Original Research Article

Comparing the Effectiveness of Oral Celecoxib with Oral Tramadol as Pre-Emptive Analgesia in Ambulatory Surgery

Abd Manaf MF[1], Azizeh A[2], Budiman M[1], Wan Mat WR[1] (✉)

[1]Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia
[2]Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

Abstract

Nociception pathway is thought to be pre-emptively inhibited in hope to reduce acute pain in an anticipated procedural related tissue injury intraoperatively or postoperatively when pre-emptive analgesics are administered preoperatively. High intensity of pain is expected after surgical removal of the third molar which is associated with jaw swelling and limited opening of the jaw. We compared the pre-emptive analgesia effect of oral celecoxib and oral tramadol in elective ambulatory dental surgery under general anaesthesia. Informed consents were obtained from 84 patients with American Society of Anesthesiologists (ASA) physical status I or II and aged between 18 to 56 years. They were randomised to receive either oral celecoxib 200 mg (Group A) or oral tramadol 50 mg (Group B) one hour before induction of anaesthesia. Intraoperative and postoperative fentanyl consumption were compared. Numeric Rating Scale (NRS), ranging from 1 to 10, was used to assess postoperative pain scores. Group A showed a significant reduction in fentanyl consumption intraoperatively compared to Group B (p=0.047). Both groups of patients experienced mild pain at various times assessed postoperatively ranging between 0-2 NRS scores. Comparison between the groups did not detect significant reduction in pain scores and postoperative fentanyl consumption. We concluded that neither medication was found to be effective as pre-emptive analgesia, however, intraoperative fentanyl consumption was reduced by pre-emptive administration of oral celecoxib.

Keywords: Ambulatory surgery; celecoxib; pre-emptive analgesia; postoperative pain; tramadol

Correspondence:

Assoc. Prof. Dato' Dr Wan Rahiza binti Wan Mat. Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia. Tel: +603-91455785
E-mail: docaweng@yahoo.com

Introduction

Nociception pathway is thought to be pre-emptively inhibited in hope to reduce acute pain in an anticipated procedural related tissue injury intraoperatively or postoperatively when pre-emptive analgesics are administered preoperatively. It also prevents pathologic pain modulation, which helps to reduce the development of chronic pain (1). Commonly delayed discharges from day care units are the result of inadequate postoperative analgesia achieved or uncontrolled postoperative nausea and vomiting (PONV) possibly leading to unanticipated hospital admission (2,3). The perioperative pains experienced by patients are influenced by the duration of surgery and type of surgical procedure (2). High intensity of pain is expected after surgical removal of the third molar which is associated with jaw swelling and limited opening of the jaw (4,5). Removal of the impacted third molar can be done under local anaesthesia. However, if multiple third molar removals are involved and anticipated difficulties, surgical removal will be done under general anaesthesia. United Kingdom National Third Molar Program reported almost 70% of third molar extractions were done under general anaesthesia, while the rest were

performed under local anaesthesia in combination with sedation or local anaesthesia alone (6).

Multimodal analgesia combining intraoperative opioids, paracetamol, non-steroid anti-inflammatory drug (NSAID), and local and regional anaesthesia is practised in ambulatory surgery (2). Few studies used ketamine and pregabalin as pre-emptive analgesia (7,8). However, they are not routinely used in ambulatory surgery because of their side effects. A systemic review by Møiniche et al. (2002) revealed no additional benefit for pre-emptive analgesic treatment with NSAID, opioids or ketamine to postoperative pain relief compared with a similar post-incisional treatment (9).

Celecoxib is a COX-2 inhibitor with potent analgesic and anti-inflammatory properties (10). As coxibs have an opioid-sparing effect, it is hoped that their use as pre-emptive analgesia will reduce intraoperative and postoperative opioid requirements. Furthermore, they have lower gastrointestinal and coagulation adverse effects as compared to other NSAIDs (10,11). However, coxibs have an increased risk for thromboembolic complications, especially in patients with underlying atherosclerotic disease (11). However, recently, Nissen et al. (2016) published via precision showed that a moderate dose of celecoxib compared to naproxen and ibuprofen was equivalent to cardiovascular events in long-standing arthritis (12).

