Cardiovasc Intervent Radiol (2019) 42:87–94
https://doi.org/10.1007/s00270-018-1980-6

CLINICAL INVESTIGATION OTHER

The Safety and Efficacy of Oxycodone Versus Fentanyl in Percutaneous Microwave Ablation of a Liver Tumour Abutting the Capsule

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Received: 19 January 2018 / Accepted: 30 April 2018 / Published online: 8 May 2018

Abstract
Purpose The present study compared the safety and efficacy of oxycodone with those of fentanyl under non-intubated general anaesthesia in percutaneous microwave ablation (MWA) of a liver tumour abutting the capsule.
Materials and Methods Thirty-eight patients underwent MWA of liver cancers abutting the capsule. Patients received 0.1 mg/kg oxycodone (O group) or 1 μg/kg fentanyl (F group) prior to the start of ablation. Both groups received continuous infusions of propofol for non-intubated general anaesthesia during ablation. The primary outcomes were the pain scores (11-point numeric rating scale, NRS) within 24 h after MWA. Vital signs, body movement during ablation, and opioid side effects after ablation were recorded. The need for additional analgesics was recorded 24 h after MWA.
Results The pain NRS scores were lower in the O group than in the F group at 0.5 ($P = 0.035$), 3 ($P = 0.002$), and 6 h ($P = 0.001$) after MWA, and fewer patients required additional analgesics in the O group (6 of 20 vs. 13 of 18, $P = 0.022$) within 24 h. The average 24-h dose of dezocine was 5.5 ± 4.1 mg in the F group and 2.1 ± 3.3 mg in the O group ($P = 0.008$). A significant reduction in the respiratory rate ($P = 0.020$) and more body movements were observed in the F group ($P = 0.027$) during ablation with non-intubated general anaesthesia. No differences in post-operative nausea and vomiting (PONV) were observed between the two groups, but dizziness occurred significantly more often in the O group ($P = 0.033$). No significant differences in other vital signs were observed before, during, and after the procedure.
Conclusions Oxycodone provides better analgesia and reduces post-operative opioid consumption without significant respiratory or hemodynamic instability.

Keywords Microwave ablation · Pain · Anaesthesia · Oxycodone · Fentanyl

Introduction

Microwave ablation (MWA) is one of the most frequently used techniques for liver tumour thermoablation. MWA has a higher output than radiofrequency ablation (RFA) because it introduces a rapid rise in temperature around the antenna [1, 2]. However, pain remains a major reason for patient dissatisfaction. Patients may experience pain during ablation procedures even with appropriate conscious sedation. Most patients also experience grade 1 or 2 pain (the common toxicity criteria of the National Cancer Institute) for several days or, occasionally, for 1–2 weeks [3, 4]. Ablation areas that abut the hepatic capsule are more likely to cause severe pain during the procedure, and post-procedural pain is generally more severe and durable than in procedures in the hepatic parenchyma [4–6].

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Oxycodone is a semisynthetic opioid that is derived from the brain that exhibits an agonistic activity at the mu and kappa receptors. Oxycodone is used to control moderate to severe pain [7, 8]. It is associated with better pain control, fewer adverse events, and faster onset of action compared to other opioids for post-surgical pain [9]. Fentanyl is the most commonly used opioid analgesic in China. Propofol and fentanyl are the commonly used drugs for non-intubated general anaesthesia in percutaneous MWA of liver tumours in our clinic, but body movement, respiratory depression, post-operative nausea and vomiting (PONV), and post-procedural pain remain problematic. We hypothesized that oxycodone would be superior to fentanyl for pain control in percutaneous MWA of a liver tumour abutting the capsule based on its pharmacology.

The present study was a prospective, non-randomized study that compared the safety and efficacy of oxycodone with those of fentanyl under non-intubated general anaesthesia in percutaneous MWA of a liver tumour abutting the capsule.

Methods

Study Design

This prospective clinical study was performed after approval from the Human Research Ethics Board of our hospital. Signed written informed consent was obtained from each patient prior to participation.

