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Original Research Article

A Comparison of Patient-Controlled Analgesia with Oxycodone and Morphine After Total Abdominal Hysterectomy Surgery

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Abstract

We compared the analgesic profile between patient-controlled analgesia (PCA) using oxycodone and morphine in post total abdominal hysterectomy patients. Eighty-four ASA I or II patients, aged 18 to 65 years who underwent total abdominal hysterectomy were recruited into this prospective, double blind, randomised controlled study. They were randomised to receive either PCA oxycodone 0.7 mg per bolus or PCA morphine 1 mg per bolus for postoperative pain relief. At the end of surgery, all patients received IV morphine 0.1 mg/kg and skin incision was infiltrated with 20 mls of bupivacaine 0.25%. Post-operative pain scores, opioids consumptions, sedation scores and side effects were assessed upon arrival and at 30 minutes after arrival to recovery area, as well as at 6 hours and 24 hours after the operation in the ward. Patients' overall satisfaction was also assessed 24 hours postoperatively.No significant differences were observed in terms of postoperative pain scores, opioids consumption, sedation scores, side effects as well as patient's overall satisfaction between the PCA oxycodone and PCA morphine group. Oxycodone was comparable to morphine as PCA in terms of total opioid consumption, pain scores and satisfaction level for patients undergoing total abdominal hysterectomy and therefore may be an alternative to morphine in postoperative pain management as PCA.

Keywords: morphine, oxycodone, pain scores, patient controlled analgesia, total abdominal hysterectomy

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Introduction

Patient-controlled analgesia (PCA) has been established as an efficient technique for post-operative analgesia (1,2). A reviewed meta-analysis conducted by Hudcova et al. showed evidence that PCA opioids provided superior analgesia in comparison to conventional intravenous opioids, with greater satisfaction reported among post-operative patients compared to conventional intravenous analgesia. Despite slightly higher opioid consumption in patients using PCA, there was no significant increase in adverse effects, with the exception of incidence of pruritus (2).

Although there were many advances in pain management over the years, the mainstay of post-operative pain control in many hospital settings are still opioids. A variety of opioids have been used for PCA, namely morphine, fentanyl, pethidine and oxycodone (3-6). Morphine remained to be the opioid of choice and is widely used as PCA in many Malaysian government hospital settings.

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Oxycodone is a synthetic opioid derived from thebaine, found in 1916 and has been used clinically since 1917 (7). It is a selective μ-opioid receptor agonist and can be administered via intravenous, intramuscular, intranasal, subcutaneous, spinal, oral and rectal routes. In comparison to morphine, it has a relatively high oral bioavailability in humans (60-87% versus 19-30% in morphine). It is metabolized through CYP3A4 and CYP2D6 isoenzymes and it has a faster passage to the central nervous system (CNS) (8-10). Oxycodone has been shown to be an effective treatment for acute postoperative pain, while some studies have indicated that its potency is 30% more than morphine in the immediate postoperative period (1-12). Similarly, Lenz et al. showed that oxycodone was more potent than morphine for visceral pain relief without increasing the incidence of sedation (4).

In two separate studies, Silvasti et al. and Lenz et al. compared the potency and efficacy between PCA oxycodone and morphine. These studies showed similar and superior potency in oxycodone, respectively (3,4). It was found that postoperative sedation level was significantly less with oxycodone, but there were no significant differences in the incidence of nausea, vomiting or pruritus (3,4). Despite the potential efficacy of oxycodone in postoperative pain management, its use in PCA is not well established in most Malaysian hospitals, including Hospital Sultanah Aminah Johor Bahru. Therefore, it is hope that the result gained from this study will be more representative of our local population, as the previous two similar studies were conducted in Finland and Norway.

Material and Methods

This prospective, double blinded, randomized clinical study was conducted after obtaining institutional ethics committee approval (research number IIR: NMRR-15-2330-28705) and patients' informed consent. Eighty-four patients aged between 18 to 65 years, American Society of Anesthesiologists (ASA) physical status I or II who were scheduled for elective total abdominal hysterectomy with or without bilateral salphingo-oopherectomy under general anaesthesia via below umbilical incision were recruited into the study. Patients with history of psychiatric, psychological or chronic pain disorders and those on chronic opioids or psychoactive drug usage that may affect the study drug were excluded. Patients who are unable to understand the usage or physically unable to use the PCA device, contraindicated or having known allergy to any drugs involved in the study were also excluded. Recruited patients who had complicated surgery requiring extension of incision or additional surgical procedure were withdrawn from the study.

