The analgesic efficacy of ibuprofen in periodontal surgery: A multicentre study

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Abstract

The efficacy of a non-steroidal anti-inflammatory agent, ibuprofen, was evaluated in pain control following periodontal surgery. This type of agent acts peripherally by inhibiting the release of prostaglandins and minimizing the local inflammatory response. Thus there may be an advantage in pre-treatment administration of the drug so as to delay or even prevent postoperative pain.

The study was multicentre, involving a Public Hospital Periodontal Unit, two specialist periodontal practices in Sydney, NSW, and two in Canberra, ACT. One hundred and twenty-seven patients who were to undergo periodontal surgery were randomly given either two 200 mg tablets of ibuprofen or two matching placebo tablets at least 30 minutes before administration of local anaesthesia. The procedure was double blind: neither the patient nor the clinician was aware of the tablet identity.

Postoperatively, all patients were given labelled ibuprofen for pain relief, but were randomly divided into two groups: As directed who were instructed to take the drug regularly for two days postoperatively, and As required, who were to take the drug only if needed for pain relief. All patients completed a diary recording quantity and time of medication, and regular assessment of pain experience utilizing a visual analogue scale.

The As directed group showed no significant difference in pain experience between pre-operative and post-operative only medication, but the As required group experienced significantly less pain and requirement for medication if the ibuprofen was administered pre-operatively.

Key words: Analgesia, pain, pain measurement, periodontal surgery, periodontics, post-operative pain.

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Introduction

Postoperative pain is a recognized sequel of periodontal surgery as documented by Strahan and Glenwright. The pain experience has been shown to peak in the first twenty-four hours following the procedure, and to decrease rapidly in subsequent days as shown by Seymour. Control of post-operative pain is thus a required part of periodontal therapy. Curtis et al. indicated that these pain levels may be anticipated to vary, depending on the category of the periodontal surgical procedure.

Non-steroidal anti-inflammatory analgesics (NSAIDs) have become an accepted part of pain control in dental treatment. Ibuprofen is an NSAID of the proprionic class. It has established application for pain relief in rheumatic and muscular pain, headache, menstrual, and dental pain. Several studies have shown that ibuprofen can effectively control pain following periodontal surgery.

As a peripherally-acting anti-inflammatory agent, ibuprofen interferes with the release of prostaglandins at the site of tissue injury. According to Insel, inhibition of prostaglandins is thought to be responsible for the minimization of the inflammatory response at the site of surgery. Because of this mode of action, an enhanced effect might be expected if the drug is administered pre-operatively, and this was demonstrated in third molar removal surgery by Dionne and Cooper, and Hill et al.

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The present study was designed to test the efficacy of ibuprofen in the control of pain following periodontal surgery, when comparing patients who were administered the drug both pre-operatively, and postoperatively, with postoperative prescription only.

**Materials and methods**

The study included 127 patients who were scheduled for routine periodontal surgery to be carried out under local anaesthesia. The surgical procedures ranged from simple flap curettage to more complex flap surgery including ostectomy, guided tissue regeneration, or root resection. The patients were selected in order of presentation and suitability, so the differing procedures were randomly distributed.

This study was approved by the Human Ethics Review Committee of the Western Sydney Area Health Service. All subjects gave fully informed written consent prior to being admitted to the study.

The study was multicentre: a specialist Periodontics Unit in a Dental Hospital (Westmead Hospital Dental Clinical School), and four private specialist Periodontal practices; two in Sydney (NSW) and two in Canberra (ACT).

Exclusion criteria eliminated patients requiring other pre-operative medication, those who were hypersensitive or allergic to NSAIDs or aspirin, patients already taking other analgesics and/or NSAIDs, asthmatics, those with evidence or history of peptic ulceration, chronic dyspepsia, ulcerative colitis, or gastrointestinal haemorrhage, or any other clinically significant systemic illness. Pregnancy was also an eliminating condition. Patients with mild to moderate disease states with appropriate medication, for example, hypertension or non-insulin dependent diabetes could be included in the study.

