

Oral Analgesic 24 Hours After Major Operation: A Comparative Study Of Oral Celecoxib And Tramadol In Patients Undergoing Major Gynaecological Operation

M. A. Hadi, MMed (Anaesth)*, A. Zamzila, MPath (Chemical Pathology)**, M.R. Azrina, MMed (Anaesth)*, A.W. Noraziana, MMed (O&G) ***, M.N. Basri MMed (Anaesth)*

Summary

Adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from a surgical facility. Furthermore, it has a major influence on the patient's ability to resume the normal activities of daily living. Tramadol is a weak opioid analgesic that acts mainly on μ -opioid receptor and has been proven to provide effective and safe analgesic to post-operative patients. Celecoxib (celebrex) is a highly selective COX-2 inhibitor. It belongs to nonsteroidal anti-inflammatory drugs (NSAIDs) group which reduces inflammation and pain while minimizing gastrointestinal adverse reaction. This selectivity feature makes celecoxib an attractive alternative to opioids for the control of postoperative pain.

The purpose of this study was to evaluate the effectiveness of oral celecoxib, in comparison with oral tramadol, in term of analgesic properties and the need for additional tablet acetaminophen as rescue pain reliever in patients undergoing elective gynecological operation.

A randomized, single-blinded study was conducted on 100 ASA I and II patients who were randomized into two groups: tramadol or celecoxib. Following major gynaecological surgery, all patients were given standard patient-controlled analgesia (PCA) regime with intravenous morphine. Patients either received oral tramadol 100 mg 8 hourly or oral celecoxib 200mg 12 hourly for analgesia 24 hours post operation. Tablet acetaminophen was available as a rescue analgesic. Patients were monitored for pain according to Modified Pain Score, haemodynamic changes and side effects. They were evaluated at 24, 32, 40 and 48 hours post operation. The mean pain score at 24, 32, 40 and 48 hours post operation were 0.86 ± 0.45 , 0.68 ± 0.47 , 0.42 ± 0.50 , and 0.14 ± 0.35 in celecoxib group and 0.92 ± 0.44 , 0.78 ± 0.41 , 0.46 ± 0.54 and 0.18 ± 0.39 in tramadol group respectively. There were no significant differences in the mean pain score and between the two groups at each point of assessment ($p > 0.05$). None of the patients requested for tablet acetaminophen. Patient satisfaction was similar in both study groups.

This study indicates that oral celecoxib 200 mg 12 hourly is adequate and suitable to be used as an alternative to oral tramadol 100 mg 8 hourly in controlling pain 24 hours following major operation without the need for additional tablet acetaminophen.

Keywords: Post operative analgesia, major gynaecological operation, celecoxib, tramadol

Introduction

Postoperative recovery after major surgery depends on various factors, such as adequate pain relief, nausea or vomiting and mobilization¹. After surgery, 77% of adult patients experience pain. Among them, around 80% experience moderate to severe pain². The goal of postoperative pain relief is to achieve optimal analgesia, facilitating a speedy return to normal physiological organ function with minimal side effects. Adequacy of postoperative

pain control is one of the most important factors in determining when a patient can be safely discharged from a surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living³. Acute pain can rapidly evolve into chronic pain, and the two should not be viewed as separate entities. Failure to achieve effective analgesia is a major predictive factor for the conversion of acute postoperative pain to chronic pain after various types of surgery.

The current armamentarium of analgesic drugs and techniques for the management of postoperative pain continues to grow at a rapid rate. Extensive use of opioids is associated with a variety of perioperative side effects, such as ventilatory depression, drowsiness and sedation, postoperative nausea and vomiting, pruritus, urinary retention, ileus and constipation that can delay discharge. Therefore, use of non-opioid analgesic techniques can lead to an improved quality of recovery for surgical patients⁴.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation by inhibiting the formation of prostaglandins⁵. Tissue injury and inflammation are associated with the upregulation of prostanoid synthesis and an abnormally exaggerated response to painful stimuli, resulting in the pain condition⁵. Cyclooxygenase is the enzyme that catalyses the first two reactions of prostaglandin, leading to the formation of prostaglandin H₂⁶. Since COX-2 inhibitors do not affect platelet function, a potential use of COX-2 inhibitors would be to alleviate pain and avoid narcotics which are associated with nausea and vomiting, without increasing the risk of postoperative bleeding⁷.

