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A placebo controlled comparison of ketorolac and fentanyl for use in day case oral surgery

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The analgesic, recovery and cardiorespiratory characteristics of ketorolac trometamol, a non-opioid analgesic, were compared with that of fentanyl and a placebo when used intraoperatively during day case oral surgery. One hundred and twenty-seven patients were entered into a double blind randomized, placebo controlled study. The results of the AUC (area under the curve) analysis of postoperative pain scores showed that patients receiving ketorolac experienced significantly less pain than those in the placebo group ($P = 0.001$). Patients in the ketorolac group recovered more quickly, as measured by the Maddox Wing test, than those in the fentanyl group ($P = 0.03$ at 1.5 h). Analysis of adverse events reported showed that patients receiving fentanyl experienced significantly more episodes of apnoea intraoperatively than patients in the other two groups ($P = 0.001$).

Key words: Ketorolac, day surgery, oral surgery

Introduction

In the UK there has been a large increase in the number of surgical procedures performed on a day case basis; a method recognized by the Royal College of Surgeons as a cost effective use of services[1]. Such a service demands that patients experience few complications during anaesthesia and surgery and that they recover promptly and are provided with adequate pain relief.

Fentanyl is a short-acting opioid that is commonly used during day case surgery. Opioids are used during anaesthesia as part of a 'balanced' anaesthetic technique to provide analgesia. Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) which has been shown to be an effective oral postoperative analgesic[2]. It is also available as an intravenous preparation and this study was designed to compare its effectiveness with fentanyl when administered at induction of anaesthesia.

Methods

One hundred and twenty-nine patients requiring surgical removal of their lower third molars and/or upper third molars if appropriate were entered into a randomized, double blind comparison of a single intravenous bolus dose of ketorolac, fentanyl or placebo.

Randomization into three groups was carried out using a computer generated set of random figures and standard exclusion and inclusion criteria were used when admitting patients to the study. All patients were of ASA type I or II fitness and had their surgery performed under general anaesthesia as day cases.

Anaesthetic regime

At induction all patients received propofol 2.5 mg kg^{-1} and suxamethonium 600 μg kg^{-1}. Patients were intubated using a nasotracheal tube and maintenance anaesthesia was provided using either isoflurane 2.5% (range 1–2.5%) or halothane 1.5% (range 0.5–2%) together with a 2 : 1 nitrous oxide : oxygen gas mixture with a fresh gas flow of 6 l min^{-1}.

Drug regime

Immediately before the start of surgery, group I received ketorolac 30 mg, group II received fentanyl 100 μg and group III received an ethanolic isotonic solution of saline as placebo. All these drugs were administered as an intravenous bolus dose of 3 ml vol over 60 s.

Postoperative rescue medication was packaged in a blind fashion and administered according to the entry code of the patient into the study in order that the patients who had received intravenous ketorolac at induction received oral ketorolac as rescue and patients who had received intravenous fentanyl or placebo received oral ibuprofen.

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Statistics

All tests were 2-tailed at the 5% significance level and examined differences between all pairs of treatments for the following clinical measurements.

Clinical measurements

Vital signs
Continuous monitoring of pulse rate (beats per min), blood pressure (systolic/diastolic mmHg) using a Datascope Accutor I (Datascope Medical Company Ltd, Huntingdon, UK).

Respiratory rate was monitored continuously using a capnograph. Oxygen saturation (SaO_2) using an Ohmeda Biox pulse oximeter 3700E (British Oxygen Co. Distributors, Birmingham, UK).

Pain severity
Using a 10 cm visual analogue scale preoperatively (as baseline) and postoperatively at: 15, 30 and 45 min and 1, 1.5, 2 and 3 h.

The area under the curve from 15 min to 3 h was measured and compared using the Wilcoxon rank sum test.

Time to rescue medication
Analysis was performed using standard survival analysis methods and the median times to remedication estimated using the Kaplan-Meier estimator.

Time to recovery
Time to recovery was measured using the Maddox Wing test[3] preoperatively (as baseline) and postoperatively at: 15, 30 and 45 min and 1, 1.5, 2 and 3 h.

Any adverse events were recorded.

Results

Demography

One hundred and twenty-nine patients were entered into the study but two did not receive their study medication and were withdrawn. The remaining 127 were all included in the safety analysis but two patients in group II were given postoperative analgesics outside the protocol and one patient in group I did not receive the correct amount of study medication. These three patients were thus withdrawn from the efficacy analysis. Results from 50 patients in group I, 47 in group II and 27 in group III were analysed. The groups were evenly matched for sex, age and weight and the median duration of surgery was similar in all groups at just over 30 min. Most patients (101) received maintenance anaesthesia as isoflurane/N_2O/O_2 the remainder (23) received halothane/N_2O/O_2.