During pre-anaesthetic clinic visits, recruited patients were educated regarding the use of a Graseby Omnifuse PCA machine pump and Numerical Rating Scale (NRS) for pain score assessment, whereby 0 denotes no pain and 10 denotes worst pain experienced. They were randomised into 2 groups, Group O and Group M by means of computer generated randomisation table. Group O patients received PCA oxycodone intravenously at 0.7 mg per bolus, while Group M patients received PCA morphine at 1.0 mg per bolus as postoperative analgesia. Both drugs were prepared by an independent pharmacist who was not involved in the study. Oxycodone was diluted into 0.7 mg/ml and morphine was diluted into 1mg/ml to gain equianalgesic dose, based on equianalgesic dose ratio of 2:3 between oxycodone and morphine as obtained in studies conducted by Kalso et al. and Lenz et al., respectively (4,12).

All patients were fasted overnight with no sedative premedication given. Standard general anaesthesia monitoring was applied to all patients including continuous electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximetry and capnography. Target-controlled infusion (TCI) remifentanil was started, and anaesthesia was induced with intravenous (IV) propofol 2 mg/kg and IV rocuronium 0.6 mg/kg to facilitate endotracheal intubation. Mask ventilation was carried out for 3 minutes using desflurane in 100% oxygen with MAC 1.0 - 1.2 before intubation.

Intra-operatively, anaesthesia was maintained with desflurane in air and oxygen mixture at MAC 1.0 and TCI remifentanil was adjusted according to hemodynamic parameters. IV morphine 0.1 mg/kg was given upon muscle layer closure, while IV ondansetron 8 mg was given upon initiation of skin closure. Twenty millilitres of 0.25% bupivacaine were infiltrated subcutaneously along the skin incision by surgeon after completion of skin closure. TCI remifentanil was discontinued after completion of bupivacaine infiltration. At the end of anaesthesia, neuromuscular blockade was antagonised by IV neostigmine 0.05 mg/kg and IV atropine 0.02 mg/kg.

Patients were transferred to and monitored in recovery room (RR) after emergence. A PCA device was connected to the patient via an intravenous line with a one-way (anti-reflux) valve. The patient, the anaesthetist and the nurses were blinded to the contents of the PCA syringe. The PCA pumps were

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programmed to deliver a bolus dose of 0.7 mg/ml oxycodone for Group O patients or 1mg/ml morphine for Group M patients upon their demand. The lockout period was set at 5 minutes and there was no background infusion.

Monitoring and interviewing of the patients were performed by assigned medical officers in RR at 2 intervals: upon arrival at RR and 30 minutes after arrival in RR. Further evaluations were done in the gynaecology ward at 6 hours and 24 hours from time of arrival to RR, respectively.

Pain scores were assessed when patient was at rest and during movement. Pain with movement was defined as pain observed in activities including lifting lower limbs, sitting, rolling, or coughing. The pain scores and the occurrence of side effects i.e. nausea and/ or vomiting, dizziness and pruritus were observed and recorded. Sedation scores were evaluated with Pasero Opioid-induced Sedation Scale, POSS (S=sleep and easily aroused, 1= awake and alert, 2= slightly drowsy, easily aroused, 3= frequently drowsy, arousable, drifts off to sleep during conversation, 4= somnolent, minimal or no response to stimulation) (13). The cumulative dose of opioids administered in PCA device was recorded in millilitres (mls). At 24 hours' interval review, patients were asked on their degree of overall satisfaction with the postoperative analgesia with a 5-point scale (1 = very unsatisfied, 2 = unsatisfied, 3 = neutral, 4 = satisfied, or 5 = very satisfied).

At any point during review where the pain scores were 4 or more, a rescue drug which consisted of 2 mls of the studied drug will (either oxycodone or morphine) will be given via the PCA device. The patient was reassessed after 10 minutes and additional 2 mls boluses of studied drugs were repeatedly given until the patient's pain score became less than 3. No other analgesics were given in the first 24 hours other than PCA.

Management of over sedation was based on steps recommended by POSS, where sedation scores of S to 2 are acceptable and PCA opioids can be continued, whereas sedation scores of 3 to 4 the opioids dose were reduced or discontinued (13). For pruritus, patients were assessed with Numerical Rating Scale (NRS), where 0 denotes no itchiness and 10 denotes worst itchiness experienced. Tablet loratadine 10 mg was given for NRS of 3 or more. For nausea and/ or vomiting, the severity was scored based on 0-3 scores (0 = nil, 1 = slight, 2 = moderate and 3 = severe), whereby IV metoclopramide 10 mg was given for scores 1 and above. IV ondansetron 4 mg was given when nausea and/ or vomiting were not relieved by IV metoclopramide (14). PCA was discontinued and substituted with non-opioids analgesics when the side effects (nausea, vomiting and pruritus) do not respond to the treatments given, or when POSS was 3 or more.

The sample size was calculated using the PASS (Power Analysis & Sample Size System) software. The calculation was derived from post-operative total PCA opioids consumption with standard deviation as quoted in Lenz et al. (4). The power of this study was set at 90%, α-value of 0.05 whereby it was estimated that 37 patients would be required for each group. Anticipating a 15% drop-out rate, 42 patients were eventually recruited in each group.

