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A double-blind randomised controlled clinical trial of the effect of preoperative ibuprofen, diclofenac, paracetamol with codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars

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Summary We conducted a randomised double-blind placebo-controlled single-centre study to compare the effect of preoperative ibuprofen 600 mg, diclofenac 100 mg, paracetamol 1 g with codeine 60 mg or placebo (Vitamin C 50 mg) tablets for relief of postoperative pain in 119 patients who had day case operations under general anaesthesia for removal of impacted third molars. Patients were given the tablets 1 h before operation. Pain was assessed using visual analogue scales and verbal rating scales preoperatively at 15 and 30 min and 1 and 3 h postoperatively. After they had gone home, patients were contacted by telephone at 6 and 24 h postoperatively to find out whether they had any adverse effects from the analgesics. There was no significant difference in the extent of postoperative pain among the four groups, but the placebo group had significantly shorter times before their first request for postoperative analgesics (median 17 min, range 14—90) than the diclofenac group (median 32, range 15—150).

Preoperative analgesics at the stated doses are effective in providing immediate postoperative pain control after operations on third molars. There were, however, some side-effects including nausea, vomiting, headaches, and gastrointestinal discomfort, but there were no significant differences among the active analgesic groups with respect to adverse events either shortly after operation or at 6 or 24 h.

Introduction

The removal of third molar teeth in a day case setting has become popular with patients, healthcare

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trusts and oral surgeons. As well as alertness and rapid recovery from anaesthesia, well-controlled pain is another indication for discharging a patient home.[1] Postoperative analgesia may be achieved by the use of local anaesthesia or by giving non-steroidal anti-inflammatory drugs (NSAIDS), opioids, or a combination. The pre-emptive use of a non-steroidal anti-inflammatory drug before operation may be more beneficial than its use after operation[2] and opioids are also more effective if given before rather than after operation.[3–5] Pre-emptive local anaesthesia has no advantages over its postoperative use.[6–8] A preoperative oral COX-2-specific inhibitor, valdecoxib also provided well-tolerated and effective analgesia for mild to moderate postoperative pain.[9] Pre-emptive analgesia prevents establishment of central sensitisation caused by incisional and inflammatory injuries. It starts before incision and covers both the period of operation and the initial postoperative period.[10]

In this randomised, double-blind, placebo-controlled trial, we wanted to find out if there was any benefit in using pre-emptive ibuprofen 600 mg, diclofenac 100 mg, paracetamol 1 g with codeine 60 mg or placebo (Vitamin C 50 mg) tablets in patients having removal of third molar teeth as day cases.

Method

One hundred and twenty-five patients in American Society of Anesthesiologists grades 1 and 2 who were to have third molar teeth removed under general anaesthesia were invited to participate in the study. The approval of the Regional Ethics Committee was obtained and all patients gave written informed consent to participate. They were randomly assigned immediately after consent had been obtained to be given 1 h preoperatively either ibuprofen 600 mg or diclofenac 100 mg or paracetamol 1 g + codeine 60 mg or Vitamin C 50 mg. Randomisation was by computer-generated tables of random numbers. Before operation, each patient was shown a visual analogue scale (VAS) and given an explanation about how this would be used to measure pain at various time after operation. The VAS was a 100 mm horizontal scale (0 = no pain; 100 = worst pain possible) and the assessment was made at 15 and 30 min, and 1 and 3 h postoperatively. After they had gone home we contacted patients by telephone at 6 and 24 h postoperatively to assess pain experienced at these times and to find out if there were any adverse effects of the analgesic. We used a verbal rating scale (VRS) to evaluate pain. Patients described their pain as mild but tolerable, moderate but tolerable, moderate not controlled by pain killers, or severe not controlled by pain killers.

Details of treatment

Third molar teeth were removed under general anaesthesia, which was induced with propofol (2–2.5 mg/kg) and in some cases fentanyl (50 μg/ml) or alfentanil (2 μg/kg) and maintained with isoflurane 2% or sevoflurane 4% and nitrous oxide 60% in oxygen. The dose of fentanyl or alfentanil did not differ significantly among the four groups. All drugs and placebo were prepared by the hospital pharmacy and given in a soluble form by the patients' named nurse. The investigators, operators and anaesthetists were unaware of which drug had been given preoperatively. Local anaesthetics were not used during the operation. Experienced surgeons did the operations using a standard technique, which included removal of bone with a water-cooled bur in a surgical drill. All the patients (except one who developed bronchospasm) were discharged the same day and were given postoperative antibiotics (metronidazole) and analgesics as described in the following.

