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Comparing cost and effectiveness of IVPCA morphine with perioperative multimodal analgesia of oral etoricoxib and oxycontin: A retrospective study☆

Pik Yu Chen[a,*], Winnie Samy[b], Chee Lun Aaron Ying[a]

[a] Department of Anaesthesia and Intensive Care, 4/F, Main Clinical Block and Trauma Centre, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong

[b] Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, 4/F, Main Clinical Block and Trauma Centre, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong

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ABSTRACT

Introduction: Good pain control modality for post total knee replacement promotes patient's comfort and facilitates functional recovery, which may prevent post-operative complications; and shorten hospital stay. Therefore, manage pain efficiently and effectively have financial implications to the hospital. This retrospective study analyzed the clinical outcomes and costs of the intravenous (IV) patient-controlled analgesia (PCA) with a new perioperative multimodal analgesia (PMA) of using etoricoxib and oxycontin.

Methods: This retrospective study analyzed a total of 102 inpatients, 53 received both IVPCA and regular oral analgesics from September 2016 to February 2017, while 49 received preemptive oral etoricoxib before surgery and duly together with oxycontin and paracetamol after surgery from September 2017 to February 2018. Pain scores as the primary outcome were measured by Numeric Rating Scale (0–10) at rest (NRS-R) and on movement (NRS-M). They were analyzed by one-way analysis of covariance (ANCOVA). Other outcomes included side effects from analgesics, range of motion (ROM°), patient satisfaction, length of hospital stay and costs of medications.

Results: Patients in PMA group achieved better outcomes than PCA group. NRS-M of PMA group shown lower mean pain score and (standard error) than PCA group (2.96 [0.31] vs 4.26 [0.29]; $p = 0.003$), side effects from analgesics (18% vs 45%), ROM $\geq 90^{\circ}$ (55.1% vs 30.2%), patient satisfaction (8.97 vs 7.5 out of 10; $p = 0.005$), and length of hospital stay (6 days vs 8 days; $p < 0.001$). Moreover, the medication cost of PMA was 59.9% lower than PCA regimen.

Conclusions: This PMA approach achieved better outcomes and saved hospital costs.

1. Introduction

Total knee replacement (TKR) is a definitive surgical procedure to relieve chronic arthritic knee pain and to restore patients' quality of life. Good post-operative pain control promotes patients' comfort and facilitates functional recovery, which may prevent post-operative complications and shorten hospital stay.[1] Therefore, manage pain efficiently and effectively have financial implications.

Traditionally, patients who have undergone major operations are given Intravenous (IV) Patient-Controlled Analgesia (PCA) as the standard post-operative pain control modality. It allows patients to self-administer small but frequent doses of analgesic according to a pre-set program to relieve pain.[2] However, it requires specific equipment, medication and consumables, with the costs quoted at US$179.74/patient/48 h.[3] Using this modality also requires extra nursing care and monitoring, which is costly (US$100.37/patient/day).[4] Its superiority on pain control is in dispute,[5] and could be affected by various patient's factors.[6] Moreover, opioids like morphine and tramadol are commonly associated with adverse effects, such as nausea and vomiting.[5]

In September 2016, our team tried a new pain management strategy that OxyContin (prolonged release oxycodone, Mundipharma) was given upon cessation of IV PCA, aiming to enhance pain control and

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* Corresponding author. Department of Anaesthesia and Intensive Care, 4/F, Main Clinical Block and Trauma Centre, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong

E-mail addresses: pro910@cuhk.edu.hk (P.Y. Chen), wsamy@cuhk.edu.hk (W. Samy), dr@claying.net (C.L. Aaron Ying).

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early mobilization. This new regimen was found to be feasible and convenient to our patients. From September 2017 onwards, all TKR patients receive perioperative multimodal oral analgesia (PMA) with combination of etoricoxib, OxyContin and paracetamol, instead of IV PCA, unless contraindicated.