The data was analysed using the SPSS (Statistical Package for The Social Sciences) software version 24. 0. Student's t-test was used for analysis of demographic data and pain scores. Mann-Whitney U test was used for analysis of total opioids consumption, sedation scores and patients' overall satisfaction level at 24 hours after surgery, while incidence of side effects was compared using Chi-square test. A value of $p < 0.05$ was regarded as statistically significant.

Results

A total of 84 patients were recruited into this study. However, a total number of 10 patients were excluded: 7 patients required extension of incision above umbilicus and another 3 patients had complicated surgeries that required intervention from general surgery team. The demographic data and the intraoperative data of the patients in both groups were shown in Table 1.

The duration of anesthesia for patients in Group O was significantly higher compared to patients in Group M (3.00 ± 0.76 hours versus 2.56 ± 0.72 hours, $p = 0.015$). The postoperative total opioids consumption for patients in both groups at different intervals were shown in Table 2. There were no significant differences for total opioids consumption in both groups at postoperative 30 minutes, 6 hours or 24 hours.

The mean postoperative pain scores at rest and on movement at different intervals were shown in Table 3. There were no significant differences in pain scores for both groups of patients upon arrival to recovery area, at 6 hours and 24 hours postoperatively. However, patients in Group O showed statistically significant higher pain scores on movement at postoperative 30 minutes compared to Group M (6.2 ± 2.0 versus 5.0 ± 1.9, $p = 0.011$).

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Table 1: Demographic data. Values are expressed in mean ± SD or numbers (percentage) where appropriate.

	Group M (n=36)	Group O (n=38)	*p* value
Age (year)	47.1 ± 8.2	48.8 ± 7.7	0.371
Race			
Malay	27 (36.5)	23 (31.1)	0.545
Chinese	3 (4.1)	7 (9.5)	
Indian	5 (6.8)	6 (8.1)	
Others	1 (1.4)	2 (2.7)	
Procedure			
TAH	13 (17.6)	9 (12.2)	0.242
TAHBSO	23 (31.1)	29 (39.2)	
Incision			
Pfannensteil	13 (17.6)	10 (13.5)	0.363
Midline	23 (31.1)	28 (37.8)	
Duration of anesthesia (hours)	2.56 ± 0.72	3.00 ± 0.76	**0.015***

Table 2: Mean postoperative opioids consumption in mililitres (mls). Value expressed in mean ± SD

	Group M (n=36)	Group O (n=38)	*p* value
At 30 minutes (ml)			
Opiods demanded	10.7 ± 14.0	7.2 ± 4.3	0.547
Opiods delivered	6.3 ± 9.8	5.1 ± 2.7	0.969
At 6 hours (ml)			
Opiods demanded	39.0 ± 36.8	33.2 ± 27.4	0.850
Opiods delivered	19.1 ± 14.2	24.2 ± 18.2	0.085
At 24 hours (ml)			
Opiods demanded	62.0 ± 54.9	56.8 ± 30.9	0.501
Opiods delivered	37.1 ± 23.4	43.7 ± 21.6	0.073

There were no significant differences observed in terms of sedation score and the incidence of side effects among both groups at different intervals as shown in Table 3 and 4, respectively.

No adverse events were noted during this study. Patient's overall satisfaction level were comparable among the two groups, with median satisfaction scale of 4 and interquartile range (IQR) of 1.

Table 3: Mean postoperative pain and sedation scores. Value expressed in mean ± SD or IQR.

	Group M (n=36)	Group O (n=38)	*p* value
Pain Score			
Upon arrival to RR			
At rest	5.2 ± 2.8	5.7 ± 2.7	0.473
At movement	5.9 ± 2.9	6.7 ± 2.5	0183
At 30 minutes			
At rest	4.2 ± 1.9	4.8 ± 2.0	0.176
At movement	5.0 ± 1.9	6.2 ± 2.0	**0.011***
At 6 hours			
At rest	2.3 ± 2.0	3.0 ± 1.6	0.085
At movement	4.8 ± 2.4	5.0 ± 1.2	0.655
At 24 hours			
At rest	1.1 ± 1.3	1.7 ± 1.4	0.097
At movement	3.4 ± 1.9	4.0 ± 1.5	0.141
Sedation Score			
Upon arrival to RR	2 (0)	2 (0)	0.707
At 30 minutes	2 (1)	1 (1)	0.464
At 6 hours	1 (0)	1 (1)	0.172
At 24 hours	1 (1)	1 (0)	0.092

Table 4: Incidence of side effects at different intervals. Values expressed in number with percentage

