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RESEARCH

Effectiveness of tramadol/paracetamol compared with etoricoxib as postoperative analgesia in daycare surgery

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Objective: The objective was to evaluate the effectiveness of a fixed, tramadol/paracetamol combination when compared with etoricoxib as postoperative analgesia following day care surgery.
Design: This was a prospective, randomised, single-blind study.
Setting and subjects: Sixty-two patients were randomised to receive either etoricoxib (n = 29) or tramadol/paracetamol (n = 33) by mouth prior to surgery. Patients were given general anaesthesia with fentanyl for intraoperative and rescue analgesia.
Outcome measures: The primary efficacy variables that were investigated were total pain relief and sum of pain intensity differences at 1, 2, 3, 4, 6, 24 and 48 hours. Data were collected by an independent observer through an interview or by telephone after discharge.
Results: Total pain relief (p-value 0.001) was significantly different between the two groups for the first four hours. The total dose of fentanyl use was comparable between the two groups. There was also a significant difference in the occurrence of nausea with tramadol/paracetamol (p-value 0.001), and dizziness with etoricoxib (p-value 0.024).
Conclusion: Tramadol/paracetamol provided significantly better pain relief than etoricoxib in the early postoperative period.

Keywords: daycare surgery, etoricoxib, paracetamol, postoperative analgesia, tramadol

Introduction

Day care surgery is cost-effective and forms 70% of hospital-based surgical procedures.[1] Postoperative pain is one of the most common causes of delayed discharge, patient dissatisfaction and unnecessary hospital admission following day care surgery.[1]

It is important for surgeons and anaesthetists to provide good pain control postoperatively and after the patient has been discharged home. Recently, it was shown that multimodal analgesia was a rational approach to pain management, and was more effective than analgesic drugs, with lesser adverse effects.[1] The "balanced analgesia" technique, involving a combination of non-opioid analgesics and smaller doses of opioid and local anaesthetic for wound infiltration or neural blockade, has become an increasingly popular approach for postoperative analgesia following day care surgery.[1]

Another important aspect of preoperative preparation is patient education with respect to pain management and patient participation in order to enhance rapid recovery and a return to work. Patients need to understand the analgesic plan, and should be given sufficient instructions on how to problem solve with respect to pain management in order to manage their own pain effectively. Similarly, patients should be motivated to enhance postoperative rehabilitation by early ambulation to improve respiratory function with deep breathing and to clear secretions by coughing.

Kehlet and Dahl recognised the important role of the anaesthetist in facilitating early postoperative recovery, and preventing a transition from acute to chronic pain by ensuring optimal intraoperative anaesthetic management, and adequate pain relief well into the postoperative period.[2] Increasingly, more major procedures, e.g. laparoscopic cholecystectomy and orthopaedic procedures involving the shoulder or hand, are being performed as same-day surgery. Watson et al reported inadequate control of postoperative pain with paracetamol and codeine, especially after discharge.[3] Fifty-five per cent of patients experienced severe pain up to seven days after shoulder surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute approximately 10% of the non-opioid analgesics. Nonpharmacological methods of pain control, e.g. cold treatment to relieve postarthroscopy shoulder pain, are utilised by only 6% of patients. Watson et al found that only 55% of their patients received simple instructions on analgesic use, and 56% of patients were unable to manage their own pain effectively. The majority of patients suffered inadequate pain relief and interference with sleep and daily living activities. Forty per cent of the patients experienced analgesic-related adverse events.[3] McHugh and Thoms, in a study on day surgery, reported that 88% of patients experienced pain at home after being discharged, and 21%, severe pain.[4]

In a pharmacological review, Raffa recommended the use of a combination of oral analgesics with different mechanisms of action which offer added advantages to the patient. Using a combination produces increased tolerability and efficacy, and synergistically increased analgesic effects in certain situations.[5] Smith et al studied the effectiveness of a combination of tramadol and paracetamol for post-surgical pain and as an alternative analgesic to NSAIDs.[6]

Tramadol has two mechanisms of action. It exhibits mild μ-opioid receptor binding and prevents noradrenaline and serotonin reuptake. This dual mechanism may explain the lower rates of abuse and respiratory depression than those experienced with other opioids.[7] The tramadol and paracetamol combination also increases benefit through enhanced pharmacokinetics when drugs with a different onset and duration of action are combined judicially.[8] Paracetamol may have multiple mechanisms of action, believed to include the

inhibition of prostaglandin E_2 release in the spinal cord and the inhibition of nitric oxide synthesis mediated by *N*-methyl-*D*-aspartate or substance P.[6]