Postoperative care

Patients who asked for postoperative analgesia were given the same analgesic as had been given preoperatively by the named nurse. Patients in the placebo group who required postoperative analgesia while in the recovery lounge were randomised to be given ibuprofen 600 mg, diclofenac 100 mg or paracetamol 1 mg + codeine 60 mg. Paracetamol 500 mg was available as escape analgesia if both pre-emptive and postoperative analgesics proved insufficient to control the pain. Discharge prescriptions were limited to two tablets of paracetamol 500 mg + codeine 30 mg once in 6 h (maximum eight tablets a day).

Preoperative data

Three different 100 mm visual analogue scales were used preoperatively to assess pain experienced during the previous week, pain expected after the operation and anxiety. Patients who reported pain preoperatively were asked to rate their pain on a VRS as follows: mild but tolerable pain; moderate but tolerable pain; moderate pain not controlled by painkillers and severe pain not controlled by pain killers.

The symptoms of pain were those experienced before the day of operation and none of the patients had taken analgesics in the 24 h preoperatively.

The VAS and VRS were recorded immediately after consent had been given and before the drugs were given.

Intraoperative and postoperative data

The anaesthetic regimen and the duration of operation were recorded. After recovery patients were asked to record the extent of their pain on a VAS 15, 30 and 60 min, and 3 h, postoperatively. Other measurements included the time of first request for postoperative analgesia and whether rescue medication was requested.

Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS Inc., 1999) and STATA (Stata Corp., 2001) software. Chi-square, Mann—Whitney *U* test, ANOVA and Kruskal—Wallis tests were used as appropriate. Survival analysis and cross-sectional time-series linear models with Generalised Estimating Equation approach (GEE) were used to adjust for potential confounders.

Results

Patients

Of 125 patients, 5 (4%) withdrew from the study during the postoperative period. One patient developed bronchospasm during induction of anaesthesia and required admission to hospital overnight. He was withdrawn from the study. Of the remaining 119 patients, 31 (26%) were in the ibuprofen group, 29 (24%) were in the diclofenac group, 30 (25%) were in the paracetamol + codeine group, and 29 (24%) were in the placebo group. Thirty-three men and 86 women participated in the study. Their mean age (S.D.) was 26 (6) years (range 18—44). There was no significant

Table 1 Comparison of the four groups.

Measure	Ibuprofen ($n = 31$)	Diclofenac ($n = 29$)	Paracetamol + codeine ($n = 30$)	Placebo ($n = 29$)	p value
Preoperative pain					
No	24 (77)	22 (76)	23 (77)	22 (76)	
Yes	7 (24)	7 (24)	7 (23)	7 (24)	0.99
Preoperative pain (VRS)					
No pain	24 (77)	22 (76)	23 (77)	22 (76)	
Mild but tolerable pain	4 (13)	4 (14)	3 (10)	5 (17)	
Moderate but tolerable pain	3 (10)	3 (10)	1 (3)	2 (7)	
Moderate pain not controlled by pain killers	—	—	3 (10)	—	
Median preoperative pain (range)	0 (0—59)	1 (0—30)	0 (0—72)	1 (0—38)	0.99
Median preoperative anxiety (range)	48 (4—99)	64 (0—100)	53 (0—178)	65 (0—100)	0.75
Median expected postoperative pain (VAS) (range)	58 (1—100)	63 (0—100)	63 (0—100)	60 (0—100)	0.84
Median duration of operation (minutes) (range)	15 (5—50)	21 (4—47)	17 (3—39)	22 (4—37)	0.32
Type of operation (third molar)					
Bilateral mandibular	13 (42)	9 (31)	8 (27)	6 (21)	
Maxillary and mandibular	18 (58)	20 (69)	22 (73)	23 (79)	0.33
Bone removal					
Yes	20 (64)	16 (55)	18 (60)	20 (69)	
No	11 (36)	13 (45)	12 (40)	9 (31)	0.73
Clinical operator					
Consultant	3 (10)	2 (7)	5 (17)	2 (7)	
Middle grade	26 (84)	21 (72)	22 (73)	23 (79)	
Senior house officer	2 (7)	6 (21)	3 (10)	4 (14)	0.56

Figures are number (%) unless otherwise stated.

difference in sex, age, height or weight among the four groups.

