PAIN CONTROL AFTER OPEN HEART SURGERY: TRAMADOL VERSUS OXYCODONE

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Abstract

Background: Pain management after open heart surgery is a priority to allow faster recovery and provide patient satisfaction. Various pain protocols have been adapted and are likely to be improved with the availability of more effective oral pain-killers.

Methods: This prospective, randomized, double blinded study compared the effectiveness of pain control and side effects between oral tramadol and oral oxycodone after open heart surgery. Eighty patients scheduled for open heart surgery were randomly assigned to receive either oral tramadol 50 mg or oral oxycodone 5 mg every 6 hours for post-operative analgesia. Intra-operatively, all patients received intravenous fentanyl 20 µg/kg during induction and morphine 0.15 mg/kg. Post-operatively, all patients were also given regular doses of paracetamol and rescue morphine as required. Pain scores using numerical rating scale and additional morphine dose requirements were documented at 1, 6, 12, 18, 24, 32, 40 and 48 hours post-extubation.

Results: The mean pain score at rest was significantly lower in the oxycodone group at all times except at 6 hours post-extubation. The pain scores on movement were mostly comparable between the two groups, with significantly less pain scores in the oxycodone group at 1 and 40 hours. Total rescue morphine was significantly lower ($p< 0.001$) with oxycodone (0.05 ± 0.22 mg) compared to tramadol (1.42 ± 1.98 mg). Number of patients requiring rescue morphine in the oxycodone group was also lower ($p< 0.001$). Post-operative nausea and vomiting (PONV) was significantly lower in the oxycodone group ($p< 0.001$). The side effects of absent bowel output and mild sedation were comparable in both groups.

Conclusion: Pain control after open heart surgery was superior with oral oxycodone, with significantly lower pain scores at rest, total rescue morphine and incidence of PONV as compared to oral tramadol.

Keywords: pain, open heart surgery, tramadol, oxycodone

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Introduction

The management of pain after open heart surgeries is one of the important issues to be addressed so as to fasten the recovery and provide superior patient satisfaction[1]. Pain from open heart surgery can arise from the sternotomy, leg vein harvesting, pericardiotomy and chest tube insertion[2,3].

Various protocols have been adapted by different cardiothoracic units to manage post open heart surgery pain. The analgesic combinations given to patients are mainly paracetamol combined with either oral dihydrocodeine (DF118), patient control analgesia with morphine (PCAM) or oral tramadol. Cyclo-oxygenase 2 (COX-2) inhibitors were not used due to concerns of their side effects and related morbidity[4]. Others have used continuous infusion of local anesthetics through an indwelling catheter at the sternostomy wound as an alternative to opioids for analgesia[5].

Tramadol is an opioid that is widely used in various medical disciplines. Oral and parenteral tramadol effectively relieves moderate to severe postoperative pain as it has an overall analgesic efficacy similar to that of morphine[6]. Bioavailability of tramadol is about 60% which increases to about 90% with multiple doses[6]. The efficacy of tramadol in cardiac surgery pain control has been shown to be significant by But *et al* (2007) whereby a single dose of tramadol administered prior to extubation following coronary artery bypass graft (CABG) surgery reduced morphine consumption by up to 25%, decreased the pain scores and improved patient comfort in the first 4 hours post-operatively[7].

Oxycodone is an old analgesic that has been used clinically for decades, and has a potency comparable to morphine[8,9]. Curtis *et al* (1999) revealed that oral controlled release oxycodone is 1.8 times more potent than oral controlled release morphine for total effect, 2.2 times more potent for peak effect and is equianalgesic in a ratio of 1 mg oxycodone to 2 mg morphine[10]. Oxycodone is a strong opioid[11], used for moderate to severe acute post-operative pain in various kinds of surgery[12-16]. In non cardiac surgeries such as total hip replacement (THR), oxycodone offered non-inferior analgesia to intravenous PCAM[17]. It is suitable for oral administration in view of its high (60%) bioavailability. A systematic review of literature revealed that both immediate-release and controlled-release oxycodone have similar efficacy in the treatment of non cancer pain and has similar side effects[12].