Moderate to severe pain can be treated using Tramadol which binds to the μ-opioid receptor and inhibits the reuptake of serotonin and norepinephrine. Tramadol causes less respiratory depression compared to morphine, which makes it suitable for analgesia in ambulatory surgery. However, caution need to be informed to patients as it can result in nausea, vomiting, headache and dry mouth (13).

A review done by Mishra et al. (2013) indicated that no study has clearly shown the best technique or approach in providing pre-emptive analgesia. However, they identified some pre-emptive analgesia modalities that influenced the postoperative pain either as a single or combination therapy (14). As we have been practicing pre-emptive analgesia in our ambulatory setting for the past few years, we would like to investigate the effectiveness of those medications used, compare their effectiveness, and review the side effects.

Materials and Methods

Ethical approvals were obtained from the Research Ethic Committee of Universiti Kebangsaan Malaysia (FF-2016-238) and registered in the National Medical Research Register (NMRR), Ministry of Health Malaysia. (Code number NMRR-15-2351-27978).

The study was performed in the Day care Unit of Hospital Kuala Lumpur. We recruited patients aged 18-56 years old with American Society of Anesthesiologists (ASA) physical status I or II who were administered general anaesthesia for elective dental surgery with anticipated duration of two hours. Written informed consent was obtained. Patients with body mass index (BMI) of more than 35 kg/m^2 and known allergies or contraindications to any of the study drugs were excluded.

The patients were assessed for eligibility during preoperative assessment in Anaesthesia clinic visit before surgery. On the day of surgery, the patients were reviewed again in the Day care ward and re-explained regarding the study. Patients were fasted for 6 hours before the procedures. A computer-generated randomisation table was used to randomised patients into two groups. Group A received oral celecoxib 200 mg, and Group B received oral tramadol 50 mg one hour before induction of general anaesthesia. The attending anaesthetist of the day care list and nursing staff were blinded to the patients' group allocations.

Standard monitoring with continuous electrocardiogram, non-invasive blood pressure and pulse oximetry applied before induction of anaesthesia. Patients were induced with intravenous (IV) fentanyl 2 mcg/kg, intravenous propofol 2 mg/kg with IV rocuronium 0.6 mg/kg. Nasal intubations were performed. Anaesthesia was maintained with desflurane in mixture of oxygen and air keeping the Minimum alveolar concentration (MAC) between 1.0-1.2. They also received 1 g of IV paracetamol for analgesia and IV dexamethasone 0.1 mg/kg after induction of anaesthesia. Intravenous ondansetron 4 mg was given 30 minutes prior to the end of anaesthesia for postoperative nausea and vomiting prophylaxis. Patient with signs of inadequate analgesia such as tachycardia or increase blood pressure, after excluding other causes, bolus of fentanyl 1 mcg/kg given to patient up to two boluses. Dosage of fentanyl used for analgesia intraoperatively recorded. Patients who received intravenous morphine intraoperatively were dropped out of this study.

Postoperatively, patients were monitored in the recovery area. Trained nurses used Numeric Rating Scale (NRS) to assess pain score which the scale was between 1 to 10. Pain scores and side effects were assessed at 30^{th} minute, 1^{st} hour, 2^{nd} hour and 4^{th} hour postoperatively. Patients with pain score more than 4,

received rescue IV fentanyl up to 1 mcg/kg during recovery period. Total dose of fentanyl used in recovery period was recorded. Patient that experienced postoperative nausea vomiting in recovery period received another dose of IV ondansetron 4 mg.

After fulfilling the criteria for discharge, which included ambulation, no nausea or vomiting, tolerated orally, able to pass urine and minimal postoperative pain, patients were discharged home. All patients were discharged with oral analgesia. Group A patients received a combination of oral paracetamol one gram six hourly with oral celecoxib 200 mg 12-hourly for three days. Meanwhile, patients in Group B received a combination of oral paracetamol one gram six hourly with oral tramadol 50 mg 8 hourly for three days. The duration of the recovery period and the time of discharge home were recorded. Postoperatively, patients were called up at 24 hours after the operation to reassess pain scores using NRS.