Patients were randomized under double blind conditions to receive either two tablets of ibuprofen, (each tablet 200 mg) 30 minutes before administration of local anaesthesia, or two matching placebo tablets. The packaging and appearance of the two medication regimes were identical, so that the administering clinician was unaware of this selection.

Both ibuprofen and placebo groups were further randomized into two treatment subgroups (so as to make four groups in all). Group 1 patients – As directed – were instructed to take two tablets one hour after completion of surgery, and then to take one tablet every four hours to a maximum of six tablets per day, for two days. Group 2 patients – As required – were instructed to take two tablets when first required for pain relief, and then one to two tablets every four hours as required. As in the As directed group, they were instructed to take no more than six tablets on either the first or second day.

The groups thus consisted of the following schema:

<table>
<thead>
<tr>
<th>Placebo group (A)</th>
<th>Ibuprofen group (B)</th>
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</thead>
<tbody>
<tr>
<td>placebo</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>As directed</td>
<td>As required</td>
</tr>
<tr>
<td>As directed</td>
<td>As required</td>
</tr>
</tbody>
</table>

The trial period included the day of surgery plus the day following surgery. Subsequently the patients could take any analgesic of choice. The surgical procedures were carried out either in a morning or early afternoon session.

The operating time, from first incision to completion of suturing was recorded, as was the quantity of anaesthetic used. The surgical area, and the actual surgical procedure were described. Any concomitant disease or medication permitted by the protocol were noted. A periodontal dressing was placed on the operated area and the patient was instructed to take the study medication for two days as described below.

Patients were asked to assess pain according to a visual analogue scale (VAS), making a vertical mark on a line 100 mm in length, from ‘no pain’ on the left end, to ‘severe pain’ on the right. Assessments were made at the following times:

1. First onset of pain
2. Time when medication was taken
3. At 1, 2, 5, and 9 hours after completion of the procedure (the 9-hour assessment was omitted if the procedure had been carried out in the afternoon)
4. At bedtime.

At the end of both days, the patients were asked to make an assessment of what pain relief the study medication had provided on a VAS scale marked ‘excellent’ on the left end of the line, and ‘none’ on the right.

Each patient was given a prepared diary. The diaries of the As directed groups requested assessments at the times detailed above, plus the medication times as scheduled. The As required group diaries contained a double series of pain assessments: one series at the above times, and a second series (on different coloured pages) at the actual times the (as required) medication was taken.

One week later, the dressing and sutures were removed, and any adverse events or postoperative bleeding experiences were recorded.

**Data analysis**

Comparisons were made between treatment groups. Efficacy data were compared for Day 1 only. The data were also analysed by gender, on the basis that males and females have different pain perceptions.

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All data were tested for normality and transformations attempted where necessary.

The schema for analysis was as below:

<table>
<thead>
<tr>
<th>As directed</th>
<th>As required</th>
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<tbody>
<tr>
<td>Pre-op placebo</td>
<td>Pre-op ibuprofen</td>
</tr>
<tr>
<td>Pre-op ibuprofen</td>
<td>Pre-op placebo</td>
</tr>
</tbody>
</table>

Statistical tests: Sample size, mean, standard deviation, median and degree of skewness were calculated for all data (desc, q=1, m=1). 'm=1' function provided a description of normality for each individual group. For data to be normally distributed, Skew=0 and Kurt=3.0. Individual data groups were tested for normality (Shapiro-Wilk or Omnibus Tests) dependent on sample size.

Where data were not normally distributed it was transformed (unless specified otherwise), and tests for normality were re-applied. Where p value >0.05, a 2-sample t test was applied. Where p value ≤0.05, the Wilcoxon Rank Sum Test was applied.

A chi-squared test was applied to data sets with Yes/No or Male/Female answers.

