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A Randomized, Double-Blind, Placebo-Controlled Study of Preemptive Oral Oxycodone with Morphine Patient-Controlled Analgesia for Postoperative Pain Management in Patients Undergoing Uterine Artery Embolization for Symptomatic Uterine Fibroids

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Abstract
Purpose To evaluate the analgesic efficacy of oral premedication of oxycodone in a group of patients undergoing elective uterine artery embolization under sedation for fibroid disease.
Methods Thirty-nine patients (mean age 42.3 years) were prospectively randomized 1:1 to receive 20 mg oxycodone or placebo orally immediately before their procedure. At the commencement of the procedure, patients were provided with a patient-controlled analgesia device for 24 h, programmed to deliver 1 mg boluses of intravenous morphine with a 5 min lockout. Mean visual analog scale pain intensity ratings (0–100 mm) were measured from both groups and evaluated over 0 to 6 h as the primary end point. Other measured parameters included opioid-related side effects and eligibility for discharge (NCT00163930; September 12, 2005).
Results Early pain intensity did not vary significantly between the active and placebo groups [mean (standard deviation): 3.2 (2.5) vs. 3.1 (2.2), $p = 0.89$]. The oxycodone group, however, experienced significantly more nausea ($p = 0.035$) and a greater incidence of vomiting ($p = 0.044$). Overall opioid requirement over 24 h, measured as oral morphine equivalent, was greater in the oxycodone group (median [interquartile range]: 64.5

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[45–90] mg vs. 22.5 [15–46.5] mg, $p < 0.0001$). The number of patients first eligible for discharge at 24 h in the oxycodone group was decreased but not significantly ($p = 0.07$).

Conclusion The addition of preprocedural oral oxycodone to morphine patient-controlled analgesia does not offer any analgesic advantage to patients having uterine artery embolization and may cause a greater incidence of nausea and vomiting.

Keywords Uterine artery embolization · Opioids · Patient controlled analgesia · Pain management

Introduction

Transcatheter uterine artery embolization (UAE) was first described as a method to treat large symptomatic fibroids to avoid bleeding complications associated with open surgical myomectomy [1, 2]. Pain associated with UAE is described as severe and variable [1, 3] and it remains the primary reason for overnight admission. Pain is due to fibroid and transient myometrial ischemia and has been characterized through reference to records of patient-controlled analgesia (PCA) with opioid [4]. The natural pain history of UAE increases in intensity to a point approximately 2 h after the procedure, remaining at this level for several hours, then rapidly decreasing [4].

Preprocedural history of heavier menstrual bleeding, pelvic pain, pressure sensation, uterine and fibroid volume are not associated with intensity of postprocedure pain [5]. Procedural factors identified that may minimize pain after UAE include selection to avoid bilateral UAE among patients with limited fibroid disease [6], type of embolic material used, Contour SE requiring less opioid analgesia compared to Embosphere/Embosphere Gold [7, 8] and the use of preemptive analgesic, anti-inflammatory and antiemetic medications.

Numerous analgesic and systemic Non Steroidal Anti-Inflammatory Drug (NSAID) therapies have been described for the postprocedure pain management of UAE. NSAIDs have been described in randomized double-blind studies, with oral rofecoxib showing similar analgesic and opioid reducing effect to ibuprofen [9]. NSAID impregnated embolic beads have been shown to develop favorable concentrations in uterine tissues in animal models [10–12]. These provided superior analgesia compared to placebo beads (containing polyvinyl alcohol) after UAE in humans [13]. Morphine PCA has been evaluated in a number of randomized double-blind studies. Addition of ketamine to morphine PCA did not reduce morphine requirement in one study [14], while comparison to remifentanil target controlled infusion showed significant reduction of early Pain Intensity (PI) in the remifentanil group [15]. Morphine PCA has also been compared to fentanyl PCA in a non-randomized study, where it was found to produce lower PI scores [16].

Favorable descriptions of epidural analgesia for UAE exist only in case series without reference to control groups [17, 18], while intra-arterial lidocaine injection was associated with significantly lower pain scores but no reduction in morphine PCA requirements in a randomized double-blind setting [19].

Sustained-release oral oxycodone is a strong analgesic that is simple and cheap to administer and that shows potential for treating pain in experimental human visceral pain models [20]. Early absorption of an oral dose of 20 mg of sustained-release oxycodone is rapid, with significant increases in blood concentration seen by 40 min, building to peak blood levels by 3.2 h [21], closely matching the profile of PI with UAE [4]. We undertook a prospective randomized double-blind study to evaluate the effects of a preprocedural oral dose of 20 mg of oxycodone with UAE, our primary hypothesis being that oral preemptive analgesia with an opioid would lead to a reduction in early PI. Secondary hypotheses examined outcomes of PI at 24 h, opioid-related side effects, satisfaction with pain management and readiness for discharge.