The 'Power and Sample Size Calculations program was used to calculate the sample size. Calculations were derived from the mean difference of the Verbal Analog Scale (VAS) of postoperative pain scores and standard deviations, as quoted in Kashefi et al. (2012). They compared the effect of celecoxib and acetaminophen as pre-emptive analgesia in lower limb orthopaedic surgery (10). From Kashefi et al. (2012) sample size calculation using standard deviation of 1.5 cm from difference of VAS scoring with power of study at 80% with a significant level (α value) of 0.05. From the values obtained, the calculation sample size was 36 patients per group and anticipating a 15% drop-out rate, 42 patients were recruited in each group.

The data was analysed using Statistical Package for The Social Sciences (SPSS) version 23.0 software. An Independent t-test was used to determine any significant differences for normal continuous variables such as weight and height. The Mann Whitney U test was used for non-normal continuous variables such as age, BMI, duration of surgery, duration of day care stays, number of teeth removed, and total intraoperative and post-operative fentanyl consumption. The Chi-square test was used for categorical variables in the demographic data and incidence of postoperative nausea and vomiting. A p-value less than 0.05 was considered statistically significant.

Results

A total of 84 patients were recruited. There were no significant differences between the groups when their demographic, surgical and day care stay durations were compared (Table 1). The number of teeth removed was also similar.

Table 2 indicated a significant increase in intravenous fentanyl requirement in Group B intraoperatively. There was no patient required intravenous morphine intraoperatively. There were no significant differences in the postoperative pain scores at various times assessed as shown in Table 3. Postoperatively, Group B had more patients that developed giddiness, dry mouth and headache than Group A. However, the differences between the groups were not statistically significant (Table 4). No patient required any rescue ondansetron postoperatively.

TABLE 1: Demographic data, number of teeth removed, duration of surgery and duration of daycare stay. Values were expressed as median [interquartile range], number (percentage) or mean ± standard deviation where appropriate

	Group A (n = 42)	**Group B (n = 42)**	***p* value**
Age (year)	26 [23.0 - 28.0]	27 [22.0 - 31.3]	0.399
ASA I	40 (95.2)	42 (100)	0.152
ASA II	2 (4.8)	0 (0)	-
Male	22 (52.4)	19 (45.2)	0.513
Female	20 (47.6)	23 (54.8)	-
Weight (kg)	63.0 ± 1.82	60.0 ± 2.06	0.227
Height (m)	1.65 ± 0.13	1.62 ± 0.15	0.091
BMI (kg/m^2)	22.4 [20.8 - 25.1]	21.7 [19.3 - 25.0]	0.345
Number of teeth removed	3.0 [2.0 - 4.0]	3.5 [2.0 - 4.0]	0.307
Duration of surgery (minute)	42.0 [36.8 - 57.8]	50.0 [37.3 - 60.0]	0.361
Duration of daycare stay (minute)	212.5 [168.8 - 255.0]	215.0 [185.8 - 250.0]	0.651

ASA: American Society of Anesthesiologists; BMI: body mass index

TABLE 2: Intravenous Fentanyl requirement intra & postoperatively. Values were expressed as number (percentage) or median [interquartile range]

	Group A (n = 42)	**Group B (n = 42)**	***p* value**
Intra Op Fentanyl usage	19 (45.2)	25 (59.5)	0.190
Post Op Fentanyl usage	8 (19.0)	10 (23.8)	0.595
Intra Op Fentanyl (mcg)	0 [0 - 50]	37.5 [0 - 100]	0.047
Post Op Rescue Fentanyl (mcg)	0 [0-0]	0 [0 - 6.25]	0.557

TABLE 3: Post-operative pain scores at various times. Values were expressed as median [interquartile range]

Time	**Group A (n = 42)**	**Group B (n = 42)**	***p* value**
30-minute	2 [1 - 3]	2 [1 - 3]	0.329
1-hour	1 [0 - 2]	1 [0 - 2]	0.324
2-hour	0 [0 - 1]	0 [0 - 0.25]	0.694
4-hour	0 [0 - 0]	0 [0 - 0]	0.080
24-hour	0 [0 - 0]	0 [0 - 0]	1.000

TABLE 4: Incidence of Post-operative side effects prior to discharge home. Values were expressed as numbers (percentage)