Preoperative pain and anxiety

Preoperative pain

The preoperative pain score did not significantly differ among the four groups (Table 1) and just over three-quarters of the patients had no pain.

Preoperative anxiety

There were no significant differences among the four groups with respect to expected preoperative anxiety (Table 1).

Expected postoperative pain

There were no significant differences among the four groups with respect to expected postoperative pain (Table 1).

The groups did not differ significantly in terms of number and site of teeth removed, duration of operation, or grade of surgeon operating.

Postoperative pain

Patients expected more pain than they had.

Preoperative anxiety compared with reported postoperative pain

There was a weak correlation (0.22) at 15 min, the highest being in the placebo group (0.38).

Table 2 Postoperative pain in the four groups.

Measure	Ibuprofen ($n = 31$)	Diclofenac ($n = 29$)	Paracetamol + codeine ($n = 30$)	Placebo ($n = 29$)	p-value
Median postoperative pain score[a] (VAS) (range)					
15 min	53 (0—100)	61 (0—100)	43 (0—96)	55 (0—97)	—
30 min	65 (0—100)	65 (0—100)	59 (2—100)	58 (4—96)	—
1 h	51 (1—98)	61 (0—100)	43 (0—97)	43 (8—97)	—
3 h	31 (0—100)	33 (0—100)	21 (0—94)	21 (1—65)	—
Mean (S.D.) area under the curve	7687 (4284)	7930 (4147)	6777 (4995)	6578 (3127)	0.56
Postoperative pain at					
3 h	27 (87)	24 (89)	24 (80)	25 (86)	—
6 h	17 (61)	10 (59)	14 (61)	13 (56)	—
24 h	16 (59)	10 (59)	12 (52)	13 (59)	—
Median total score (range)	2 (0—3)	2 (1—3)	2 (0—3)	2 (0—3)	0.91
Postoperative pain intensity (VRS)					
3 h					
Mild but tolerable pain	9 (33)	10 (42)	11 (44)	6 (24)	
Moderate but tolerable pain	12 (44)	10 (42)	7 (28)	16 (64)	
Moderate pain not controlled by pain-killers	4 (15)	4 (17)	6 (24)	3 (12)	
Severe pain not controlled by pain-killers	2 (7)	—	1 (4)	—	
6 h					
Mild but tolerable pain	7 (41)	4 (40)	6 (43)	3 (25)	—
Moderate but tolerable pain	9 (53)	6 (60)	7 (50)	7 (58)	
Moderate pain not controlled by pain-killers	1 (6)	—	1 (7)	2 (17)	
24 h					
Mild but tolerable pain	9 (56)	5 (50)	6 (50)	4 (31)	—
Moderate but tolerable pain	6 (37)	5 (50)	6 (50)	9 (69)	
Moderate pain not controlled by pain-killers	1 (6)	—	—	—	
Median total pain intensity score (range)	4 (0—8)	4 (1—6)	3 (0—8)	4 (0—7)	0.93

Figures are number (%) unless otherwise stated.
[a] Observations are missing for one patient in the placebo group and one patient in diclofenac group at 1 and 3 h, therefore, numbers do not always add up to total.

Table 3 Results of estimates of time-series linear model using GEE for pain on VAS.

Variable	Coefficient (S.E.)	*P*-value
Group		
Ibuprofen	5.15 (5.52)	0.35
Diclofenac	10.15 (5.69)	0.08
Paracetamol + codeine	−0.89 (5.48)	0.87
Time since operation	1.46 (0.44)	0.001
Time since operation[a]	−0.027 (0.008)	<0.0001
Time since operation[b]	0.0001 (0.00003)	<0.0001
Sex		
Female	10.54 (4.63)	0.02
Age (years)	0.11 (0.39)	0.78
Expected postoperative pain (VAS)	0.17 (0.09)	0.04
Preoperative anxiety (VAS)	−0.005 (0.06)	0.94
Duration of operation (minutes)	0.26 (0.22)	0.25
Type of operation (third molar)		
Maxillary and mandibular	4.59 (4.48)	0.31
Bone removal		
Yes	2.22 (4.60)	0.63
Time to first request of postoperative analgesia	9.30 (0.06)	<0.0001
Constant	13.04 (16.35)	0.42

[a] Second degree of time since operation.
[b] Third degree of time since operation.