Immunohistochemical investigation shows that cyclooxygenase is expressed in various reproductive tissues. In the uterus, COX is primarily localized to endometrial epithelium, fallopian tube, perivascular cells of blood vessels in endometrium and deciduas. COX-2 is clearly involved in many normal gynaecological processes and in the etiology of several gynaecological disorders. It is used in specific applications, including the treatment of acute and chronic gynaecological pain as well as post-operative pain⁸.

Celecoxib is a highly-selective COX-2 inhibitor. It belongs to the nonsteroidal anti-inflammatory drugs (NSAIDs) group which reduces inflammation and pain while minimizing gastrointestinal adverse reaction⁹. Its half-life is 11 hours and therefore, the usual dosage is 200 mg twice a day^{10,11}. The actual prevalence of side effects from NSAIDs is low and in the relief of postoperative pain, they are excellent analgesic. The majority of data regarding adverse effects of NSAIDs have arisen from its long-term use in chronic arthritis¹².

Apart from NSAIDs, tramadol is also a potent drug which can be used for post operative analgesia. Tramadol has been used in a number of European countries for many years and has been approved

by the Food and Drug Administration (FDA) in the United States¹³. It is a weak opioid analgesic, acting mainly on μ opioids receptors but also has additional analgesic action through the inhibition of neuronal re-uptake of neurotransmitter 5-hydroxytryptamine and noradrenaline as well as stimulation of 5-hydroxytryptamine release. Unlike conventional opioids, tramadol has not been associated with clinically significant respiratory depression⁵.

The purpose of this study was to evaluate whether an analgesic dose of oral celecoxib is similar to oral tramadol in terms of analgesic properties, and whether supplement of tablet acetaminophen is required to control the pain. This study was also aimed to evaluate whether celecoxib can serve as an alternative analgesic in acute pain service (APS) 24 hours after operation (24 to 48 hours post operation) in our community.

Methodology

This is a randomized, single blinded, prospective study which was carried out from June 2005 until June 2006. A total number of 100 subjects who had undergone various major gynaecological operations were included in this study with equal number in celecoxib and tramadol group. Types of gynaecological operation include total abdominal hysterectomy with or without bilateral salpingo-oophorectomy, cystectomy and myomectomy. Inclusion criteria include age 18 – 55 years, weight > 25 kg but < 100 kg and classification of American Society of Anaesthesiologist Physical Status I or II. Exclusion criteria include lactating mothers, pregnancy and renal or liver impairment identified after routine preoperative screening of blood biochemistry.

This study has been approved by the Ethical Committee, International Islamic University Malaysia and Tengku Ampuan Afzan Hospital, Kuantan, Pahang. Patients who fulfilled inclusion criteria were included in the study after obtaining informed consent. Patient-controlled analgesia morphine (PCAM) was given to all patients only within the first 24 post-operative hours. After 24 hours, closed-envelope techniques were used to allocate patients randomly to receive either oral celecoxib 200mg twice daily or oral tramadol 100mg 3 times daily for postoperative analgesia. Hence, all patients received at least 48 hours of APS^{14,15}. All patients were encouraged to ambulate during this study.

Protocol

The anaesthetic regimen was standardized for all patients¹⁶. Premedication with 7.5 mg midazolam orally was given the night and 2 hours before surgery. Three to four mg.kg⁻¹ of thiopentone and 3 µg.kg⁻¹ fentanyl were given for induction of anaesthesia with non depolarizing muscle relaxant given once patient was under anaesthesia. Inhalational anaesthesia with O₂, N₂O and isoflurane was given, dosed to maintain a clinically adequate depth of anaesthesia. Patients were reversed with 1.0 mg atropine and 2.5 mg.kg⁻¹ neostigmine at the end of operation.