Oral and intravenous opioids have been found to provide a comparable analgesic quality, suggesting that postoperative pain even after very painful procedures, can be sufficiently managed with oral opioids[18]. Using oral medications post operatively has the advantage of easier administration and generally less expensive.

Pharmacologically, both tramadol and oxycodone have the same profile of side effects of opiates[19]. However, Tarkkilla *et al* (1997) reported that intravenous oxycodone caused significant respiratory depression whereas, tramadol was similar to placebo and did not cause respiratory depression[20]. Wirz *et al* (2005) found that controlled release oxycodone caused less nausea and vomiting than controlled release tramadol[21].

The aim of this study is to compare the effectiveness of pain relief provided by oral immediate release tramadol with the oral immediate release oxycodone (OxyNorm®) after open heart surgeries and their side effects.

METHODS

This was a prospective, randomized, and double blinded study conducted at Hospital Pulau Pinang (HPP), Malaysia following approval from the Medical Research Committee of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and the National Medical Research and Ethics Committee Malaysia. Patients scheduled for elective open heart surgery, aged between 18 to 70 years old, American Society of Anesthesiologists (ASA) physical status class II or III and planned for extubation within 6 hours after surgery were enrolled in the study. The exclusion criteria were known allergy to the study drugs, body mass index (BMI) > 35 kg/m^2, regular use of analgesics before the surgery, and significant renal impairment measured by creatinine clearance < 60 mL/min. During the preoperative anesthetic assessment, explanation was given and written informed consent was obtained from all patients recruited.

All patients were assigned by computer-generated randomization to either the Tramadol Group or Oxycodone Group. Patients were taught to score their pain using the numerical rating scale (NRS) ranging 0 to 10, where 0 indicated no pain and 10 the worst imaginable pain.

Patients were fasted overnight and given oral midazolam 3.75 mg (≥ 60 years old) or 7.5 mg (< 60 years old) the night before surgery. Intra-muscular morphine (0.1 mg/kg) and promethazine 25 mg was administered before transfer to the operating theatre.

Upon arrival at the operating theater, the monitoring of electrocardiography, pulse oximetry, capnography, as well as invasive arterial blood pressure and central venous pressure monitoring were established. A pulmonary artery catheter sheath was inserted into the internal jugular vein if deemed necessary.

The patient was pre-oxygenated for three minutes, followed by induction with intravenous (IV) fentanyl 20 μg/kg and IV midazolam 0.05-0.1 mg/kg titrated till loss of consciousness. The patient was then mask ventilated with oxygen and sevoflurane 2 % for 20 seconds before given IV rocuronium 0.6 mg/kg. The patient was intubated three minutes thereafter and ventilated with a tidal volume of 6-8 mL/kg, and respiratory rate adjusted to achieve an end-tidal carbon dioxide of 30-35 mmHg. Anesthesia was maintained with oxygen, air and sevoflurane, titrated to achieve a minimum alveolar concentration (MAC) of 0.8-1.0. Intra-operatively, the patient's blood pressure was maintained within 20 % of baseline reading and vasopressor (e.g. noradrenaline) and/or inotrope (e.g. dopamine, adrenaline) was commenced as necessary.

Cardiopulmonary bypass (CPB) was standardized where a crystalloid/colloid prime and membrane oxygenator was used. The patient was kept moderately hypothermic (32-34^{o}C) and on coming off the CPB machine, IV morphine 0.15 mg/kg was administered to all patients for postoperative analgesia. Sevoflurane was discontinued upon transferring the patient out of the operation theatre. Nasogastric tube was inserted before transfer to cardiac intensive care unit (CICU). All patients remained intubated, and were transferred to the CICU where they were weaned from the ventilator and extubated within 6 hours. Patients who were not extubated within this time or had to be re-intubated were considered as drop-outs.