	Group Morphine (n=36)	Group Oxycodone (n=38)	*p* value
Nausea and vomiting			
Upon arrival	3 (8.3)	4 (10.5)	1.000
At 30 minutes	2 (5.6)	3 (7.9)	1.000
At 6 hours	6 (16.7)	2 (5.3)	0.147
At 24 hours	6 (16.7)	9 (23.7)	0.453
Pruritus			
Upon arrival	0	0	-
At 30 minutes	0 (0)	1 (2.6)	1.000
At 6 hours	2 (5.6)	1 (2.6)	0.610
At 24 hours	1 (2.8)	3 (7.9)	0.615
Dizziness			
Upon arrival	5 (13.9)	12 (31.6)	0.710
At 30 minutes	4 (11.1)	4 (10.5)	1.000
At 6 hours	5 (13.9)	7 (18.4)	0.597
At 24 hours	4 (11.1)	1 (2.6)	0.194

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Discussion

In this study, there were no significant differences in total opioids consumption in PCA oxycodone and PCA morphine groups at 30 minutes, 6 hours or 24 hours postoperatively. This finding was in contrast to the study conducted by Lenz et al., who showed that the accumulated postoperative 24 hours' oxycodone consumption was significantly less compared with morphine (4). Similarly, Park et al. showed the same results in patients undergoing laparoscopic gynecological surgery comparing PCA fentanyl and PCA oxycodone (6). There have been various suggestions of potency ratio between oxycodone and morphine; Hwang et al. (5) suggested that oxycodone might be more potent than morphine with the potency ratio of 4:3, while other literature by Silvasti et al. suggested that intravenous oxycodone appears to be equipotent with morphine (3). In view of the comparable results of opioids consumption and analgesic profile as shown, the findings in our study may support the likelihood of equianalgesic dose ratio of 2:3 between oxycodone and morphine as suggested by Kalso et al. and Lenz et al (4,12).

The mean postoperative pain scores at rest and on movement upon arrival in recovery area, after 6 hours and after 12 hours were not significantly different for both groups of patients in this study. This was again in contrast with the study findings by Lenz et al., who had shown that pain scores were significantly lower in the first hour postoperatively with PCA oxycodone (4). Our study finding was similar to Silvasti et al., who had shown that there was no difference in the quality of analgesia in terms of pain scores among patients who received PCA oxycodone and morphine (3). However, patients in Group O showed statistically significant higher pain scores on movement at postoperative 30 minutes compared to Group M (6.2 ± 2.0 versus 5.0 ± 1.9, p value 0.011). This was possibly attributed to the inadequacy of intraoperative analgesia rather than due to the effect of PCA opioids at around post-operative period per se. In addition, the duration of anesthesia for Group O in our study was shown to be significantly longer than Group O (3.00 ± 0.76 hours versus 2.56 ± 0.72 hours with p value of 0.015), which may indicate that this group of patients had more difficult surgery and thus the higher pain scores at immediate postoperative period in recovery room.

There were no significant differences in sedation scores among both groups at different postoperative intervals in our study. In the immediate postoperative period in the recovery area, the median sedation score was 2, which indicated that patients were generally drowsier but easily arousable. The median sedation score for patients upon review in the ward at 6 hours and 24 hours postoperatively was 1, indicating that they were mostly awake and alert despite the usage of PCA opioids. None of the patients in this study had sedation score of 3 and above at any time of review, in which the usage of opioids might need to be reduced or withheld. This finding supported the result obtained by Lenz et al., who had shown although oxycodone was more potent, it has not resulted in sedation (4). Similarly, studies conducted by Hwang et al. and Park et al. showed no significant differences in sedation scores among patients on PCA oxycodone or fentanyl after laparoscopic cholecystectomy and laparoscopic gynecological surgery, respectively (5,6).

There was no significance difference in incidence of side effects for both groups at different postoperative intervals, and no other adverse events were noted during this study which was consistent with other studies. (3,4,12). However, Park et al. showed that the total occurrence of dizziness during postoperative 48 hours was significantly higher in patients who received PCA oxycodone compared to fentanyl (6). Both groups of patients were satisfied with the PCA opioids as postoperative analgesia modality in our study.

There were a few limitations in this study. The dosage of PCA opioids used per bolus was based on the potency ratio of oxycodone to morphine of 2:3 as suggested by Kalso et al. and Lenz et al, but different potency ratio had also been suggested in various other literatures as discussed above (4,12). Thus, a study conducted using various potency ratios with larger sample size may be needed to ascertain the potency ratio. In addition, this study was limited to female patients with ASA classification 1 and 2 undergoing similar type of surgery. In order to obtain a more representative of a general population, studies involving various demographic and clinical characteristics with various types of surgery should be performed.

Conclusion

This study showed that oxycodone was comparable to morphine as PCA in terms of total opioid consumption, pain scores and satisfaction level for patients undergoing total abdominal hysterectomy. There were no significant differences observed on side effects in both groups.

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