Vital signs

A summary of the changes in vital signs can be seen in Table 1. Baseline signs were similar in all groups.

Pulse rate and systolic blood pressure tended to increase during surgery but there were no significant differences in the median change between the groups. Oxygen saturation remained within acceptable limits throughout anaesthesia.

Respiration tended to decrease during surgery. Patients in the ketorolac and the placebo group changed by −3 breaths and −6 breaths per min respectively.

Patients in the fentanyl group however, behaved in a markedly different way. More than half of the patients receiving fentanyl experienced apnoea and thus the median value for minimum respiration rate in this group was 0 breaths per min. Hence the median change was −20 breaths per min, a significant difference from patients in the placebo and ketorolac groups ($P = 0.001$).

Postoperative pain scores

Analysis of the AUC values (15 min – 3 h) revealed that the pain experienced by patients in group I was less than that experienced by patients in group III and that this difference was statistically significant ($P = 0.01$).

Table 1. Summary of vital signs

	Ketorolac	*Placebo*	*Fentanyl*
Systolic BP (mmHg)			
Baseline (median)	110	110	110
Surgery max (median)	128	133	130
Change (median)	14	20	21
Pulse rate (beats min^{-1})			
Baseline (median)	76	78	76
Surgery max (median)	105	105	97
Change (median)	29	26	19
Respiration rate (breaths min^{-1})			
Baseline (median)	22	24	24
Surgery min (median)	19	18	0
Change (median)	−3	−6	−20
Oxygen saturation (%)			
Range during surgery	91–100	92–100	91–100

Table 2. Area under the VAS curve from 15 min to 3 h (mm)

	Ketorolac	*Placebo*	*Fentanyl*
Number of patients	50	27	47
Median	24.8	31.4	24.7
Range	0.00–70.2	10.4–81.6	3.0–92.8

Treatment comparisons (Wilcoxon rank sum test)
Ketorolac vs fentanyl $P = 0.27$
Ketorolac vs placebo $P = 0.01$
Fentanyl vs placebo $P = 0.14$

Table 3. Time to first postoperative remedication (min)

	Ketorolac	*Placebo*	*Fentanyl*
Number of patients	50	27	47
Estimated time* by which 75% patients remedicated	214.0	130.0	146.0

*By Kaplan-Meier test.
Treatment comparisons (Wilcoxon rank sum test)
Ketorolac vs fentanyl $P = 0.48$
Ketorolac vs placebo $P = 0.73$
Fentanyl vs placebo $P = 0.95$

There were no other significant differences between the treatments (Table 2).

Time to rescue medication

There was no difference in the overall shape of the survival curves when these were examined using the Wilcoxon analysis (Table 3).

Time to recovery

At 1.5 h patients in group I were significantly more recovered as measured by the criteria of the Maddox Wing test than those in group II ($P = 0.03$). At 2 h the difference in recovery between these two groups approached significance again in favour of group I ($P = 0.06$), no other treatment comparisons showed significance (Figure 1).

Adverse events

Eighty-seven adverse events were recorded for 66 patients (Table 4). Of these events nine (10%) in group I, 44 (50%) in group II and eight (9%) in group III required action. It is suggested that if the treatment regimes were of equal efficacy then there would be the same proportion of actionable events in each study group. The observed proportions indicate a statistically significant difference ($P = 0.01$) in the number of events in each group and this is almost entirely due to the large number in group II, most of which were due to apnoea during the intraoperative period (Figure 2). Other adverse events were of small numbers only and there was no statistical difference in frequency between groups.

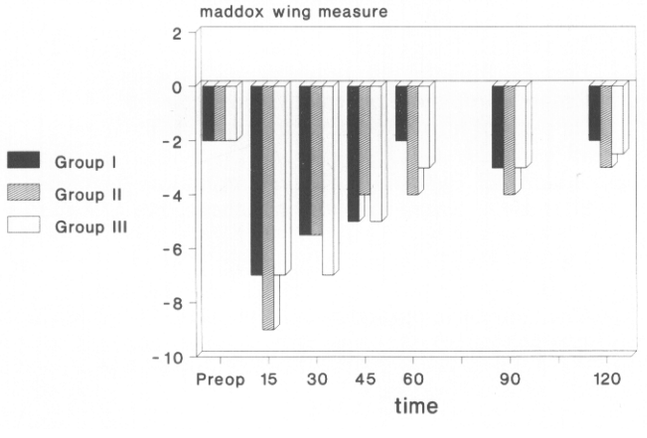

Figure 1. Time to recovery (Maddox Wing).