In Recovery Room

Loading dose of 0.1 mg.kg⁻¹ IV morphine¹⁷ up to a maximum dose of 10 mg¹⁸ was administered by slow intravenous injection before starting the patient-controlled analgesia (PCA). Morphine solutions were diluted as 1 mg.ml⁻¹. The devices were set to deliver 1.0 mg IV bolus dose of morphine with 10 minutes lockout time. No baseline infusion was given. Rescue intravenous bolus of 1.0 mg morphine was prepared as standby PCA morphine. Patients were instructed properly on the use of standard PCA machine. This PCA technique was continued until 24 hours post operation.

The patients were monitored using standard monitor in the recovery room for at least 30 minutes and supplemented with oxygen via face mask. Patients were evaluated at the end of 30 minutes before being discharged to the general ward. They were again evaluated in ward 24 hours prior to cessation of PCA use. Patients were then started on either oral celecoxib 200mg twice daily or oral tramadol 100 mg 3 times daily¹⁹ and monitored at 24, 32, 40 and 48 hours post operatively. Patients were encouraged to ambulate during this period. Tablet acetaminophen 500 mg were to be given for rescue analgesia.

The monitored parameters in this study were pain scores, patient satisfaction and the need for rescue (supplementary) analgesics (acetaminophen 500 mg). Pain scores were monitored using modified pain score (0=no pain; 1=slight pain; 2=tolerable pain; 3=severe pain; 4=worst pain imaginable²⁰) Side effects were also evaluated, such as nausea and vomiting, headache, dizziness, respiratory depression, dry mouth and bleeding tendencies.

Statistical analysis

Power analysis was done at the design stage of the study. Sample size calculation revealed that 29 patients per study group were required in order to achieve a significance level of 5% ($\alpha=0.05$) and power of study of 80% ($\beta=0.2$). Assuming an overall 20% dropout rate, a total sample size of 70 would be necessary. Thus, sample size of 100 (50 per group) was considered sufficient to answer the principal objective of the study. The data were analyzed using computer software SPSS version 12.0. $P < 0.05$ was considered as statistically significant. Comparison of parametric/continuous data presented as mean \pm SD (such as age, weight, height, and body mass index) were analyzed using independent t-test, while categorical data (such as ethnic groups, types of operation, patient satisfaction and the need for tab acetaminophen supplement) were analyzed using Pearson chi-square. All the categorical data were expressed as number and percentage (%). The pain score was analyzed using independent t-test and general linear model repeated measures. Results were presented as mean \pm SD.

Results

Demographic Characteristics

A total number of 100 female patients post major gynecological surgery who fulfilled inclusion criteria were included in this study after they consented. 80% of the subjects were Malay, compared with 17.0% Chinese and 3% Indians. This is in line with the racial representation in the East Coast community in Malaysia²¹.

There were no significant statistical differences in ethnic group, age, weight, height and body mass index between the two study groups ($p>0.05$). Table 1 summarizes and compares the patient characteristics in term of ethnic group distribution, age, weight, height and body mass index.

Types of operation

There were no statistical differences in the types of major gynaecological operations between the two study groups ($p>0.05$). Table 2 summarizes and compares the types of different major gynecological operations in celecoxib and tramadol groups.