Materials and Methods

After approval from our intuition's Human Research and Ethics Committee (trial registration NCT00163930, September 12, 2005), a total of 42 women, mean age 42.3 years, American Society of Anesthesiologists (ASA) status I to III, gave written informed consent to participate before their scheduled elective UAE procedure. Participants had no allergy to oxycodone and morphine, no history of opioid analgesia requirement 2 weeks before the procedure and no preexisting hepatic or renal disease.

The study was randomized and double-blind; reporting was in accordance with CONSORT guidelines (Fig. 1). Patients were randomly assigned to receive 20 mg of oral sustained-release oxycodone (OxyContin SR) or matched placebo by blinded researchers, according to a computer-generated simple randomization code. Group allocation was concealed and controlled by our institution's pharmacy department, thus ensuring blinding of patients, researchers and proceduralists. Other preprocedural medications provided to all patients were oral paracetamol 1.5 g, pyroxicam 20 mg and ondansetron 8 mg.

Procedures were performed or supervised by two interventional radiologists, both with over two decades of UAE experience. All procedures were bilateral, with local anesthetic infiltration of the access site and involved

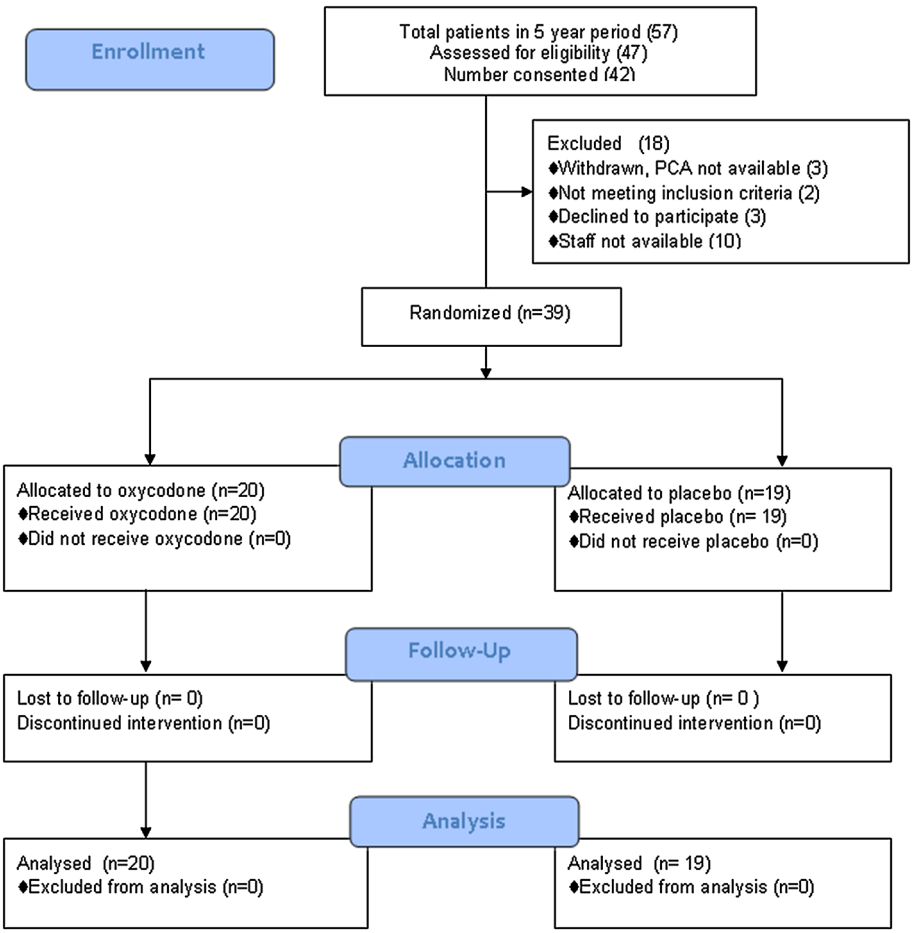

Fig. 1 CONSORT flow diagram. All patients who were randomly assigned to analgesia premedication were included in the intent-to-treat population

uterine artery injection of polyvinyl alcohol foam particles (500–700 um Contour SE; Cook Australia). End point was stasis of the main uterine artery confirmed for a minimum of five heartbeats. All participants had intravenous conscious sedation with midazolam and received antibiotics (Cephalothin 1 g) and an antiemetic (Maxolon 10 mg). They were provided with a device for administering PCA programmed to deliver 1 mg bolus morphine with a 5 min lockout interval (Gemstar; Abbot Laboratories, North Chicago, IL) up to 24 h after commencement of the procedure. Instructions were for participants to deliver morphine boluses as needed to control their pain. After PCA, patients were offered 5 mg of oral oxycodone, immediate release (Endone), every 2 h if required.