	Group A (n=42)	**Group B (n=42)**	***p* value**
Nausea	3 (7.1)	3 (7.1)	1.000
Giddiness	11 (26.2)	14 (33.3)	0.474
Vomiting	1 (2.4)	0 (0)	0.314
Dry mouth	7 (16.7)	12 (28.6)	0.297
Headache	2 (4.8)	4 (9.6)	0.676

Discussion

This study showed that pre-emptive celecoxib 200 mg can reduce IV fentanyl consumption during the intraoperative period only. Both groups showed reduced post-operative pain scores at various times, but we could not show any significant difference between the groups. This finding could have been confounded by the local anaesthesia that was routinely given by the surgeons prior to the removal of the third molars. No IV morphine was given but a few numbers of patients required bolus of fentanyl for analgesia during intra and postoperative.

Removal of the third molar involves an incision of the mucoperiosteum and osteotomy, resulting in the release of inflammatory mediators, so NSAIDs are the best choice of analgesia for dental surgery (17). Zamiri et al. (2009) compared celecoxib 200 mg, ibuprofen 600 mg and tramadol 50 mg given preoperatively on third molar extractions, and they found that pre-emptive ibuprofen and celecoxib reduced the pain severity postoperatively compared to tramadol (13). A meta-analysis from Moore et al. (1997) found that tramadol was less effective in controlling dental pain in controlling dental pain in comparison to post-surgical procedures (intra-abdominal surgery or Caesarean section) which involved visceral pain (18).

In the present study, in addition to pre-emptive celecoxib or tramadol, IV paracetamol one gram was also given as part of a multimodal analgesic technique. Therefore, the low pain scores observed postoperatively were unable to show a significant difference in postoperative use of intravenous fentanyl for both groups. Regarding multimodal analgesia, Hugland et al. (2006) reported combination of paracetamol and rofecoxib improved the analgesic effect compared with rofecoxib alone in the early hours postoperatively after third molar removal surgery (19).

The groups had no significant differences regarding postoperative side effects before discharge from day

care ward. Median duration of day care ward stay was equal in both groups. There was no anticipated ward admission documented. Our practice of combining IV dexamethasone and ondansetron in this study may explain the reduced number of PONV postoperatively seen even with the usage of tramadol as pre-emptive analgesia. A meta-analysis by Si et al. (2015) suggested that a combination of dexamethasone with ondansetron provided better prophylaxis against PONV than a single antiemetic drug after laparoscopic cholecystectomy (20).

Nowadays, medical costs are very high and have become a burden to the public health system (21). From the Malaysia Ministry of Health expenditure report from 2007 to 2014, there were noticeably a gradual rise of public healthcare expenditure from £757 million (RM 4.3 billion) in 2004 to £4.5 billion (RM 25.8 billion) in 2014 (22). Anaesthesiologists should be able to choose medications, which are cost-effective. The current price of oral celecoxib is £0.35 (Ringgit Malaysia, RM 2) per tablet and oral tramadol cost of £0.09 (RM 0.50) per tablet base on our pharmacy price. Total cost per patient in this study was about £2.47 (RM 14) in the celecoxib group and £0.88 (RM 5) in the tramadol group. As we found that postoperatively, there were no significant differences between post-operative pain scores or PONV, we suggest with the anaesthetic technique we applied, when costs are a concern, pre-emptive tramadol or celecoxib is not required in the removal of third molars in the ambulatory setting.

There were few limitations to this study. Firstly, the sample size calculation was based on detecting the difference of pain scores postoperatively between the groups. Therefore, our study was not powered to detect any difference of postoperative side effects and PONV between the groups. Secondly, this study focused on dental surgery in day care units instead of another surgical discipline. In dental surgery, intraoperative surgeons administered local anaesthesia infiltration before removal of the third molar, which may confound the analgesic requirements and postoperative pain scores observed in our study. Furthermore, patients were not blinded to the randomisation, which could have affected the pain score ratings during postoperative periods. They were insufficient data of side effects beyond 24-hour post-surgery. We must also keep in mind that side effects like nausea or vomiting may be contributed by the general anaesthesia itself.

Conclusion

Pre-emptive celecoxib was able to significantly reduce intraoperative fentanyl consumption. However, neither medication was found to be effective as pre-emptive analgesia.

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