Results

**Age, sex and mass of patients**

Of a total of 130 subjects recruited, 62 were female and 68 male. As evaluated by a chi-square test, there was no significant difference (p=0.284) in the number of females to males, randomized to either the placebo or ibuprofen group.

The age distribution of subjects is shown in Table 1. Statistically, this was a normal distribution. Similarly, the mass of patients, as shown in Table 2, was of normal distribution.

**Surgical sites**

Surgical procedures were carried out in any of the four quadrants of the mouth as therapeutic needs indicated. The distribution of sites in the two groups was compared and found to be random. For example, there was no significant difference (p=0.926) in the numbers of surgical procedures carried out in the upper right quadrant between the two groups.

Almost all surgical procedures were of 3 to 8 teeth in extent. In both treatment groups the mean was 5 (±2). There were a few cases in both groups where the surgical procedures involved either one or two tooth sites, or at the other extreme, 9 to 13 tooth sites.

**Concomitant disease/medication**

Of the 130 subjects overall, 27 reported concomitant disease or medication (acceptable within the described guidelines): 14 in the placebo group, and 13 in the ibuprofen group.

**Postoperative bleeding**

As some NSAIDs can influence bleeding time, the incidence of postoperative bleeding was monitored. Only one patient in the placebo group and two in the ibuprofen group reported noticeable postoperative bleeding.

**Postoperative assessment**

Adverse events, such as gastro-intestinal disturbance or headache, were recorded. There were seven incidences in the ibuprofen, and three in the placebo group. These included abdominal upset (nausea, constipation, diarrhoea), loss of taste, dizziness, chest pain, warm flushes, unstable blood glucose level. However, when tested statistically (chi-squared), there was no significant difference in frequency of adverse events, either between treatment groups (p=0.205) or between groups compared by sex (male: p=0.544, female: p=0.241).

Nine patients withdrew from the ibuprofen group, and three from the placebo group, although neither the number of withdrawals, nor the reasons for withdrawal were significant between groups (chi-squared: p=0.088). The reasons were various: in some cases the patients experienced discomfort of some kind, which they felt was a side effect of the medication.

**Pain assessment**

1. **As directed groups**

The pain level at first onset is shown in Fig. 1. The mean pain score for the placebo group was 13 (±15), and for the ibuprofen group was 15 (±20), and these differences were not statistically significant (Wilcoxon Rank Sum Test: p=0.766).

One hour after surgery the mean pain score for the placebo group of 11 (±15) was not significantly different from the 9 (±18) of the ibuprofen group (Wilcoxon Rank Sum Test: p=0.195). The pain

<table>
<thead>
<tr>
<th>Table 1. Age distribution of subjects (years)</th>
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<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>Sample size</td>
</tr>
<tr>
<td>Mean age</td>
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<tr>
<td>Standard deviation</td>
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<tr>
<td>Youngest</td>
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<td>Oldest</td>
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<table>
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<tr>
<th>Table 2. Body mass distribution of subjects (kg)</th>
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<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>Sample size</td>
</tr>
<tr>
<td>Mean mass</td>
</tr>
<tr>
<td>Standard deviation</td>
</tr>
<tr>
<td>Minimum mass</td>
</tr>
<tr>
<td>Maximum mass</td>
</tr>
</tbody>
</table>
experience was similar for both groups; no subjects reported severe pain (91-100 on the visual analogue scale) one hour post-surgery, one subject from each group reported moderate pain (61-90), and the majority of subjects reported mild pain (1-30).

Two hours postoperatively there were again no significant differences (Wilcoxon Rank Sum Test: p=0.217) between the ibuprofen and placebo groups. In both groups, the majority reported only mild pain (1-30).

Pain assessment 1-9 hours postoperatively on Day 1 (Fig. 2), shows low overall pain levels, and no apparent differences between the test and control groups. Comparison of pain assessment for Day 2 similarly showed no significant difference between the two groups. As noted above, the patients were asked to assess the worth of the medication in pain relief at the end of each test day, on a VAS scale, from zero to excellent. In both groups, the medication was assessed as providing very effective pain relief on both days.