Participants received supplemental oxygen throughout the procedure. They were monitored with continuous pulse oximetry, electrocardiography and noninvasive blood pressure measurements at 5 min intervals (Phillips Suresigns Medical Systems, Koninklijke-Philips Electronics, Andover, MA). Participants experiencing nausea/vomiting were immediately treated with 4 mg intravenous ondansetron.

Demographic information included age, weight, coexisting health status, time from premedication to procedure commencement, procedure duration and name of interventionalist. Baseline size of uterus and number and size of fibroids were recorded.

PI was measured on a 10 cm visual analog scale (VAS) (left-hand margin representing no pain, right-hand margin representing the worst pain possible). PI was measured at 2, 4 and 6 h after commencement of the UAE and a mean level was calculated for the primary end point. PI was also measured at 24 h via VAS. Cumulative opioid requirement was measured with reference to the Abbot Gemstar. Opioid requirement was measured as intravenous morphine equivalent from the time of premedication until the patient ceased to require postprocedural opioid treatment after discharge, with 1 mg of oral oxycodone taken to be equivalent to 0.5 mg of intravenous morphine [22]. Patients were followed up by phone after discharge until they did not require oral opioid treatment.

Participants were encouraged to report any opioid-related side effects at any time during or after the procedure. Researchers enquired about nausea, vomiting and pruritus and measured the level of sedation hourly for the first 6 h and then every 4 h until discharge. Pruritus, nausea, vomiting and sedation were measured as secondary end points.

Patients were deemed suitable for discharge if, on the next day, they had pain easily controlled by oral analgesics, nausea and/or vomiting easily controlled without the need for intravenous antiemetics and no uterine bleeding. Time to suitability for discharge was recorded as a secondary end point.

Satisfaction with analgesia was assessed using a 10 cm VAS (left-hand margin reflecting no satisfaction at all and right-hand margin reflecting fully satisfied). Participants also provided an assessment of their satisfaction with the whole experience (procedure, sedation and analgesia) using a 4 point scale where 1 reflected that they were unsatisfied, 2 a little, 3 moderately and 4 fully satisfied.

Mean Pain Intensity (MPI) data from a population of patients undergoing UAE at our institution formed the basis for power analysis. Assuming an alpha error of 0.05, a beta error of 0.2, and a predicted difference of MPI score of 30 %, we aimed to recruit 40 patients.

MPI data for 0 to 6 h, age, time from premedication to procedure commencement, procedure duration, and satisfaction of the procedure were tested for normality and analyzed by Student's *t*-test. Number of fibroids, mass of dominant fibroid, size of uterus, number of ampoules of embolic agent, PI at 24 h, presence of nausea, opioid requirement, satisfaction and sedation scores showed non-parametric characteristics and were analyzed by Wilcoxon rank sum test. Binomial data, pruritus, respiratory depression, eligibility for discharge and interventionalist were analyzed by the chi-square or Fisher's exact test, as appropriate. p values of less than 0.05 were considered significant.

Results

Recruitment was from November 2006 to March 2012. Fifty-seven UAE procedures were performed at our institution during this period. Forty-two eligible patients provided informed consent and 39 of 42 enrolled; 20 received pre-procedural oral oxycodone and 19 placebo (Fig. 1). Three of 42 were withdrawn from the study because the PCA on the procedure day was not available, 2 of 57 were unsuitable because of comorbidities/disabilities, 3 of 57 declined and 10 of 57 were not queried about consent because trial interventionalists and/or research staff were not available.

Baseline characteristics between the two groups were similar for mean age, ASA ranking, size of uterus, number of fibroids, mass of dominant fibroid, volume and size of embolic agent, body mass index, time from premedication to procedure commencement, procedure duration and interventionalist (Table 1).

Technical success was 97.4 % (38 of 39), with one patient going on to a total hysterectomy at 6 months. MPI over 0 to 6 h after procedure commencement, the primary end point, did not vary significantly between the active and placebo groups [mean (standard deviation): 3.2 (2.5) vs. 3.1 (2.2), $p = 0.89$]. Similarly, PI at 24 h did not show a significant difference (median [interquartile range (IQR)]: 1.1 [0.8–2.7] and 1.5 [0.2–4.7], $p = 0.98$) (Table 2).