Table 1: Distribution of subjects according to ethnic group, age, weight, height and body mass index in celecoxib and tramadol groups

Parameters	Celecoxib Group n = 50 (%)	Tramadol Group n = 50 (%)	p Value
Ethnic group			
Malay	40 (80)	40 (80)	0.822
Chinese	9 (18)	8 (16)	
Indian	1 (2)	2 (4)	
Age (years)	39.1 ± 9.1	40.6 ± 10.1	0.437
Weight (kg)	58.0 ± 11.1	59.7 ± 11.7	0.462
Height (cm)	158.4 ± 6.9	157.2 ± 9.1	0.460
Body Mass Index	23.0 ± 3.3	24.0 ± 3.2	0.109

Results are presented in n (%) and mean ± SD

Table 2: Types of gynecological operations in celecoxib and tramadol groups

Types of operation	Celecoxib Group n = 50 (%)	Tramadol Group n = 50 (%)	p Value
TAHBSO	18 (36)	20 (40)	p = 0.825
Hysterectomy	9 (18)	6(12)	
Cystectomy	16 (32)	18 (36)	
Myomectomy	7 (14)	6 (12)	

Results are presented in n (%)

Pain score

Figure 1 demonstrates mean pain scores at 24, 32, 40 and 48 hours post operation in celecoxib and tramadol groups. There were no significant statistical differences in the pain scores at each point of assessment in both study groups (p>0.05). None of the patients in the study group required tablet acetaminophen for pain rescue.

Side effects

Both celecoxib and tramadol were well tolerated

by the patients, with no refusal of medication and no episodes of nausea and vomiting, headache, dizziness, allergic reaction or episodes of bleeding requiring intervention within the study periods.

Patient Satisfaction

Table 3 summarized and compared patient satisfaction in both study groups. There was no statistical difference in patient satisfaction between the two study groups (p>0.05).

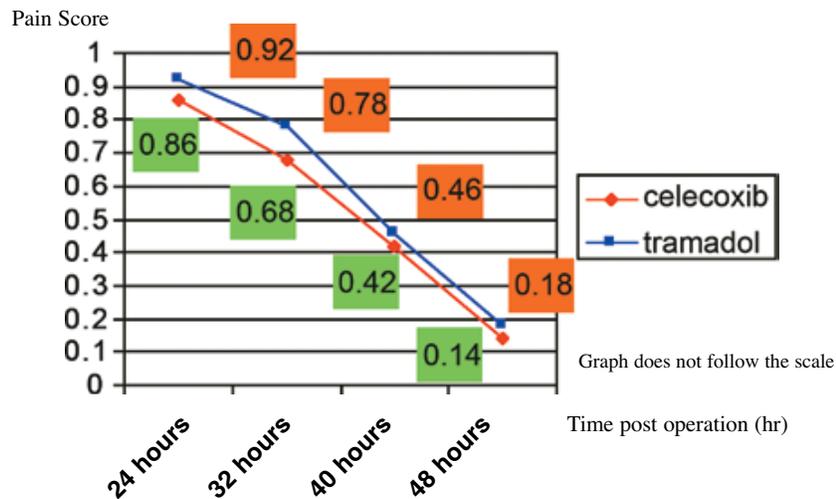


Figure 1: Mean post operative pain score at each duration of assessment in celecoxib and tramadol groups.

Table 3: Patient satisfaction in celecoxib and tramadol groups

Patient satisfaction	Celecoxib Group n = 50 (%)	Tramadol Group n = 50 (%)	p Value
Excellent	4 (8)	6 (12)	p = 0.447
Good	36 (72)	30(60)	
Satisfactory	10 (20)	14 (28)	
Poor	0 (0)	0 (12)	

Results are presented in n (%)

Discussion

Currents needs for improvement in postoperative pain management include (1) more effective relief of pain and suffering for all postoperative patients; (2) preventing and /or treating other postoperative symptoms (which may or may not be related to analgesic therapies) such as nausea, pruritus, sedation, and cognitive dysfunction; and (3) promoting recovery from surgery by preventing and/or treating postoperative physiologic dysfunction such as atelectasis and ileus²².