2. As required groups

Figure 3 shows the times to first onset of pain in the As required groups. The mean time of the ibuprofen group was much longer (181 ± 142 minutes), than the placebo group (125 ± 78 minutes). However, these differences were not statistically significant (Wilcoxon Rank Sum Test: p=0.104).

There were no differences in pain intensity between the two groups at first onset: no patients reported severe pain, and as in the As directed groups, the majority of patients experienced mild pain at this time. The means of pain intensity were 19 (±19) for the ibuprofen group, and 28 (±22) for the placebo group. Although the test group had a lower mean of pain intensity, the difference was not statistically valid (Wilcoxon Rank Sum Test: p=0.087).

In the As required groups, the subjects had the choice of whether or not to take medication at first onset of pain. As in Fig. 4, 62.5 per cent of the placebo group required medication at the first onset of pain, compared with 28 per cent of the ibuprofen group. This difference was significant as tested by chi-square (p=0.031).

At one hour post-surgery, mean pain levels were lower in the ibuprofen group, 10 (±21), than in the placebo group, 19 (±25), but these differences were not statistically significant (Wilcoxon Rank Sum Test: p=0.178). Most patients reported pain of mild/moderate (31-60) level, and within this category, there was a significant difference between the mean of 49 for the placebo group, and 39 for the ibuprofen group (t test: p=0.045).
Two hours after surgery the mean pain level of the ibuprofen group was 8 (±10), compared with 17 (±20) for the placebo group. The difference in these levels was significant as evaluated by the Wilcoxon Rank Sum Test (p=0.037).

By five hours after surgery, this difference between the two groups had dissipated. The mean pain scores at this time were 19 (±23.5) for the placebo group, and 19 (±22) for the ibuprofen group. The similarity in scores continued into Day 2.

The variation in pain levels over the first nine hours following surgery in the As required groups is shown graphically in Fig. 5, depicting the difference at one hour, continuing through the two hour period, with a subsequent merging of pain levels from 5 hours onwards.

At the completion of the study, most patients in both groups rated the effect of medication (using a VAS scale of 0 to 100) in the excellent (91-100) range (Fig. 6).

**Discussion**

The subjects who participated in this study were divided randomly into one of two administrations: the As directed group, and the As required group. This division, as the names imply, was based on prescription of the test drug, the one according to a set regimen, and the other according to the patient’s perceived need for analgesic relief from pain or discomfort. According to the protocol of the study, within each of these groups, the test sub-group had been administered ibuprofen prior to surgery, while the control cohort had received a placebo pre-operatively, and had taken ibuprofen only following the surgery.

The results of these groups differed: in the As directed group, there was no statistically significant difference between the test and control sub-groups in perception of pain following periodontal surgery. In the As required group, however, differences emerged between the pre-operative administration of active drug and placebo. Twice as many patients (20) in the placebo sub-group had detected pain in the first two hours post-surgery than the test sub-group (10 patients), although this did not achieve statistical significance (Fig. 3). The patients in the As required group were not obligated to take medication at the first detection of pain, and a greater number (at significant level) of patients who had received the placebo pre-operatively took tablets on experiencing pain than those who had been given the active drug prior to surgery (Fig. 4).

Although the assessment of pain level at first onset showed no difference in the As required group, the pain level at 1 hour following surgery was significantly lower in the test sub-group than in the control in the mild/moderate range, and the difference was significant in all ranges at 2 hours.

At 5 hours following surgery, and through to the end of Day 1, the test and control sub-groups had similar pain experience (Fig. 5).