VAS pain scores at 15 and 30 min and 1 and 3 h postoperatively

Median values decreased after 30 min postoperatively (Table 2) There was no significant difference among the four groups.

Regression analysis was done by applying a cross-sectional time-series model using GEE (Table 3). This model takes into account the fact that information is collected from the same patients over time. Time since operation, sex, expected postoperative pain and time when first additional analgesia was requested were significant predictors of pain. Although there was no significant difference in preoperative pain experienced between men and women, women reported more pain postoperatively.

Verbal rating pain scores at 3, 6, and 24 h

Verbal rating pain scores showed that at 3 h, 17 patients (14%) had moderate pain not controlled

Table 4 Postoperative analgesia and adverse events in the four groups.

Measure	Ibuprofen ($n = 31$)	Diclofenac ($n = 29$)	Paracetamol + codeine ($n = 30$)	Placebo ($n = 29$)
Median (range) time to first request for postoperative analgesics	30 (10—105)	32 (15—150)	26 (15—150)	17 (14—90)
Use of escape analgesia				
Yes	6 (19)	3 (10)	6 (20)	5 (17)
Would you be prepared to take the same soluble tablet for a similar condition (tooth extraction) in the future?				
Yes	25 (89)	14 (74)	22 (88)	22 (81)
No	2 (7)	4 (21)	2 (8)	4 (15)
Don't know	1 (4)	1 (5)	1 (4)	1 (4)

Figures are number (%) unless otherwise stated.

by pain killers and 3 patients (3%) had severe pain (Table 2). By 24 h, 68 patients (57%) reported no pain, 24 (20%) had mild pain, 26 (22%) had moderate pain, and 1 patient had moderate pain not controlled by painkillers.

There were no significant differences in total pain and pain intensity scores among the four groups.

Time to first requirement for postoperative analgesics

The lowest median time before the first postoperative demand for analgesia was in the placebo group, 17 min and the highest in the diclofenac group 32 min (Table 4).

There was a significant difference between the placebo and diclofenac groups ($P = 0.009$). To adjust for other factors, we did a Cox regression analysis (Table 5). The following variables, in addition to treatment group, were entered into the model: sex, age, type of operation, duration of operation, removal of bone, expected postoperative pain and preoperative anxiety. The only significant difference was in the diclofenac group compared with the placebo group (relative risk (RR) 0.49; 95% confidence interval (CI) 0.28–0.86).

Table 5 Results of Cox regression analysis for time to first request for postoperative analgesia.

Variable	Full model RR[a] (95% CI)
Group	
Placebo	1.00
Ibuprofen	0.75 (0.44–1.29)
Diclofenac	0.49 (0.28–0.86)
Paracetamol + codeine	0.62 (0.36–1.07)
Sex	
Male	1.00
Female	0.93 (0.60–1.44)
Age (years)	0.99 (0.95–1.03)
Expected postoperative pain (VAS)	1.00 (0.99–1.01)
Preoperative anxiety (VAS)	1.00 (0.99–1.01)
Duration of operation (minutes)	1.01 (0.98–1.03)
Type of operation (third molar)	
Bilateral mandibular	1.00
Maxillary and mandibular	1.07 (0.68–1.69)
Bone removal	
No	1.00
Yes	0.88 (0.54–1.41)

[a] Relative risk (RR) of requesting postoperative analgesia.

Comparison between types of analgesia in the placebo group

Three patients in the placebo group did not request any analgesia before they went home, eight were randomised to receive ibuprofen, seven diclofenac and ten paracetamol + codeine. Information about one patient was missing. There was no significant difference when areas under the curve were compared among the three types of analgesia (ANOVA $P = 0.41$).

Use of escape analgesia

When the pre-emptive and postoperative analgesics were not sufficient to control pain, paracetamol 500 mg was available as rescue analgesia. Ninety-nine patients (83%) did not require rescue medication and of the 20 patients (17%) who requested analgesia, the proportion in each group was not dissimilar.

Adverse events

Adverse events reported 6 h postoperatively included: nausea (19%), vomiting (7%); headaches (13%); gastrointestinal discomfort (12%); dizziness (24%) and other discomforts (29%). The other discomforts included sore throats, neck stiffness, earache, pain around temporomandibular joints and 4% had temporary altered sensation of the lip or tongue. There was no significant difference among the groups with respect to adverse events or when they were compared at 6 or 24 h. Some of the symptoms may have been related to the preoperative and postoperative analgesics, but the general anaesthetic may have contributed to most of the discomforts.