Traditional NSAIDs, and more recently cyclo-oxygenase-2 (COX-2) selective inhibitors, have also been used as postoperative analgesia after daycare surgery. Etoricoxib is one of the newer available COX-2 inhibitors for oral use. It inhibits the enzyme, COX, which catalyses the first step in the pathway of prostanoids synthesis. Some of these are implicated in the pathogenesis of inflammation and nociceptive pain.[9] Liu et al found that preoperative use of etoricoxib 120 mg given orally was associated with a lower opioid requirement and better pain scores after day care gynaecological surgery.[10]

The aim of this study was to evaluate the effectiveness of a fixed tramadol/paracetamol combination compared with etoricoxib as postoperative analgesia following day care surgery. Although these drugs have been found to be efficacious and safe, not many studies have been conducted that directly compare etoricoxib with the tramadol/paracetamol combination. Day care surgery patients were chosen as usually they experience mild to moderate pain, and an oral analgesic is convenient for patients once they have been discharged home.

Method

This prospective, randomised, single-blinded clinical trial was performed following approval from the Dissertation Committee of the Department of Anesthesiology and Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), and the UKMMC Research Ethics Committee (Research No FF-305-2011).

After obtaining written consent, 62 American Society of Anesthesiologists class I or II adult patients, who fulfilled the criteria for day care surgery, were included in the study. Exclusion criteria were morbid obesity and chronic alcohol or substance abuse, and patient contraindication to tramadol, paracetamol or etoricoxib. Based on randomised numbers, patients were divided into two groups. Group A patients were given etoricoxib, and group B patients, tramadol/paracetamol.

Patients were reviewed early in the morning during the preoperative assessment. A test drug was given one hour preoperatively. General anaesthesia was administered to patients, with standard monitoring. Intravenous (IV) access was secured prior to the induction of anaesthesia with IV fentanyl, given up to 2 µg/kg bolus. Intermittent boluses of IV fentanyl were used intraoperatively based on the clinical indication. Airway management involved the use of a laryngeal mask airway device. Other opioid or NSAIDs were not given during the surgery. Prophylaxis was administered for postoperative nausea and vomiting (PONV), and included IV dexamethasone 4 mg and IV metoclopramide 10 mg. Balanced anaesthesia was maintained with air and oxygen mixed with sevoflurane, with a targeted minimum alveolar concentration value of 1. Fluids were calculated according to the duration of fasting and the deficit replaced depending on the judgement of the anaesthetist. At the end of surgery, local infiltration of the wound with levobupivacaine, based on a dosage of 2 mg/kg, was given by the surgeon.

Pain assessment was carried out postoperatively in the recovery room, based on the pain score via the visual analogue score (VAS) card and pain relief score using the pain relief scale. Excessive pain was controlled with small multiple doses of IV fentanyl 25 µg. The pain score was documented and taken as a baseline after one hour, commencing from the end of the surgery. The subsequent pain score was documented until four hours postoperatively. The duration of the procedure was noted, as well as the number of patients who required rescue fentanyl, and the total fentanyl dosage used by each patient.

Upon discharge, demographic data and phone numbers were obtained from the patients. VAS cards and patient pain diary sheets were given to patients. Subsequent pain assessments took place at 6, 12, 24 and 48 hours. This was carried out by a single independent operator through a direct interview or by telephone after discharge. The patient was discharged with etoricoxib 120 mg daily, or tramadol/paracetamol (37.5 mg/325 mg) three times daily, according to the groups.

During analysis, pain severity was based on the VAS scale. A pain relief scale was also used. Assessed pain parameters were total pain relief based on a numerical scale, whereby "0" was no relief and "4" was complete relief, as well as sum of pain intensity differences. Sum of pain intensity differences were derived from the total pain intensity differences calculated by subtracting each recorded pain intensity score from the baseline pain intensity score. These efficacy variables were calculated from the pain relief and pain intensity differences at 1, 2, 3, 4, 6, 24 and 48 hours postoperatively. The sample size was calculated using PS: Power and Sample Size Calculations® version 3.