Patients with a subcapsular hepatic tumour with a plan to undergo percutaneous MWA of the lesion between August 2016 and April 2017 were deemed to be alternative candidates of this study at our institution. Each patient received non-intubated general anaesthesia with oxycodone (Hamol Limited; Nottinghamshire, UK), which is designated the O group, or fentanyl (Yichangrenfu; Hubei province, China), which is designated the F group, in combination with propofol (Corden Pharma S.P.A.; Cheshire, UK). All patients were informed of the advantages and disadvantages of the two analgesia options, including the efficacy, potential adverse events, and costs. The physician and the patient jointly decided on the treatment used.

Patient Selection

The following inclusion criteria were used: (I) patients who refused or were not suitable for surgical resection; (II) a single nodule with a diameter $\leq$ 5 cm or no more than two nodules with a total diameter $\leq$ 5 cm; (III) a hepatic lesion margin within 1 cm of the liver capsule; (IV) Child–Pugh class A or B; (V) patients aged 40–75 years; and (VI) American Society of Anesthesiologists (ASA) physical status I or II. The following exclusion criteria were used: (I) patients with vascular invasion or distant metastases; (II) patients with a history of opioid usage; (III) patients with chronic obstructive pulmonary or cardiac disease; (IV) renal failure, uncontrolled diabetes, or hypertension; and (V) obesity (body mass index > 30 kg/m^2). Patient characteristics, including age, sex, body mass index (BMI), hypertension, diabetes, tumour type, tumour number, previous tumour treatment, and maximum tumour diameter, were recorded.

Intra-procedural Anaesthetic and Post-ablation Management

All patients fasted for more than 8 h. Anaesthetic monitoring included pulse oximetry, non-invasive blood pressure, electrocardiography, and capnography. All patients received oxygen at 5 L/min using a simple facemask. The anaesthetist who obtained the informed consent from the patients administered all non-intubated general anaesthesia. Another anaesthetist who was blinded to the medicine used during the procedure recorded all the body movements and collected vital signs. The anaesthesia protocol consisted of conscious sedation with 0.1 mg/kg oxycodone (the O group) or 1 μg/kg fentanyl (the F group) administered intravenously for 5 min prior to puncture. Local analgesia was 1% lidocaine in 10 mL via local puncture. The antenna was placed, and 1.5 mg/kg propofol was administered as a single bolus infusion for anaesthesia induction. Propofol was infused at 4–6 mg/kg/h with an infusion pump in both groups. An additional dose of 0.5 mg/kg propofol was administered if the patient did not fall asleep or exhibited body movements during the ablation. The Ramsay sedation score (RSS) was used to classify the sedation level into 6 grades: 1 = anxious, agitated, restless; 2 = cooperative, oriented, tranquil; 3 = responds to commands only; 4 = brisk response to light glabellar tap or loud noise; 5 = sluggish response to light glabellar tap or loud noise; and 6 = no response [10]. Body movements were divided into class A, when only the limbs quivered, and class B, when the torso quivered. Nine patients in the F group and 4 patients in the O group required additional propofol. Assisted ventilation with oxygen was provided via a facial mask when oxygen saturation fell to 90%. No other analgesia or antiemetic drugs were administered during the procedure and recovery periods (Fig. 1).

Intra-procedural data, including the mean blood pressure (MBP), heart rate (HR), peripheral oxygen saturation (SpO_2), and respiratory rate (RR), were collected. The procedure time, anaesthetic time, awakening from anaesthesia time, and total amount of propofol administered were also recorded. Intra-procedural adverse events,