Etoricoxib is a cyclo-oxygenase (COX-2) inhibitor, which has less platelet dysfunction and therefore less bleeding risks than non-selective non-steroidal anti-inflammatory drug (NSAID).[7] It has been shown to be effective for post-TKR pain relief.[8] OxyContin is a strong opioid, formulated as prolonged release to be given twice a day. It may cause less nausea and vomiting when compared to morphine.[9] Paracetamol is the most commonly used analgesic, which provide opioid-sparing effect and has least side effects among others.[10] The use of multimodal analgesia can address different pain mechanisms to achieve synergistic effect and reduces overall side effects.[11]

This is a retrospective study to compare the costs and effectiveness in clinical outcomes of IV PCA regimen with PMA regimen for patients underwent TKR.

2. Methods

2.1. Study design and patient

This retrospective study was performed in a hospital and approved by their Clinical Research Ethics Committee. Patients underwent TKR from 1 September 2016 to 28 February 2017 was allocated as PCA group, while from 1 September 2017 to 28 February 2018 were allocated as PMA group.

In order to ensure both groups were comparable, similar demographics including age between 18 and 90, body weight ≥ 44 kg, operation, anaesthesia type, American Society of Anesthesiogists (ASA) physical status 1 to 3, and post-operative treatment data (analgesics used) were included for comparison. Patients who had not attended our hospital's pain management class or pre-operative anaesthesia assessment clinic to receive post-operative pain management information, patients with metastatic cancer, acute knee fractures, had emergency operation, underwent bilateral TKR, IV PCA did not start immediately after operation (for PCA group), mental retardation, severe psychological illness, active or history of drug abuse, or contraindicated to the analgesics required were excluded.

In PCA group, immediately after operation, they were given IV PCA with bolus dose of morphine 1 mg, lockout time interval of 6 min and 4-h limit of 20 mg as the default programme. Most of them were also supplemented with regular oral paracetamol 1 g and tramadol 50 mg every 6 h. Upon cessation of IV PCA, they were added regular oral OxyContin 5 mg every 12 h up to day 4.

In PMA group, patients were given etoricoxib 90 mg premedication before the operation. Post-operatively, OxyContin 10 mg was given immediately after returned to ward, along with paracetamol 1 g every 6 h once oral intake was tolerated. Starting on the next day, etoricoxib 90 mg daily was given for 1 week, OxyContin 5 mg every 12 h was given until post-operative day 4, on top of paracetamol. IV or oral tramadol 50 mg was the rescue analgesic as requested.

2.2. Data collection

The primary outcome was the pain score measured by Numeric Rating Scale at rest (NRS-R) and on movement (NRS-M), both ranged from 0 (no pain) to 10 (the worst imaginable pain). Secondary outcomes included side effects of analgesics, e.g. nausea, knee flexion range of motion (ROM°), overall patient satisfaction to analgesia on a self-report grading scale from 0 (no good at all) to 10 (excellent), length of hospital stay, and costs involved.

Pain control was assessed on post-operative day 1, when patient had not mobilized yet, and on day 4 after rehabilitation programme had begun. Pain scores, side effects and satisfaction scores and ROM were obtained from acute pain service database and patient's progress notes. Demographic data, length of hospital stay were found in hospital computer record. Costs involved were retrieved from hospital pharmacy and procurement.

2.3. Statistical analyses

With our current sample of 53 participants in PCA group and 49 in PMA group, we have achieved 85% power ($\alpha = 0.05$) with a moderate effect size (0.6) using a two tailed *t*-test calculated by G power (Version 3.1.9.2).[12] All statistical analyses were conducted with SPSS 24.0 for Windows software (SPSS Inc., Chicago, IL). Shapiro-Wilk test were used to test the normality of the data recorded.

The primary outcome, pain score was analyzed by analysis of covariance (ANCOVA) to determine the effect of each treatment group on post intervention pain scores after controlling for baseline pain score. Data were reported as mean, standard deviation (SD) or standard error (SE) and 95% confidence interval (CI) if the data were normally distributed or median and interquartile range (IQR) if the data were not normally distributed. We used chi-square and Fisher's exact tests to compare ROM and demographic characteristics between groups, such as gender, ASA physical status, anaesthesia type, and side effects of analgesics used.

Depending on the normality of data, weight, length of hospital stay and overall satisfaction were compared by independent Student's t-test or Mann-Whitney *U* test. A 2-sided $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

One hundred and thirty-three patients underwent TKR during the study periods. Among them, 31 did not meet the inclusion criteria. From 1 September 2016 to 28 February 2017, 53 patients were included in PCA group; and from 1 September 2017 to 28 February 2018, 49 patients were included in PMA group. The demographic data of PCA and PMA groups were comparable (Table 1).