Non-selective NSAIDs are frequently used

analgesics for minor surgery and useful adjunctive analgesics in patients undergoing major surgery, decreasing pain and opioid requirements¹⁹. The introduction of a COX-2-specific inhibitor with analgesic properties could represent a significant therapeutic advance in the management of acute postoperative pain. The recommended dose of celecoxib in acute pain is 200mg twice daily, and studies have shown that this dose has prolonged effect and produced effective analgesic effects.⁸

Since tramadol is available in oral form and is not widely used in our acute pain service, it was chosen in comparison with celecoxib, a commonly used

analgesic in our hospital. We chose PCA as a post operative analgesic for the first 24 hours because of patient safety and to avoid bias from the health care personnel¹⁶. This study was conducted for 24 hours after we stopped PCA. This will give a total analgesic coverage of 48 hours since patients need 48 hours for complete control of pain postoperatively^{23,24}.

Early assisted ambulation within 48 hours post surgery was recommended²⁵. Keeping patient in bed longer than 2 days post-surgery can contribute to delayed functional recovery, delayed discharge and higher levels of dependency at discharge from acute care. In order to assist early ambulation, oral analgesic is a better choice of analgesic drug administration 24 hours after operation.

Immobilized patients have deleterious effects on muscle, volume status, respiratory function, urinary tract, and skin integrity²⁶. Patients who are obese or immobile are at risk of developing venous circulatory problems and predisposed to develop deep vein thrombosis. Early ambulation will significantly help to reduce deficits in venous blood flow by activating skeletal calf muscle pumps. It is also important to make optimum use of the respiratory system (respiratory pumps) to encourage specified breathing mechanism and to initiate collaborative skeletal and respiratory pump exercise.

All patients in both study groups were satisfied with the acute pain service given with none of them giving a poor response to both the analgesics. This suggests that oral celecoxib and tramadol were similar in terms of patient satisfaction with their analgesic coverage.

In our institution, the cost of oral analgesic is very much lower, compared to that of parenteral form, including PCA. The total cost for oral celecoxib per patient per day is RM 3.70 (USD 1.06) and RM 3.90 (USD 1.11) for oral tramadol. In contrast, the use of PCA morphine 100 mg for 48 hours would cost the patient RM 11.80 (USD 3.40), without factoring in the cost of the accessories such as PCA pump, syringes, tubing and preparation. Therefore, these oral forms are cost-effective alternatives for post operative analgesia in our context of acute pain service.

Apart from that, there may be indirect cost savings from the elimination of opioid-induced side-effects that may could increase nursing requirement and lead to delayed recovery. Murphy *et al.* in 1997²⁷ reported that despite its conventional opioid structure

and qualitatively similar pharmacological profile, tramadol has less effect on gastric motility, compared with opioids. Nausea, vomiting, headache and dizziness were not observed in our study. No patients in both groups developed allergic reactions during this study. There were no cutaneous manifestations due to histamine release such as mild flushing or urticaria over the hand at the site or cannula. The optimal non-opioid analgesic technique for postoperative pain management would not only reduce pain scores and enhance patient satisfaction but also facilitate earlier mobilization and rehabilitation by reducing pain-related complications after surgery.

In our study, we did not calculate the total usage of PCA morphine in each patient during the first 24 hours post operation. This may contribute to bias as patients who had utilized more PCA morphine during the first 24 hours may have residual analgesic effects of morphine during the start of the study.

Conclusion

Oral Celecoxib 200mg twice daily is as effective as oral Tramadol 100 mg 3 times daily in controlling post operative pain 24 hours after major gynaecological operation without the need for tablet acetaminophen 500 mg supplement.

Acknowledgements

This study received support from IRPA Prioritized Research Project No. IIUM 504 / 022 / 3 / LT 26 for the Department of Anaesthesia and Critical Care, Kulliyyah of Medicine in Kuantan. We would like to express our appreciation to the Kulliyyah of Medicine and the Department of Anaesthesiology, Tengku Ampuan Afzan Hospital for their support.

References

1. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Ther* 2001; 26: 257-262.
2. McCrory CR., Lindahl SGE. Cyclooxygenase inhibition for postoperative analgesia. *Anesth Analg* 2002; 95:169-76.
3. Bardiau FM, Taviaux NF, Albert A, Boogaerts JG, *et al.* An intervention study to enhance postoperative pain management. *Anesth Analg* 2003; 96: 179-85.
4. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesth Analg* 2005; 101:S5-S22.