In the CICU, IV dexmedetomedine 0.2-0.4 μg/kg/hour was commenced in all patients. It was titrated according to hemodynamic parameters and sedation score. Richmond Agitation Sedation Scale (RASS) was used for monitoring degree of sedation and kept at -1 to 0. Dexmedetomedine infusion was stopped once patient was extubated.

Patients were extubated when their hemodynamics were stable (on minimal dopamine infusion ≤ 5 μg/kg/min), core body temperature > 36^{o}C, oxygenation was within normal range, obeying commands and had no active bleeding from surgical wound sites.

Patients randomized to the Tramadol Group received oral tramadol 50 mg, and those randomized to the Oxycodone Group received oral oxycodone 5 g via the nasogastric tube after extubation and at six hours thereafter. Patients in both groups also received oral paracetamol 1g every 6 hours. Post-operative pain assessment was done at 1, 6, 12, 18, 24, 32, 40 and 48 hours after extubation. The Acute Pain Service (APS) team who were blinded to the study groups assessed the patient's pain score at rest and on movement (deep breathing) using NRS. When the patient had a pain score > 4, IV morphine 1 mg was titrated every 5 minutes to achieve pain score < 4.

Apart from assessing pain score, the side effects of the medications namely nausea, vomiting, absent bowel output, respiratory depression and sedation were also assessed and documented. Patients who complained of nausea or vomiting were given IV metoclopramide 10 mg immediately and were started on regular IV metoclopramide 10 mg 8 hourly. Patients who persistently nauseated or vomited were given additional IV granisetron 1 mg and repeated every 8 hours if needed.

All patients in this study received syrup lactulose 30 mL 8 hourly as prophylaxis for constipation as per unit protocol. Patients with adequate oral intake but absent bowel output 48 hours after surgery were given enema.

Statistical Analysis

The study was designed with type I error of $\alpha = 0.05$, type II error of $\beta = 0.2$ and power of 80% based on study by Wirz *et al* (2005)[21]. Calculated sample size was 80 including 20% dropout rate. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 22.0 IBM Corp, Armonk, NY) software. Patient demographic data was analysed using the independent *t* test and chi square for continuous and categorical data respectively. Mann-Whitney test was used for non-parametric data. A *p* value of < 0.05 was considered statistically significant.

Results

A total of eighty patients were recruited into this study but two patients dropped out due to delayed extubation (after 6 hours). Demographic data are shown in Table 1. There were no significant differences between the two groups with regards to age, gender and race but there was a significant difference in BMI.

The pain scores at rest were significantly lower in the oxycodone group compared to the tramadol group for all the time intervals recorded, except at 6 hours post extubation. The pain scores on movement were mostly comparable between the two groups, with significantly less pain scores in the oxycodone group at 1 and 40 hours post extubation (Table 2).

The total morphine requirement post operatively was significantly higher in the tramadol group 1.42 ± 1.98 as compared to oxycodone group 0.05 ± 0.22 ($p < 0.001$).

The number of patients that required rescue morphine was also significantly higher in tramadol group [18 (47.4 %)] compared to oxycodone group [2 (5.0 %)]with *p* value < 0.001.

Post-operative nausea and vomiting was significantly less in the oxycodone group. There was no significant difference in bowel output between the two groups (Table 3).

Sedation scores were not significantly different between the two groups at all time intervals. None of the patients developed respiratory depression or excessive sedation. The highest sedation score documented was 1 which reflecting was mild sedation (Table 4).

Discussion

Open heart surgeries such as coronary vessels grafting and valve repairs or replacements are major procedures with painful post-operative wounds that are mainly attributed to the median sternostomy[3]. Pain control after open heart surgery is important as pain relief is one of the key factors in multimodal interventions towards accelerated convalescence and reduced morbidity[22]. Without adequate pain relief, these patients may return after a few months of successful surgery with chronic pain syndrome. Chronic pain which can continue beyond 1.5 years after thoracic surgery can be predicted by the intensity of pain within the first day after surgery[1].