3.2. Primary outcomes

There was no significant difference between two groups on pain scores at rest and on movement on post-operative day 1. In contrast, on day 4, NRS-R in PCA group was significantly higher than that in PMA group (0.871 [SE 0.16] vs. 0.374 [SE 0.16], p = 0.030) with a mean difference of 0.5, 95% confidence interval 0.49 to 0.94. NRS-M in PCA group was also greater than that in PMA group (4.259 [SE 0.29] vs. 2.964 [0.31], p = 0.003) with a mean difference of 1.29, 95% confidence interval 0.46 to 2.13.

Table 1
Demographic and baseline characteristic of PCA and PMA groups.

	PCA group (n = 53)	PMA group (n = 49)	P value
Age, years	67.4 (8.07)	69.6 (8.11)	0.53
Gender (male/ female)	11/ 42	10/ 39	1.0
*ASA (I/ II/ III)	6/ 37/ 10	3/ 33/ 13	0.48
Weight, kg	66.59 (10.22)	69.63 (13.78)	0.09
Anaesthesia type (GA/ SA/ CSE/ GA + peripheral block)	13/ 35/ 2/ 3	8/ 40/ 0/ 1	0.22

Data are presented as mean (SD) except for gender,ASA, and anaesthesia type, which are presented as frequency (n).ASA = American Society of Anesthesiologists; GA = general anaesthesia; SA = spinal anaesthesia; CSE = combine spinal epidural.

Table 2
Incidence of opioid related adverse events on different days after surgery.

	Post op Day 1		Any time within 4 days follow up	
	PCA group (n = 53)	PMA group (n = 49)	PCA group (n = 53)	PMA group (n = 49)
Nausea	6 (11.3%)	5 (10.2%)	10 (18.9%)	6 (12.2%)
Vomiting	14 (26.4%)	1 (2%)	16 (30.2%)	5 (10.2%)
Dizziness	3 (5.7%)	3 (6.1%)	4 (7.5%)	3 (6.1%)
Itchiness	1 (1.9%)	0	2 (3.8%)	0
P value	0.007		0.015	

Data are presented as frequency (n).

3.3. Secondary outcomes

3.3.1. Side effects of analgesics

Higher proportion of patients in PCA group experienced at least one adverse effect than PMA group on the first day after operation (45% vs. 18%, p = 0.007). More patients of PCA group than PMA group reported vomiting (26% vs 2%). With the cessation of IVPCA and the introduction of regular oral OxyContin, PCA group still had higher incidence of opioid related adverse effects than PMA group, such as nausea, vomiting, itchiness, and dizziness (p = 0.015) within the period of pain team follow up. Table 2 summarised the findings.

3.4. ROM

There was no significant difference between groups on post-operative day 1 to day 3. On day 4, more patients in PMA group could achieve knee flexion of 90° or above than PCA group (55.1% vs. 30.2%, p = 0.01). Fig. 1 summarised the ROM of both groups over the data collection period.

3.5. Patient satisfaction and length of stay

The mean patient satisfaction scores were higher in PMA group than PCA group (8.97 [SD 0.96] vs. 7.5 [SD 2.22], p = 0.005). PMA group had shorter length of hospital stay, median 6 [IQR 5–7] days, by contrast to PCA group was 8 with IQR 6–8.5 days.

3.6. Medication costs of both groups

For PCA group, the total costs of medications and consumables from day 0 to day 4 including morphine, normal saline, specific tubing for IV PCA, consumables to set up a dedicated IV access, and other analgesics were HK$5460 (US$700), which equalled to $103 (US$13.2) per patient. For PMA group, the total analgesics costs were HK$2190 (US $280.8), which equalled to $44.7 (US$5.7) per patient. Fig. 2 illustrated the average cost of the medication used for each group.

4. Discussion

TKR is considered as the definitive treatment for severe knee osteoarthritis to relieve pain and improves function. As at 31 December 2018, the estimated average waiting time for TKR in public hospitals is 67 months.[13] Delay of operation could affect post-surgery outcomes.[14] It asserts pressure to hospital administration to shorten patients' hospital stay. On the other hand, restoration of knee's range of motion is a major factor affecting patient satisfaction. Satisfactory post-operative pain control allows patient to participate in physiotherapy in their early post-operative period, which improves clinical, economic and patient-reported outcomes.[15–17] PMA approach has demonstrated its effectiveness and efficacy in these aspects.