Discussion

The essence of day case surgery is that patients are discharged early and safely to their home environment. A good service aims for minimization of anaesthetic side-effects, few surgical complications and good postoperative analgesia.

Patients receiving fentanyl throughout this study encountered more intraoperative adverse events in the form of apnoeic episodes than patients in the other two groups and it is suggested that since intervention was required for most of these events this is an undesirable effect of fentanyl.

Due to its rapid onset and short duration of action fentanyl is often used in anaesthesia[4]. Others however, have expressed anxiety due to the degree of respiratory depression observed in patients receiving fentanyl[5] and it has been noted that fentanyl may even produce such effects in the postoperative period[6]. This study supports some of these findings in that there was a significant difference in the incidence of apnoea in the group of patients who received fentanyl perioperatively compared with those patients who received either ketorolac or placebo. Others have also used ketorolac during anaesthesia and have shown that no respiratory depressant effects are observed[7]. Murray et al. (1989) also showed that patients receiving ketorolac showed no

Table 4. Summary of adverse events

Adverse event	*Group I No. of patients*	*Group II No. of patients*	*Group III No. of patients*
Pain	1 (5%)	1 (2%)	1 (8%)
Apnoea	2 (10%)	30 (56%)	3 (25%)
Hypoventilation	9 (43%)	5 (9%)	1 (8%)
Nausea	1 (5%)	5 (9%)	2 (17%)
Multifocal extrasystoles	1 (5%)	2 (4%)	2 (17%)
Dizziness	1 (5%)	1 (2%)	1 (8%)
Sore throat	–	–	–
Vomiting	–	4 (7%)	–
Bradycardia	1 (5%)	2 (4%)	–
Haemorrhage	2 (10%)	1 (2%)	–
Syncope	1 (5%)	1 (2%)	–
Bigemminy	1 (5%)	1 (2%)	–
Headache	–	–	–
Ventricular extrasystoles	–	1 (2%)	1 (8%)

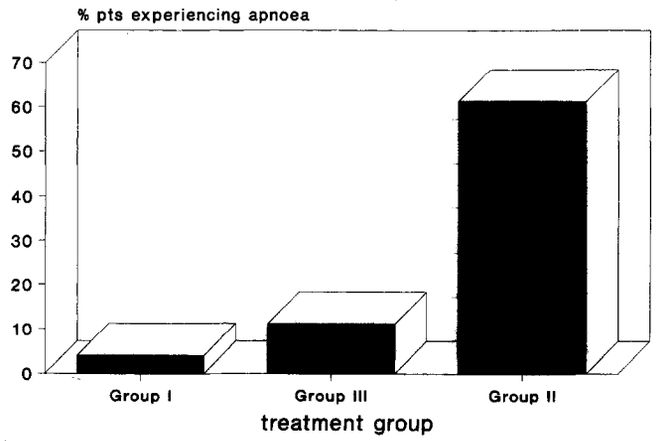

Figure 2. Frequency of occurrence of apnoea.

changes in heart rate and mean arterial blood pressure compared with a group receiving alfentanyl who experienced a fall in the value of both of these variables.

In this study, blood pressure and pulse rate increased during surgery in all study groups. However there were no significant differences in the changes between groups.

There was little difference in postoperative pain scores between the treatment groups, this was perhaps due to the relatively short duration of analgesic action of both active preparations when administered intravenously. The AUC analysis showed that ketorolac provided better pain relief than placebo and this may be useful as patients, once recovered, can be given an oral ketorolac regime before loss of analgesia from the intraoperative dose occurs.

Examination of time taken to recovery as measured using the Maddox Wing test showed that patients who had received ketorolac were significantly more recovered than those who had received fentanyl at 1.5 h (P = 0.03) and even by 2 h postoperatively the difference in recovery values still approached significance in favour of the patients receiving ketorolac (P = 0.06). This suggests that fentanyl may prolong recovery from anaesthesia in the early postoperative period and this may ultimately lead to a delay in the discharge of patients.

In conclusion, it is suggested that for patients undergoing day case surgery where a rapid recovery time allied to good pain control is required, the use of intravenous ketorolac during surgery may offer advantages over the current practice of administration of short and ultra-short acting opioid preparations.

Acknowledgements

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