The response within each subject group was normally distributed with a standard deviation of 0.33 in a previous study.[9] If the true difference in the experimental and control means was 0.35, 28 experimental subjects and 28 control subjects would need to be studied in order to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 0.8. The type I error probability associated with the test of this null hypothesis is 0.05. Data analysis was performed using the chi-square test for nonparametric data and Student's *t*-test for parametric data. A p-value < 0.05 was considered to be statistically significant. Data analysis was performed using SPSS® for Windows® version 20.

Results

Sixty-two patients were enrolled in the study. There were no significant differences between the two groups in terms of patient characteristics, such as gender, ethnicity, weight, height and BMI (Table 1). None of the patients withdrew from this study.

Table 1: Demographic data

Demographic data	Group A (etoricoxib) $n = 29$	Group B (tramadol/paracetamol) $n = 33$
Mean age (years)	37.93 (12.27)	38.18 (13.87)
Sex		
Male	10 (34.5)	9 (27.3)
Female	19 (65.5)	24 (72.7)
Race		
Malay	21 (72.4)	19 (57.6)
Chinese	3 (10.3)	6 (18.2)
Indian	3 (10.3)	4 (12.1)
Others	2 (6.9)	4 (12.1)
Weight (kg)	61.26 (11.64)	60.90 (13.62)
Height (m)	1.60 (0.07)	1.58 (0.08)
Body mass index (kg/m^2)	23.73 (3.88)	24.30 (4.87)

Values are expressed as mean ± standard deviation or numbers (%)

A large number of cases were excision biopsy of unilateral fibroadenoma, with a total of 20 cases (Table 2). The mean duration of the surgical procedures for the etoricoxib group was 85.7 [standard deviation (SD) of 39.5] minutes and 72.7 (SD of 27.2) minutes for the tramadol/paracetamol group (*p*-value 0.35).

The sum of pain intensity differences for etoricoxib were 0.77 (SD of 0.35) and 0.59 (SD of 0.31) for tramadol/paracetamol (*p*-value 0.14). Total pain relief with etoricoxib was 3.21 (SD of 0.68) and 3.69 (SD of 0.32) with tramadol/paracetamol (*p*-value 0.001). This was shown to be statistically significant (Table 3). Seventeen patients in each group required rescue fentanyl in the recovery room. There was no difference between the two groups with regard to the mean total fentanyl requirement (*p*-value 0.89).

Figure 1 shows the mean pain score over time for both groups. There was no statistical difference between the two groups from the first to the fourth hour. The mean pain score for the etoricoxib group and the tramadol/paracetamol group at the sixth hour was 0.89 and 0.35, respectively. This difference was statistically significant, with a *p*-value *of* 0.03.

There was a statistically significant difference in the mean pain relief score from the first to the fourth hour (*p*-value < 0.05) (Figure 2).

The side-effect profile is shown in Table 4. Some patients experienced more than one side-effect. Our study showed *p*-value < 0.05 for nausea and dizziness (*p*-value 0.001),