There was no difference in pain severity between both groups on the first day after operation, as patients had not started active physiotherapy yet. However, on day 4, when intensive physiotherapy had been started, the PMA regimen demonstrated better pain relief than the PCA regimen, with lower pain score especially during movement.

Because of lower pain intensity on movement and less adverse effects from the analgesics, PMA patients may be able to start earlier or tolerate better to the intensive physiotherapy. Patients' knee flexion ROM should have 90° in order to perform various daily activities.[18] The ROM of PMA group was significantly better than PCA group (55.1% vs. 30.2% able to achieve 90° on day 4). With better treatment outcomes and shorter length of hospital stays, thus patient satisfaction were higher in the PMA group.

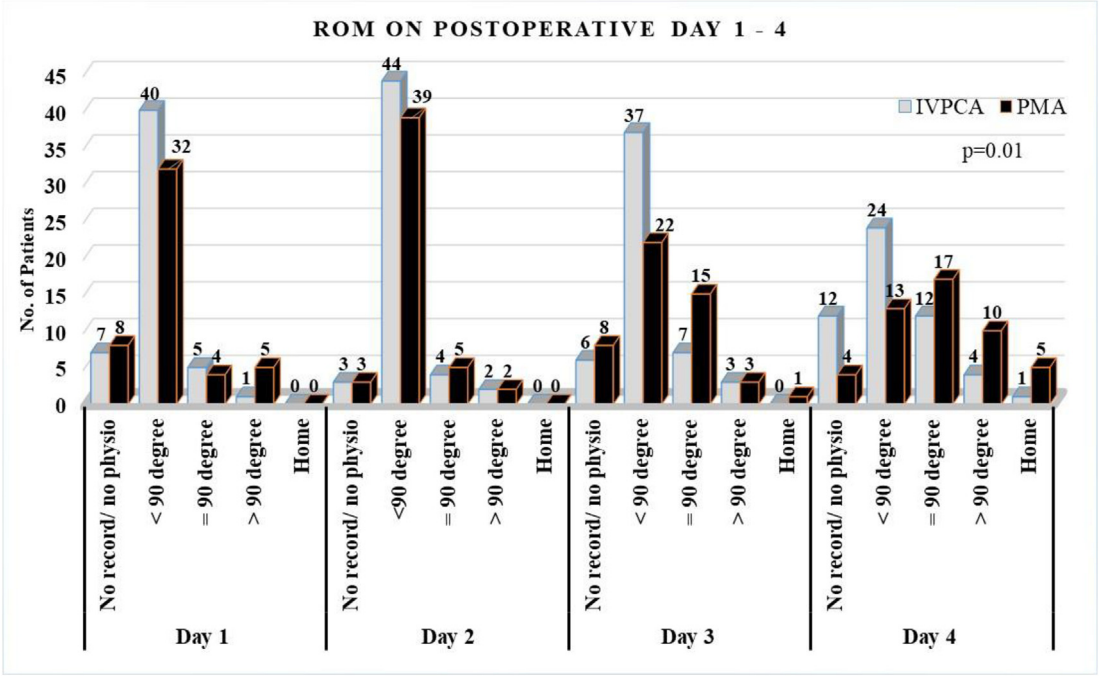

Fig. 1. Flexion Range of Motion from Post-operative Day 1–4. Data are presented as frequency.