Oxycodone exerts its analgesic effect by acting on opioid receptors, namely μ, κ and δ receptors. Tramadol exerts its analgesic effect via a few other mechanisms apart from acting on the opioid receptors μ, κ and δ. Tramadol also inhibits the neuronal reuptake of noradrenaline and enhances serotonin release, thereby causing inhibition of the pain perception by activation of descending serotonergic and noradrenergic pathways. From the pharmacological point of view, these numerous mechanisms of action should give tramadol stronger analgesic effects or at least equivalent analgesic effects to oxycodone. However, this was not supported by the findings of the current study.

Our study showed that immediate release oxycodone was significantly more effective than tramadol in managing the pain relief at rest, from the first hour after extubation up to 48 hours. This may be due to tramadol being a weak μ agonist as compared to oxycodone a full μ agonist[6]. This early pain control and better analgesia are desirable for patient comfort and faster recovery. Kogan *et al* (2007) reported immediate release oxycodone to be effective for early pain control after fast track cardiac anesthesia, compared to controlled release oxycodone[23]. To date, there are no other studies done comparing the use of immediate release oxycodone with other methods of postoperative pain management in patients undergoing open heart surgery.

In our study, the post-operative pain intensity gradually reduced as reflected by the decreasing pain

scores. This however, was not in concordance with findings by Mueller *et al* (2000) where the mean pain intensity after cardiac surgery increased from 3.7 to 3.9 at 48 hours[3]. This is probably because the paracetamol dose (500mg every 6 hours) used in their study could have contributed to reduced pain control despite the use of opioids. The combination of oxycodone and paracetamol has been shown to be a superior analgesic compared to oxycodone alone[9]. Hynninen *et al* (2000) reported that non-steroidal anti-inflammatory drugs (NSAIDs) could also be used as an adjunct for analgesia management after cardiac surgery as it reduced opioids requirement[24]. The role of multi-modal pain therapy using adequate analgesic dosages is therefore important, because apart from being effective with their different pain pathway inhibition, they offer benefits such as lack of respiratory depression and sedation as with the use of paracetamol or NSAIDs[5,22].

Oxycodone is a strong opioid used for the relief of moderate to severe pain and yet it produced less nausea and vomiting compared to tramadol in our study. This finding was similarly demonstrated in other studies (maxillofacial, orthopedics and cardiac surgery)[12,21,25]. Oral oxycodone is a promising analgesic for open heart surgery with its effective pain relief and reduced side effects of nausea and vomiting.

Although a higher percentage of our patients on oxycodone (85.0%) had a bowel output within the 48 hours of observation, it was not significantly different to those on tramadol (73.7%). One reason why absent bowel output was less seen in our study was due to the prophylactic lactulose prescribed to all patients after open heart surgery, as a required protocol in our cardiothoracic center to avoid defecation problems and ileus which could exaggerate pain during straining and defecation. Opioids with μ receptor agonist effects at central nervous system will also have μ receptor agonist effects at gastrointestinal tract aggravating postoperative ileus which cause constipation[19]. A study on patients after Caesarean section revealed that oral oxycodone actually shortened the time to first defecation compared to IV morphine and oral codeine[26].

Oxycodone induces central nervous system depression through their action on opioid receptors. However, in our study both analgesics did not cause more than mild sedation and any respiratory depression in our patients. Tarkkilla *et al* (1997) reported that oxycodone could cause significant respiratory depression[20]. Tramadol is known to have a ceiling respiratory depression effect and was not associated with respiratory depression[6,20].

We conclude that pain control after open heart surgery was superior with oral oxycodone, with significantly lower pain scores at rest, total rescue morphine and incidence of postoperative nausea and vomiting compared to oral tramadol.

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