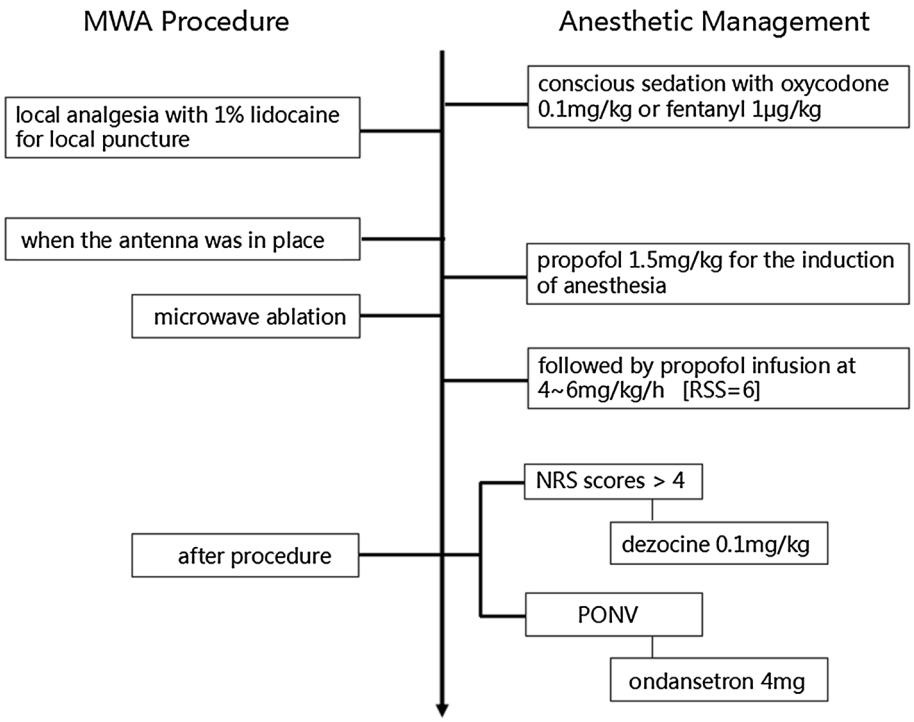

Fig. 1 MWA procedure and anaesthetic management. *MWA* microwave ablation, *RSS* Ramsay sedation score, *NRS* numeric rating scale, *PONV* post-operative nausea and vomiting

including respiratory depression ($SpO_2 < 90\%$ or respiratory rate less than 8 breaths per minute) and body movement (A or B), were recorded. Opioid side effects (PONV and dizziness) were also recorded.

The Ramsay sedation score evaluated the level of sedation 10 min after awakening.

Pain intensity was assessed at 0.5, 3, 6, 12, and 24 h after MWA using a numeric rating scale (NRS). Dezocine (0.1 mg/kg) was administered intravenously if the NRS score was greater than 4. Patients with severe PONV received an intravenous injection of 4 mg of ondansetron.

Microwave Ablation Procedure and Ablation Zone Characteristics

Microwave ablation was performed under computed tomography (CT) guidance (Somatom Definition 16, Siemens Erlangen, Germany) using a microwave ablation system (ECO-100A, Yigao, Nanjing, China). One experienced interventional radiologist performed all procedures. The output power and duration of ablation were recorded. All patients underwent a post-ablation MRI scan (Signa Horizon; GE Medical Systems, USA) within 48 h to evaluate the size of the ablation zone. The interventional radiologist, who was blinded to the medicine used in the procedure and body movement, analysed all imaging data.

The locations of the ablation zones were classified into five regions abutting the liver capsule: parietal peritoneum, diaphragm, left or right portal veins, gallbladder, and kidney. The shortest distance from the ablation zone margin to the five adjacent organs was evaluated on post-ablation MRI images, and the distance (< 5 mm) from the ablation zone margin to adjacent organs was recorded. The ablation zone size on post-ablation MRI was recorded. The ablation zone size was defined as the mean of the longest and orthogonal diameters (Fig. 2).

Statistical Analysis

Continuous data were analysed using the *t* test or Mann–Whitney rank-sum *U* test, and categorical data were tested using Pearson's χ^2 or Fisher's exact test, as appropriate. Repeated measures data were analysed using repeated measures analysis of variance (ANOVA) with post hoc analysis. Values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed using IBM's SPSS 17.0 for Windows.

Results

Forty patients were enrolled in this prospective, non-randomized study between August 2016 and April 2017. Two patients in the F group were excluded because of newly identified multiple tumours and ablation of > 2 lesions. Therefore, 38 patients were included in the final analyses.

