as co-codamol (codeine 8 mg and paracetamol 500 mg), two tablets every 4 h, as required.

Differences in pain between the two sides in each patient, as assessed by VAS and McGill pain questionnaires, was analysed using the Wilcoxon matched pairs signed ranks test. The Mann–Whitney \(U\) test was used to determine if there was a significant difference in pain between the first and second side operated on. Kruskal–Wallis one-way analysis of variance was used to detect differences in pain caused by surgical difficulty. The results of similar research by us indicated that at least 30 subjects would be needed to detect a difference in pain of 10 mm in VAS at 24 h between the two sides in each patient and achieve a power of 90% at the 5% level of significance.

### Table 1

<table>
<thead>
<tr>
<th>Pain after surgery</th>
<th>Median (IQR)</th>
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<tbody>
<tr>
<td>Visual analogue scale rating (0–100 mm)</td>
<td></td>
</tr>
<tr>
<td>First side 6 h</td>
<td>11 (1, 23)</td>
</tr>
<tr>
<td>Second side 6 h</td>
<td>9 (2, 38)</td>
</tr>
<tr>
<td>First side 1 day</td>
<td>8 (4, 28)</td>
</tr>
<tr>
<td>Second side 1 day</td>
<td>9 (3, 30)</td>
</tr>
<tr>
<td>First side 3 days</td>
<td>7 (2, 33)</td>
</tr>
<tr>
<td>Second side 3 days</td>
<td>7 (1, 29)</td>
</tr>
<tr>
<td>First side 6 days</td>
<td>4 (1, 12)</td>
</tr>
<tr>
<td>Second side 6 days</td>
<td>4 (1, 13)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Differences in pain intensity (second–first side)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analogue scale differences at 6 h</td>
<td>0 (–1, 4)</td>
</tr>
<tr>
<td>1 days</td>
<td>1 (0, 5)</td>
</tr>
<tr>
<td>3 days</td>
<td>0 (–1, 2)</td>
</tr>
<tr>
<td>6 days</td>
<td>0 (–1, 4)</td>
</tr>
<tr>
<td>McGill pain questionnaire differences at 1 day</td>
<td>0 (0, 1)</td>
</tr>
</tbody>
</table>

**Results**

We studied 24 women and eight men, but one woman was excluded from group B as one side was not numb after operation. That randomization envelope was used on the next case meeting the entry criteria for the study.

Mean age was 25 (range 18–44) yr. Mean weight was 66 (SD 10.3) kg. The number of patients within each difficulty of surgery grading (rated i–iv) was 6, 10, 12 and 4, respectively. Pain scores for each side are given in Table 1 but it was the difference in pain between the two sides of each individual that was used for statistical purposes. Pain intensity did not correlate with difficulty of surgery on the first side operated on. All data were therefore pooled and the difference in pain between the first and second sides operated on in each patient was used to establish if there was an overall meaningful difference in pain intensity (Table 2). There was no significant difference in pain at any time between the two sides.

**Discussion**

Administration of opioids before noceception has been shown to prevent central sensitization but the dose of opioid used must be sufficient to completely block the release of the excitatory amino acids involved in initiating sensitization. Despite this, the apparent value of pre-emptive opioid use does not improve by increasing the dose in excess of the therapeutic norm. In our study, the potent opioid alfentanil was used in a sufficiently large dose to slow heart rate and stop respiration in all patients, until shortly after surgery was complete. Some researchers have illustrated the benefits of pre-emptive opioids in
clinical situations. However, others have been unable to substantiate such a hypothesis. Alfentanil was chosen as the opioid for this study because of its rapid onset and short duration.

A non-steroidal anti-inflammatory drug was also used in this study as it is known to prevent peripheral sensitization. Its use may be beneficial if administered before rather than after tissue injury. This class of drug is known to have central analgesic properties. Tenoxicam was used as it can be given i.v. and it has been shown that analgesia occurs very rapidly even after i.m. use. In a study by Rice and colleagues, comparison of i.m. morphine and ketorolac rapidly even after i.m. use. In a study by Rice and colleagues, comparison of i.m. morphine and ketorolac has been shown that analgesia occurs very rapidly even after i.m. use. In a study by Rice and colleagues, comparison of i.m. morphine and ketorolac.

The difference in pain scores between the two sides was not significant at any time after surgery. However, all patients had complete analgesia from neural blockade for the first few hours after surgery. Neither the local anaesthetic nor tenoxicam would have had any new clinical effect by 24 h after surgery. In particular, the dose of alfentanil used would not have any clinical effect several hours after surgery because of its short half-life. Therefore these drugs would not be expected to interfere with pain assessments carried out in the days after surgery, as their therapeutic actions would have ceased on both sides.

It could be argued that the model of bilateral symmetrical surgery is not sound, yet this type of model is used widely by basic scientists, providing much of our physiological knowledge on pain. However, the unilateral biochemical changes which have been identified within the spinal cord after ipsilateral limb injury gradually become bilateral over days to weeks in animals. The biochemical changes which eventually involve the contralateral side of the spinal cord together with diminishing pain magnitude in the days after surgery may explain the difficulty in identifying any late benefits of pre-emptive analgesia.

The results of this study were disappointing. At no time was there any benefit of pre-emptive analgesia compared with postoperative use, despite administration of analgesics working at three different sites concurrently. Attempts to reduce postoperative pain by pre-emptive techniques using conventional analgesics and techniques are probably unrealistic. Analgesia probably has to be extended well into the healing period to be beneficial but how do we determine that there is an advantage in administering analgesics before rather than after surgery starts, when pain intensity is likely to be very low with both techniques?

References