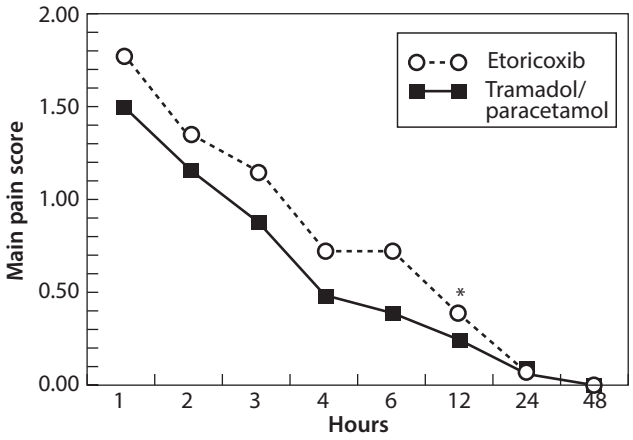

Figure 1: Pain score over 48 hours

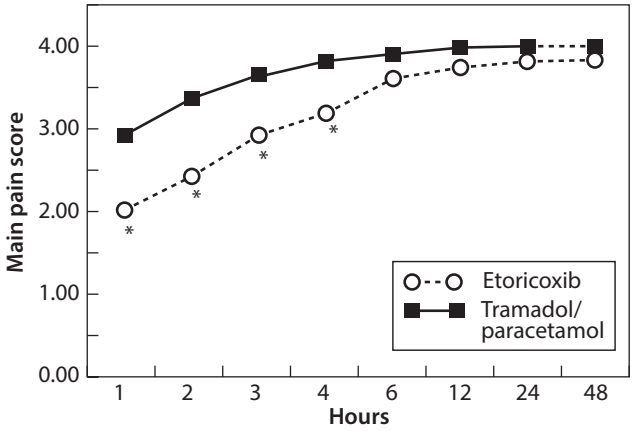

Figure 2: Pain relief score over 48 hours

Table 2: Types of operative procedure and the duration of the operation

Operative procedure	Etoricoxib	Tramadol/ paracetamol
Excision biopsy of unilateral fibroadenoma	8	12
Open unilateral inguinal hernia repair	8	7
Excision biopsy of lipoma	5	4
Laparoscopic bilateral tubal ligation	3	2
Examination under anaesthesia for anal fistula	1	2
J stent removal and reinsertion	0	3
Unilateral nephrostomy tube insertion	1	0
Hysteroscopy and biopsy	1	0
Removal of radius implant	0	1
Removal of tibial external fixation	1	0
Excision biopsy of unilateral wrist ganglion	1	0
Removal of multiple radius K-wire	0	1
Secondary suturing	0	1
Duration of operation (minute)	85.7 (39.5)	72.7 (27.2)

Values are expressed as numbers or mean ± standard deviation

Table 3: Analgesic efficacy measures and fentanyl requirements

Analgesic measures	Etoricoxib	Tramadol/paracetamol	*p*-value
The sum of pain intensity differences	0.77 (0.35)	0.59 (0.31)	0.14
Total pain relief	3.21 (0.68)	3.69 (0.32)	0.001*
Rescue fentanyl (μg)	17 (58.6)	17 (51.5)	0.35
Total fentanyl (μg)	99.5 (16.6)	100.2 (21.5)	0.89

Values are expressed as mean ± standard deviation or numbers (%)
* significant *p*-value < 0.05

Table 4: Frequency of adverse events

Side-effects	Etoricoxib	Tramadol/paracetamol	*p*-value
< 1	12 (41.4)	15 (45.5)	0.75
≥ 2	17 (58.6)	18 (54.5)	
Nausea	5 (27.7)	18 (78.2)	0.001*
Dizziness	11 (61.1)	6 (26.1)	0.024*
Vomiting	8 (44.4)	4 (17.4)	0.059
Headaches	13 (72.2)	10 (43.5)	0.066
Somnolence	4 (22.2)	4 (17.4)	0.69

Values are expressed as numbers (%)
* significant *p*-value < 0.05

suggesting that more nausea was associated with tramadol/paracetamol. Dizziness was significantly more frequent in the etoricoxib group (*p*-value 0.024). Significant differences were not found for other adverse events.

Discussion

In a national survey in the USA, Apfelbaum et al demonstrated that approximately 80% of a random sample of 250 patients experienced acute pain after surgery.[11] They revealed that patients experienced more pain once they had been discharged and were at home.[11] Unrelieved pain, prolonged recovery and minor anaesthetic complications often lead to unanticipated hospital admission following day care surgery, resulting in increased healthcare costs and unnecessary patient dissatisfaction.[11-12] Shnaider and Chung found that the incidence of pain following day care surgery ranged from 40–70%. They found that as a predictor of postoperative pain, after a 90-minute operation, 10% of patients experienced severe pain, while the number of patients with severe pain increased twofold following a 120-minute operation.[12] Pavlin et al found that unrelieved pain was a major factor in delayed recovery following a survey of 175 ambulatory surgical patients.[13] They found that as more major procedures, e.g. pelvic laparoscopies and transvaginal uterine procedures, as well as more complicated plastic surgery, were performed in an ambulatory setting, postoperative pain control became more important. They reported that 24% of their patients experienced delayed phase 1 recovery because of severe pain.

Both etoricoxib and tramadol/paracetamol provide good analgesia for mild to moderate pain, although they use different mechanisms.[8] In their study on acute postoperative dental pain, Chang et al found that the requirement for rescue analgesia within six hours postoperatively ranged from 22–41%, and that the amount used was significantly less in the etoricoxib group than it was in the oxycodone or acetaminophen group.[14] In this study, the majority of patients underwent minor procedures, e.g. excision of fibroadenoma of the breast. Most patients experienced mild pain, and there was no significant difference between the two groups with regard to the requirement for rescue fentanyl.