Thirty-eight patients (28 males and 10 females, 57.7 ± 9.5 years) with 46 hepatic tumours were included in this study. Twenty patients with 24 hepatic tumours

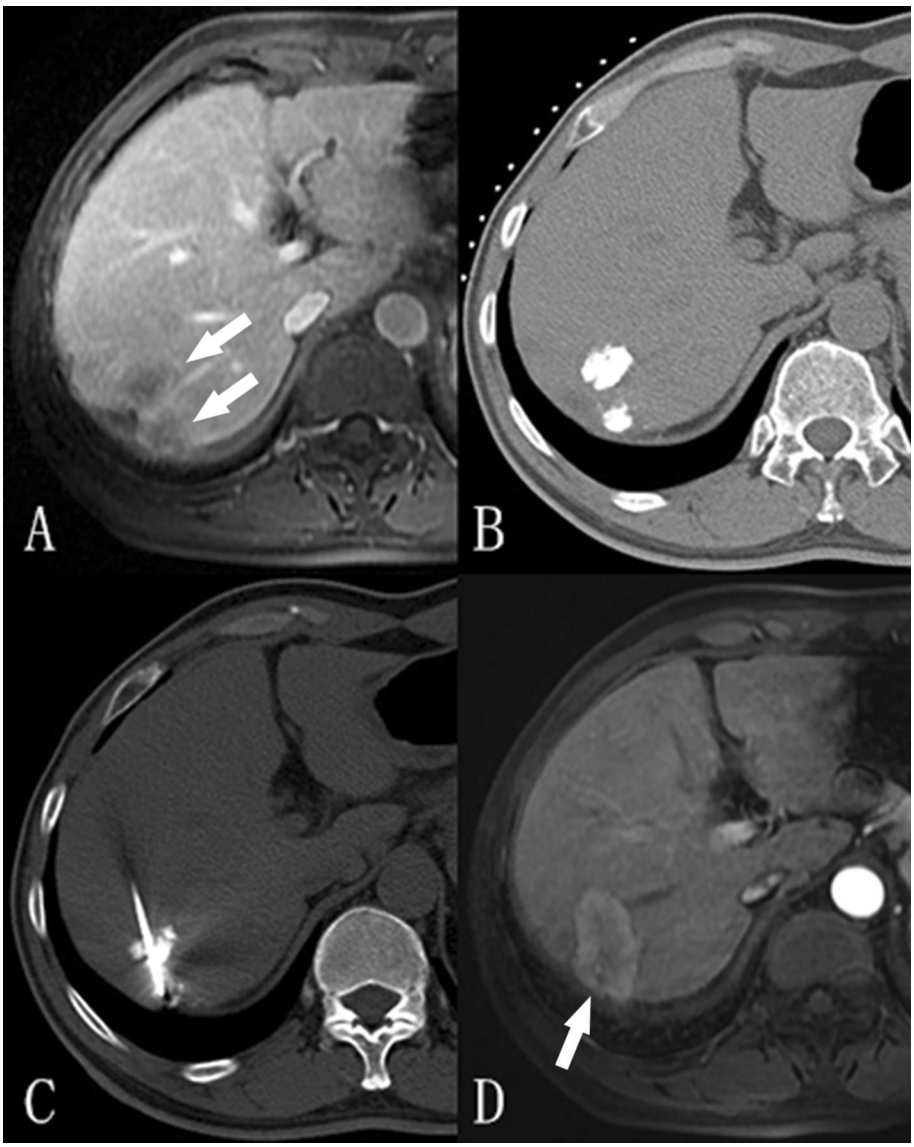

Fig. 2 Representative images of subcapsular tumour ablation (male, 52 years, hepatocellular carcinoma; oxycodone group). **A** The patient initially underwent transarterial chemoembolization (TACE). Follow-up MRI shows enhancement at the peripheral area of the lesions (arrows), which means local tumour recurrence. **B**, **C** CT-guided tumour ablation. A lesion with lipidol deposition is observed in (**B**), and the microwave antenna was inserted in the middle of lesions (**C**). **D** Post-ablation MRI shows that the lesions were completely covered by the ablation zone, which is against the liver capsule (arrow). Microwave output, 60 W × 8 min. Vital signs were stable during ablation, and no obvious body movement was observed. NRS scores were 1, 3, 2, 1, and 0 at 0.5, 3, 6, 12, and 24 h after MWA, respectively

received intravenous analgesia with oxycodone (the O group), and 18 patients with 22 hepatic tumours received fentanyl (the F group). Post-ablation MRI revealed that the ablation zone completely covered all lesions (Fig. 2). There were no statistically significant differences between the two groups according to the baseline data (Table 1), MWA technical details, or distance (< 5 mm) from the ablation zone margin to adjacent organs (Table 2).