5. Joshi GP, White PF. Management of acute and postoperative pain. *Curr Opin Anaesthesiol* 2001; 14: 417-421.
6. Samad T, Abdi S. Cyclooxygenase-2 and antagonists in pain management. *Curr Opin Anaesthesiol* 2001; 14:527-532.
7. Gajraj NM. Cyclooxygenase-2 inhibitor. *Anesth Analg* 2003; 96:1720-38.
8. Houston AM, Teach SJ. COX-2 Inhibitor. *Pediatr Emerg Care*. 2004; 20: 396-401.
9. Hayes EC, Rock JA. COX-2 inhibitors and their role in gynaecology. *Obstet Gynecol Surv* 2002; 57:768-780.
10. Davis NM, McLachlan AJ, Day RO, Williams KM. Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib: A selective Cyclo-Oxygenase-2 Inhibitor. *Clin Pharmacokinet* 2000; 38: 225-242.
11. Watcha MF, Issioui T, Klein KW, White PF. Cost and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. *Anaesth Analg* 2003 Apr; 96(4): 987-94.
12. Clement D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; 59: 957-80.
13. Miller, R.D. *Anaesthesia*. Philadelphia: Churchill Livingstone. 1999; 5th edition.
14. Bloch MB, Dyer RA, Heijke SA and James MF. Tramadol infusion for postthoracotomy pain relief: A placebo-controlled comparison with epidural morphine. *Anesth Analg* 2002; 94: 523-528.
15. Pang WW, Mok MS, Lin CH, Yang TF, *et al*. Comparison of patient controlled analgesia (PCA) with tramadol or morphine. *Can J Anaesth* 1999; 46: 1030-1035.
16. Wilder-Smith CH, Lauren H, Justin W and Lynnette D. Effects of morphine and Tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anesthesiology*. 1999; 91: 639-648.
17. Pang WW, Huang S, Tung CC and Huang MH. Patient-controlled analgesia with tramadol versus tramadol plus lysine acetyl salicylate. *Anesth Analg* 2000; 91: 1226-9.
18. Silvasti M, Svartling N, Pitkanen M. and Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* 2000; 17: 448-455.
19. le Roux,PJ, Coetzee JF. Tramadol today. *Curr Opin Anaesthesiol* 2000; 13: 457-461.
20. Chapman R, Casey KL, Dubner R, Foley KM, *et al*. Pain measurement: an overview. *Pain* 1985; 22: 1-31.
21. Malaysia Department of Statistics. (2000). Population distribution by local authority areas and mukims population and housing census 2000. *Bibliographic formats for citing electronic information*, [<http://www.statistics.gov.my/Bahasa/mediademo.htm>].
22. Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management. *Anesthesiology* 2003; 99: 1198-1208.
23. Miaskowski C, Crews J, Ready LB, Paul SM., *et al*. Anesthesia-based pain service improves the quality of postoperative pain management. *Pain* 1999; 80: 23-29.
24. Singelyn FJ, Gouverneur JMA. Postoperative analgesia after total hip arthroplasty: IV PCA with morphine, patient controlled epidural analgesia, or continuous "3-in-1" block?: a prospective evaluation by our acute pain service in more than 1,300 patients. *J Clin Anesth* 1999; 11: 550-554.
25. Siu AL, Penrod JD, Boockvar KS, Koval K, *et al*. Early ambulation after hip fracture. *Arch Intern Med* 2005; 166: 766-771.
26. Oldmeadow LB, Edwards ER, Kimmel LA, Kipen E, *et al*. No rest for the wound: Early ambulation after hip surgery accelerates recovery. *Aust N Z J Surg* 2006; 76: 607-611.
27. Murphy DB, Sutton A, Prescott LF, Murphy MB. A comparison of the effects of Tramadol and morphine on gastric emptying in man. *Anaesthesia* 1997; 52: 1224-1229.