In our study, we showed that pain at home was adequately treated with analgesics given to both groups, although pain relief was significantly better with tramadol/paracetamol in the early postoperative period. It may be difficult to credit tramadol/paracetamol as the use of fentanyl as rescue analgesia continued in the recovery room. Also, there was no difference between the two groups with regard to rescue analgesia requirements. We postulate that this may be owing to other factors, such as differences in pain perception and individual pain tolerance thresholds, varying socio-economic backgrounds and previous post-surgical experience.

Smith et al reported that a combination of tramadol and paracetamol in an approximate 1:8 ratio resulted in synergistically enhanced analgesia, when a lower dosage of each drug was given to achieve a similar analgesic effect.[6] Paracetamol acts quickly, with an onset time of 20 minutes, peaks rapidly, and then declines thereafter.[6] By contrast, tramadol has an onset time of 50 minutes, followed by a plateau effect.[6] This may explain the significantly better pain relief demonstrated by the tramadol/paracetamol group in this study in the first four hours after surgery.

Smirnov et al showed that etoricoxib provided insufficient analgesia in the first few hours.[9] Etoricoxib is slow in onset, with daily dosing, reaching peak efficacy 3–4 hours after oral administration.[9,14] We did not find any significant difference in the sum of pain intensity differences between the two groups. Also, there was difficulty explaining the significant differences in total pain relief between the two groups in the first four hours. Perhaps a larger sample is needed to clarify this issue.

A multimodal strategy for postoperative analgesia should begin prior to the surgical procedure.[15] By activating multiple pain inhibitory pathways, combination analgesics can provide effective pain relief and lesser side-effects than an individual drug alone.[16] We included local infiltration of levobupivacaine up to 2 mg/kg, given by a surgeon. Pavlin et al demonstrated that pain scores were lower in patients who received local anaesthetic infiltration at the wound site.[13] In many studies, local anaesthetic agents have been shown to be useful in the management of postoperative pain.[15] White emphasised the important role of non-opioid analgesics for postoperative analgesia following day care surgery in a review. Although opioids may be required for more severe pain, the judicial use of adjuvants used in combinaiton is the ultimate way of achieving success. Potentially useful options include ketamine, alpha 2-adrenergic agents and adenosine.[16]

In terms of side-effects, nausea occured more frequently in the tramadol/paracetamol group than it did in the etoricoxib group, probably because of the tramadol. Tramadol exhibits mild μ-opioid receptor binding, and noradrenaline and serotonin reuptake inhibition.[6,7] The use of an opioid is commonly associated with a higher rate of PONV.[16,17] Schug et al reported that paracetamol plus tramadol showed a significantly reduced incidence of adverse events, compared to tramadol alone.[8] However Jung et al demonstrated an extremely low incidence of PONV (3.1%), compared to that noted in previous reports.[7]

Smirnov et al showed that the incidence of PONV was lower in the etoricoxib group, compared with placebo, in thyroid surgery.[9] The incidence of nausea was much higher in this study, but significantly worse with the use of tramadol/paracetamol. Cicconetti et al found that etoricoxib was an effective analgesic agent, with clinical advantages in terms of gastrointestinal safety and unimpaired platelet function in maxillofacial surgery.[18] Liu et al also confirmed that etoricoxib did not increase the risk of postoperative bleeding after day care gynaecological surgery.[10] Dizziness is a less common side-effect associated with the use of COX-2 inhibitors.[9,14] Smirnov et al reported a 2.9% incidence of dizziness in the etoricoxib group with respect to pain management in thyroid surgery.[9] The incidence of dizziness was much higher in this study, and was significantly higher in the etoricoxib group than it was in the tramadol/paracetamol group. We postulated that the residual effects of general anaesthesia were the cause of this problem, although the incidence of somnolence did not support prolonged recovery from general anaesthesia. The cause of a higher incidence of dizziness in the etoricoxib group could not be established with certainty from the available data in our study. Again, the incidence of headaches was much higher in this study, although there was a comparable incidence in both groups, and it was not significantly different. The study sample was small as the study was not designed with enough power for secondary outcomes, such as the frequency of adverse effects. However, patients in this study did not experience problems relating to the side-effect of analgesics. None of the patients

required readmission to hospital. None of the patients withdrew from this study because of adverse events.

In conclusion, successful pain management after day care surgery can be achieved with non-opioid analgesics. Tramadol/paracetamol provided significantly better pain relief than etoricoxib in the early postoperative period.

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