There was no perioperative death in either group. One patient in the O group experienced a mild complication of a small pleural effusion 2 days after the MW ablation without dyspnoea, which disappeared at the 1-month follow-up.

No differences in respiratory depression during ablation with non-intubated general anaesthesia were observed between the two groups ($P = 0.170$), but a significant reduction in RR ($P = 0.020$) was observed in the F group. More body movement was observed in the F group ($P = 0.027$). No significant differences were found in HR ($F = 0.003$; $P = 0.959$), MBP ($F = 0.964$; $P = 0.333$) (Table 4), or awakening from anaesthesia times (O group = 4.4 ± 1.7 min, F group = 4.0 ± 1.1 min; $P = 0.459$) (Table 2). There was no delayed awakening in the two groups, and no statistically significant differences in the Ramsay sedation scores ($P = 0.603$) were detected 10 min after awakening (Table 4). No significant difference was found in the amount of propofol administered ($P = 0.579$) (Table 2).

The pain NRS scores were lower in the O group than in the F group 0.5 ($P = 0.035$), 3 ($P = 0.002$), and 6 h ($P = 0.001$) after MWA (Table 3, Fig. 3). Fewer patients received additional analgesics in the O group (6 of 20 vs. 13 of 18, $P = 0.022$) within 24 h (Table 3). The average 24-hour cumulative dezocine dose was 5.5 ± 4.1 mg and 2.1 ± 3.3 mg in the F and O groups, respectively

Table 1 Baseline characteristics

	Oxycodone (n = 20)	Fentanyl (n = 18)	P
Age (year)	55.5 ± 9.2	60.2 ± 9.8	0.140
Sex, male	14 (70.0)	14 (78.0)	0.719
Body mass index (kg/m^2)	22.3 ± 2.9	22.8 ± 3.5	0.640
Hypertension	4 (20.0)	7 (38.9)	0.288
Diabetes	1 (5.0)	5 (27.8)	0.083
Tumour type			1.000
HCC	16 (80.0)	14 (77.8)	
Metastasis	4 (20.0)	4 (22.2)	
Tumour number (per patient)			0.724
One	15 (75.0)	12 (66.7)	
Two	5 (25.0)	6 (33.3)	
Previous treatment			0.692
Liver surgery	4 (20.0)	4 (22.2)	
TACE	13 (65.0)	16 (88.9)	
MWA	4 (20.0)	8 (44.4)	
Maximum tumour diameter at CT (mm)	33.0 ± 19.0	30.0 ± 18.0	0.629
Smoker	4 (20.0)	2 (11.1)	0.663
History of motion sickness or PONV	7 (35.0)	5 (27.8)	0.734

Values are presented as the mean ± SD. Values in parentheses are percentages

HCC hepatic cellular carcinoma, *TACE* transcatheter arterial chemoembolization, *MWA* microwave ablation, *PONV* post-operative nausea and vomiting

Table 2 Technical details of the MWA procedure

	Oxycodone (n = 20)	Fentanyl (n = 18)	P
Ablation duration (min)	8.3 ± 3.2	8.1 ± 3.1	0.893
Ablation power (W)	65.5 ± 9.4	59.7 ± 14.6	0.152
Ablation zone size (mm)	43.8 ± 10.3	41.8 ± 6.7	0.489
One-needle ablation (%)	16 (80.0)	14 (77.8)	1.000
Two-needle ablation	4 (20.0)	4 (22.2)	
Total procedure time (min)	36.8 ± 4.7	36.7 ± 8.4	0.970
Anaesthesia time (min)	12.8 ± 2.9	12.1 ± 3.5	0.479
Recovery time (min)	4.35 ± 1.7	4.00 ± 1.1	0.459
Propofol (mg)	119.0 ± 18.5	120.0 ± 16.2	0.579
Distance < 5 mm from ablation zone to capsule	24	22	0.478
Parietal peritoneum	9 (45.0)	12 (54.5)	
Diaphragm	10 (50.0)	6 (27.3)	
Portal vein	3 (15.0)	2 (9.1)	
Gallbladder	1 (5.0)	0 (0.0)	
Kidney	1 (5.0)	2 (9.1)	

Values are presented as the mean ± SD. Values in parentheses are percentages

(P = 0.008). Dizziness occurred more often in the O group (P = 0.033). No differences of post-operative nausea and vomiting (PONV) were observed between the two groups (Table 4).