The oxycodone group experienced significantly more nausea than the placebo group (median [IQR]: 0.35 [0–1.95] vs. 0 [0–0.1], respectively, $p = 0.035$). A significantly greater proportion of participants from the oxycodone group experienced vomiting (30 %) compared with counterparts receiving placebo (5 %); ($p = 0.044$) (Table 3).

Table 1 Demographic characteristics of patients presenting for uterine embolization

Characteristic	Preoperative placebo ($n = 19$)	Preoperative opioid ($n = 20$)	p
Age, y	41.7 (6.3)	42.8 (6.3)	0.58
ASA class			
I	84 %	74 %	
II	11 %	16 %	
III	5 %	10 %	
Body mass index, kg/m^2	28.2 (8.0)	26.0 (6.5)	0.54
Size of uterus, cm^3	374 [249.5–969.0]	512 [255.3–1200]	0.83
No. of fibroids	1 [1–2]	1 [1–3]	0.34
Dominant fibroid, cm^3	538 [185.9–1950]	512 [124–605.6]	0.43
Premedication to start of procedure time, min	19.0 (11.1)	18.4 (12.8)	0.87
Embolic agent			
No. of ampoules	1 [1–2]	2 [1–3]	0.27
Particle size, μm	600 (70.71)	596 (88.38)	0.89
Procedure duration, min	74.7 (30.0)	66.9 (22.2)	0.49
Operator			
1	48 %	47 %	0.9
2	52 %	53 %	1.0

Data are presented as mean (standard deviation), median [interquartile range] or proportions as appropriate

ASA American Society of Anesthesiologists

ASA physical status classification system: (1) a normal healthy patient; (2) a patient with mild systemic disease; (3) a patient with severe systemic disease; (4) a patient with severe systemic disease that is a constant threat to life; (5) a moribundd patient who is not expected to survive without the operation; (6) a declared brain-dead patient whose organs are being removed for donor purposes

Table 2 Pain intensity ratings measured by visual analog scale at 0 to 6 h and 24 h after commencement of uterine embolization procedure

Pain intensity	Preoperative placebo	Preoperative opioid	p
0–6 h	3.1 (2.2)	3.2 (2.5)	0.89
24 h	1.5 [0.2–4.7]	1.1 [0.8–2.7]	0.98

Data are presented as mean (SD) or median [interquartile range]

Table 3 Opioid requirement, opioid related side effects and suitability for discharge

Characteristic	Preoperative placebo	Preoperative opioid	*p*
Total opioid requirement (oral morphine equivalents)	22.5 [15–46.5]	64.5 [45–90]	<0.0001
Nausea 0–24 h	0 [0–0.1]	0.35 [0–1.95]	0.035
Vomiting 0–24 h	5 %	30 %	0.044
Pruritus	0 %	5 %	1.00
Postprocedure sedation	0 [0–1]	1 [0.5–1]	0.89
Suitability for discharge at 24 h	35 %	11 %	0.07

Data are presented as mean (SD), median [interquartile range] or proportion as appropriate

Pruritus was of low incidence in both groups, with the difference being nonsignificant (5 % in the oxycodone group vs. 0 % in the placebo group; $p = 1.00$), while sedation levels did not vary significantly between the two groups, with a median (IQR) score of 0 [0–1] in the placebo group compared to 1 [0.5–1] ($p = 0.89$) (Table 3). No patients experienced respiratory depression ($p = 1.00$). Overall opioid requirement over 24 h, measured as oral morphine equivalent, was significantly greater in the oxycodone group (median [IQR]: 64.5 [45–90] mg vs. 22.5 [15–46.5] mg, $p < 0.0001$).

Although the proportion of participants eligible for discharge after 24 h was less in the group receiving oxycodone (11 vs. 35 %), this difference was not statistically significant ($p = 0.07$) and no participants required more than a single night's stay in the hospital (Table 3).

Mean satisfaction with pain management did not vary significantly between the oxycodone and placebo groups (mean (SD): 8.3 (1.2) and 7.8 (2.6), $p = 0.43$). Similarly, level of satisfaction with the procedure, sedation and analgesia did not vary significantly between groups (median [IQR]: 3.5 [3–4] and 4 [3–4], $p = 0.65$).

There were two adverse events. One patient experienced persistent pain, nausea and vomiting and presented to the emergency department 2 h after discharge. The patient was treated with analgesics and antinausea medication, was discharged and reported a full recovery when contacted the next day. The other patient was involved with the procedure that was technically unsuccessful.