Patients were asked to make an assessment at the end of each day of the overall relief of pain provided by the medication, since all sub-groups were taking the active drug postoperatively. In both As directed and As required groups, the rating was overwhelmingly towards the ‘excellent’ end of the VAS scale (Fig. 6). Interpretation of this assessment is limited by the surgical experience of the patients: in many and perhaps most cases, this was their first episode of periodontal surgery. Nevertheless, it seems evident that pain registration overall was low, the actual levels of pain at first onset averaged approximately 14 in a scale of 0 to 100 in the As directed groups, and around 24 in the As required groups.

Assessment of the ability of ibuprofen to control pain is predicated on measurable pain following
periodontal surgery. Reports of pain levels following this type of surgery indicate low postoperative pain. Curtis et al." reported that 51.3 per cent of patients indicated zero or minimal pain following periodontal surgery. They further found that the type of surgery was a factor, with plastic soft tissue periodontal procedures much less painful postoperatively than osseous or mucogingival surgery. The present study included a variety of surgical modalities, including osseous and mucogingival surgery, but the majority of cases were essentially plastic soft tissue categories. Cooper6 compared pain experience following dental impaction and periodontal surgery, and rated impacted third molar removal as causing a greater intensity of pain than periodontal surgery. Furthermore, he found that a greater proportion of periodontal surgery patients did not bother to take medication than those undergoing impaction surgery. Factors other than the defined surgical procedure affect postoperative pain: Capuzzi et al.17 showed that sex of the patient, age of the patient, and expertise of the surgeon, all affected pain experience following third molar extraction. Gallardo and Rossi,12 in a study on efficacy of the NSAID flurbiprofen following periodontal surgery, had to eliminate from the study 25 patients (of 97 at commencement) because they either took no medication at all, or reported only slight postoperative pain. The assessment of pain is of course a subjective exercise, and affects the results of any test of analgesic efficacy. In a study on the psychological factors in postoperative pain control, Perry et al.18 found that subsequent to a hysterectomy procedure, whilst older patients reported less pain, they nevertheless used the same amount of medication as younger patients. Pre-operative trait anxiety correlated with increased demand for analgesia, but not with assessment of postoperative pain. Skoglund and Jorkjend19 utilized a VAS scale assessment after gingivectomy procedures in a study of local anaesthetic agents. On a VAS scale of 0 to 100 (as used in the present study), the postoperative pain responses were all between 0 and 15.

The comparatively low level of pain following periodontal surgery thus hinders demonstration of efficacy of an analgesic medication.

Efficacy of ibuprofen in controlling pain following periodontal surgery was more evident in the As required groups than in the As directed groups, as discussed above. The former schedule, by definition, involved more understanding and decision making by the patient, than the As directed instructions. The As required diary took more time to explain to patients because of its greater need for conceptual understanding. The As directed diary by contrast, called for a simpler following of direct instructions: the patient had merely be able to read and follow the clear directions in the diary as to when and how much medication to take. It might be theorized that, since the As required patients had to think about, and make decisions on levels of pain and need for medication, they might have been more likely to register meaningful assessments.

Wilder-Smith and Schuler20 showed that education of patients in pain therapy to change attitudes and expectations induced a more positive attitude towards postoperative pain and a consequent improvement in postoperative analgesia. Behavioural strategies to enhance a patient’s ability to cope with pain, called ‘patient empowerment’, was utilized by Selden.21 The more active involvement of the As required groups in decisions about postoperative analgesia might be a form of empowerment.

This study would seem to indicate that in assessing medication efficacy it is beneficial to invoke choice. Involving the subjects themselves in decision making appears to elicit more definite results.

Conclusions

A non-steroidal anti-inflammatory analgesic agent such as ibuprofen appears to be more effective in limiting pain following periodontal surgery if the administration is begun some time prior to the procedure.

One of the difficulties encountered in a study of analgesia in periodontal surgery is that, as has been documented in previous studies and occurred in the present one, the pain levels following this type of oral surgery are relatively mild.

The results of this study, in comparing two administration regimes of medication, indicate that patients are more likely to make meaningful assessment of pain control if they are faced with choice of consumption rather than a fixed regimen.

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