Would patients take pre-emptive medication before another operation in their mouth?

Of the 99 patients who answered this question, 83 (83%) would and 4 (4%) said that they did not know.

Discussion

Management of pain after third molar operations is important particularly as most patients are treated as day-cases. Postoperative non-steroidal anti-inflammatory drugs such as ibuprofen[11–14] and paracetamol with codeine[14,15] have been reported to be effective after removal of third molars. Basic scientific evidence suggests that an analgesic given before operation should produce a better outcome than the same drug given after operation. Reviews of clinical findings have been mostly unfavourable,[16–19] but there is still a widespread belief of the efficacy of pre-emptive analgesia

among clinicians. Three randomised controlled trials with NSAIDs[20–22] and one with paracetamol[23] showed no evidence of a pre-emptive effect, whereas better analgesia was obtained when flurbiprofen was given preoperatively compared with only after operation.[24]

It has been suggested that a NSAID has a pre-emptive effect, however, it is unlikely to be seen with conventional doses and, secondly, any anti-nociceptive treatment should be extended into the initial postoperative period, when generation of nociceptive stimuli from the inflammatory process may be intense for 12–48 h, depending on the type of operation.[10] The treatment should cover the entire duration of the high intensity noxious stimulation that initiates the altered sensory processing. High-intensity noxious stimulation is generated not only by incisions (primary phase of injury) but also by the release of chemicals and enzymes from damaged tissues (secondary phase of injury extended well into the postoperative period).[25]

It is now accepted that the policy of waiting for a patient to report severe pain before prescribing an analgesic produces unnecessary discomfort and may reduce the efficacy of any subsequent treatment.[9] In this single-centre, randomised, double-blind placebo-controlled study we showed that pre-emptive analgesia is effective in immediate postoperative pain control, and that there were no significant differences between ibuprofen 600 mg, paracetamol 1 g + codeine 60 mg or diclofenac 100 mg. The lowest median time for first request for postoperative analgesia was in the placebo group and this was significant lower than with diclofenac.

There were no significant differences among the groups with respect to adverse events, which included nausea, vomiting, gastrointestinal discomfort and dizziness. NSAIDs have a number of side-effects[12–15] including their influence on platelet function. However, the increased risk of bleeding from the perioperative use of NSAIDs is clinically unimportant.[16] Careful selection of patients and history taking before the use of NSAIDs should avoid any adverse events. Combinations of paracetamol and codeine have been reported to have more side-effects than ibuprofen.[17]

Ibuprofen, paracetamol and codeine or diclofenac, or placebo reduced pain 30 min after operation, but there was no significant difference between the groups. There was, however, a reduction in the time before a request for postoperative analgesia between placebo and diclofenac groups. This is an interesting finding as patients who had taken placebo reported similar results to the pre-emptive analgesic groups. Perhaps the pre-emptive effect is unlikely to be seen with conventional doses and anti-nociceptive treatment should be extended into the initial postoperative period and continued up to 12–24 h postoperatively. It is therefore important to consider strategies other than a single pre-emptive dose of analgesic to control pain in the postoperative period.

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HISTORICAL CASE

THOMAS WHARTON (1614-1673)

English anatomist. Most famous eponym: Wharton's duct—the duct of the submandibular salivary gland.

Thomas Wharton studied at Pembroke College, Cambridge, Trinity College, Oxford, and obtaining his MD in 1647, after the city of Oxford had surrendered to Cromwell's army. Upon qualifying, Wharton had a medical practice in London, and worked with John Bathurst, Oliver Cromwell's personal physician. He was elected a fellow of the Royal College of Physicians in 1650, and was appointed physician to St Thomas' Hospital 7 years later.

In 1656, he published, at his own expense, his Latin treatise Adenographia, ''a description of the glands of the entire body''. This was the first thorough account of the glands of the human body, which Wharton classified as excretory, reductive, and nutrient. He differentiated the viscera from the glands and explained their relationship, describing the spleen and pancreas.

Wharton discovered the duct of the submandibular salivary gland, and explained the role of saliva in mastication and digestion. He also provided the first adequate account of the thyroid gland and stated that one of its functions was to fill the neck and make it shapely! He also described Wharton's jelly—a gelatinous primitive mucoid connective tissue of the umbilical cord.

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