Discussion

Preemptive oral oxycodone was found not to reduce PI during and immediately after UAE. Previous studies [14–16] showed that morphine PCA provided superior PI ratings after UAE in a nonrandomized setting compared with fentanyl PCA [16]. In the remaining randomized controlled studies, morphine PCA was associated with greater early PI compared with target-controlled remifentanil [15] and when compared with morphine PCA combined with localized intra-arterial lidocaine injection [19]. Morphine PCA alone showed no difference in PI compared to a combination of morphine and ketamine PCA [14]. Our approach of combining preemptive opioid analgesia with morphine PCA did not offer any advantage over morphine PCA alone; it produced greater opioid requirement and increased incidence of vomiting among participants.

Preemptive analgesia has been hypothesized as providing an advantage because pain pathways are inhibited before the onset of a painful stimulus [23]. However, there is no current evidence supporting any advantage for preemptive analgesia with opioids after two detailed reviews across a broad range of surgical procedures [23, 24]. Our findings of a lack of preemptive analgesia with oral opioid for UAE support the findings of these reviews.

The mechanisms of uterine pain with UAE are thought to involve pelvic cramping associated with postinfarction myometrial ischemia [25], a type of visceral pain. The natural history of PI associated with UAE is that it remains severe during and for several hours after UAE and then decreases in intensity [4]. This has been reflected in other studies [15] that have measured the pattern of opioid use in the 24 h after UAE, and also in our study where mean PCA opioid across both groups was much less in the 6 to 24 h period (6.28 mg) compared to the 0 to 6 h period (14.9 mg). We also provided an oral dose of oxycodone which should have provided a peak concentration at approximately 3.2 h [21, 22], theoretically matching the time period of peak analgesic requirement. However, this did not appear to offer any analgesic advantage.

The oxycodone group in our study showed an increase in opioid requirement and was subject to significantly greater levels of nausea and vomiting, despite all subjects receiving a preprocedural dose of oral ondansetron. A study comparing morphine and fentanyl PCA for UAE described a high incidence of nausea and vomiting affecting both the morphine and fentanyl PCA groups [16]. In a postoperative survey, vomiting was ranked as the first and nausea the fourth most undesirable outcome, in contrast to postoperative pain, which was ranked third [26]. Female gender and increasing postoperative opioid requirement are the two greatest major risk factors for postoperative nausea and vomiting [27]. This suggests that there may be too much reliance on opioid techniques for analgesia for a procedure performed in a population at high risk for opioid-induced nausea and vomiting.

Epidural analgesia appears to have the greatest advantage as a preemptive analgesic because it provides reduced PI, reduces the need for supplemental analgesia and

prolongs the time to rescue analgesia [24]. Epidural analgesia has been researched in the context of UAE with promising results but only in case series [17, 18] and needs to be evaluated in the context of a prospective randomized blinded study compared to morphine PCA, which is currently the most researched therapy and has been shown to be a useful control.

Nausea and vomiting are known to delay discharge from postanesthesia care units [28] and from the hospital after surgery [29]. A greater number of patients in the oxycodone group became eligible for discharge after 24 h in our study, but the result did not reach significance and none required more than a 24 h stay. Delay in discharge assumes great importance in modern practice because of associated patient morbidity and because of costs and inefficiencies associated with prolonged admission; many centers are beginning to mandate single-day admission for UAE procedures [30, 31].

We measured satisfaction with analgesia and with the procedure. Satisfaction with the analgesia was satisfactory. We provided information before the procedure and regular review of pain, both known to improve satisfaction with analgesia [32]. Access to PCA analgesia can improve autonomy and produce higher levels of patient satisfaction with pain management [33]. Presence of low PI, observed in both our oxycodone and placebo groups, have been previously shown to improve patient satisfaction with pain management [34, 35].

Satisfaction with sedation and procedure did not vary significantly between the groups and was satisfactory. There are no known comparators for satisfaction with radiological procedures. However, our patients were exposed to sedation, a form of anesthesia, and satisfaction after anesthesia has been linked to the presence of postanesthetic complications as well as severity of pain and nausea [36]. Our interpretation is that patients reported reasonable levels of satisfaction with their radiological procedure because of low complication rates.

In conclusion, we could not show any analgesic advantage for adding oral oxycodone before UAE and we have highlighted the adverse effects of nausea and vomiting with the possible implications of delayed discharge. Future studies should explore analgesic therapies that are opioid sparing or avoid opioid altogether.

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Conflict of interest Alex H. Konstantatos, Helen Kavnoudias, James R. Stegeman, Dana Boyd, Maryann Street, Michael Bailey, Stuart M. Lyon, and Kenneth R. Thomson declare that they have no conflict of interest.

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