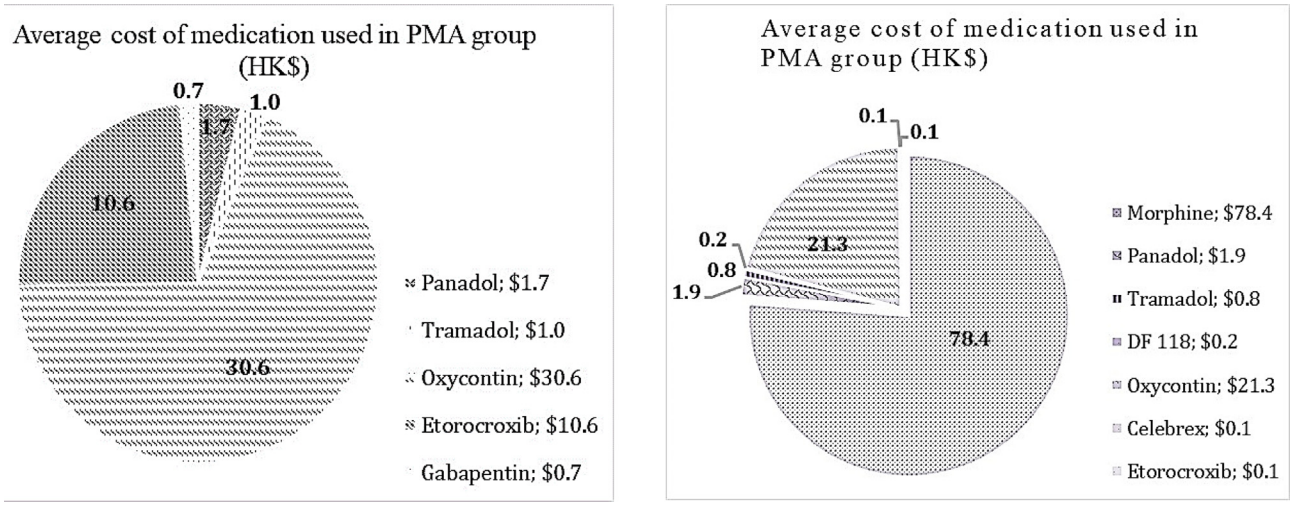

Fig. 2. Average cost of medication used in each group.

Apart from the clinical outcomes, PMA may reduce costs and healthcare resources. Shortened length of stay of two days relieves bed occupancy. With the availability of hospital beds, hospital management may add slot for TKR operation to shorten patients' waiting time and holiday physiotherapy to facilitate rehabilitation progress. Moreover, early discharge potentially reduces patient at risk of hospital-acquired infections. The cost of PMA analgesics was not only 59.9% lower than the IV PCA regimen but also oral route of administration is more convenient and less labour intensive. On the contrary, IV PCA requires extra training of medical staff to supervise and monitor patients. Patients' comprehensibility in using IV PCA is an essential factor that affects satisfactory pain control. Our medication cost analysis did not take staffing and PCA machines into account, because they are considered as fixed assets.

We are aware of the concern on using slow release strong opioids in the management of acute pain.[19–22] The criticisms are against inappropriate prescription, lack of patient education and lack of supervision, especially after discharge from the hospital. These problems can be minimized by employing appropriate measures. For instance, patients have to attend pain management education session before TKR to receive information regarding purpose of using OxyContin, its side effects, duration and risks. During their hospital stay, OxyContin will be given at a fixed dosage, frequency and duration. Patients' drug compliance and response are being monitored by medical staff. Upon discharge, OxyContin will be ceased and is not prescribed as discharge medication. With these safety measures, risk of addiction is minimized. After implementation of this PMA in our hospital, opioid dependence after TKR has not been reported.

Limitation of this single institution retrospective report includes change in analgesic regimen in both groups. One patient from PMA group did not receive the first dose of OxyContin because of sedation immediate post-operation. Another patient refused regular OxyContin because of minimal pain. There were 12 (22.6%) patients in PCA group needed to stop IV PCA or tramadol because of the side effects, which was replaced by diclofenac, dihydrocodeine and/or gabapentin. In PMA group, there were 20 (40.8%) patients requested one rescue dose of tramadol, and 5 (10.2%) patients had more than one rescue doses of tramadol and regular gabapentin to enhance pain control. Moreover, there were report bias and Hawthorn effects. Physiotherpay may be interrupted by weekend and public holidays, which affects pain intensity reported and rehabilitation progress. Some of the ROM data was missing in the medical notes.

5. Conclusion

The perioperative oral analgesia approach after total knee replacement may offer superior pain relief that improve clinical, economic and patient-reported outcomes. With implementation of appropriate clinical guidelines, risk of substance use disorder shall be avoided. This study provides information for clinicians and administrators to consider using this PMA approach. The efficacy and optimal regimen in different surgical procedures could also be investigated.

Declarations of interest

None.

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