Discussion

Percutaneous thermal ablation of hepatic tumours abutting the liver capsule generally causes more severe pain during the procedure and a longer duration of post-ablation pain [4–6]. This pain is related to the presence of thermal or polymodal nociceptors in the parietal peritoneum and

Table 3 Pain NRS scores and analgesics within 24 h

	Oxycodone (n = 20)	Fentanyl (n = 18)	P
NRS scores (median) (IQR)[a]			
At 0.5 h	1.0 (1–1)	1.5 (1–2)	0.035
At 3 h	3.0 (2–4)	4.0 (3–5)	0.002
At 6 h	2.0 (2–3)	3.0 (3–4)	0.001
At 12 h	1.0 (1–2)	1.0 (1–2)	0.938
At 24 h	0.0 (0–1)	0.5 (1–1)	0.744
Analgesics (%)[b]	6 (30.0)	13 (72.2)	0.022

[a]Mann–Whitney U test; [b]Fisher's exact test

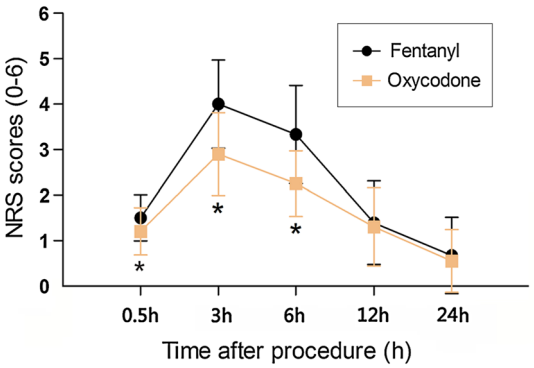

Fig. 3 NRS at 0.5–24 h post-operatively (mean ± SD). *$P < 0.05$ for an interaction effect between group and time. *NRS* numeric rating scale

diaphragm, which are innervated by branches of nerves that supply the muscles and skin [5, 11]. Severe pain in the muscles and viscera occurs frequently and poses a significant challenge in clinical practice. Oxycodone exhibited better performance than fentanyl in non-intubated general anaesthesia during ablation in the present study. Oxycodone reduced body movement incidence without significantly altering MBP, HR, or RR. Oxycodone provided better post-operative analgesia.

Fewer body movements were observed during ablation in the O group compared with the F group, which indicates a stronger analgesic effect of oxycodone. Oxycodone is a semisynthetic opioid that is a mu and kappa receptor agonist. Previous studies demonstrated that oxycodone exhibited a good therapeutic effect on visceral pain and that peripheral nerve kappa opioid receptors may play an important role in the analgesic effect [12, 13]. Opioid drugs in clinical practice, such as fentanyl, morphine, and pethidine, are commonly used to treat severe pain via targeting the mu receptors. Patients in the O group reported a lower NRS value and need for analgesics than patients in the F group within 24 h after ablation, which indicates that oxycodone was superior to fentanyl in the treatment of post-procedural hepatalgia symptoms and exhibited a longer working time than fentanyl. Previous studies also demonstrated that the action duration of oxycodone was longer than that of fentanyl (4 h 52 min vs. 3 h 39 min) [14].

Greater than 28% of patients exhibit PONV after MWA under general anaesthesia, which is mediated via an inflammatory response to necrotic tissue after ablation [6]. Opioids are also a risk factor for PONV, and previous studies demonstrated that oxycodone produced more PONV than fentanyl [15, 16]. However, no significant difference in the occurrence of PONV was observed between the two groups in the current study. Patients in the F group required more of the post-operative dezocine analgesic, which may have increased the incidence of PONV. More patients in the O group experienced dizziness than those in the F group, which is consistent with previous studies [15, 16]. The dizziness may have been caused by

Table 4 Intra-procedural vital signs and adverse events

	Oxycodone (n = 20)	Fentanyl (n = 18)	P
Vital signs			
Mean arterial pressure (mmHg)	99.5 ± 13.7	105.1 ± 16.5	0.259
Heart rate	76.3 ± 12.4	77.6 ± 15.7	0.786
SPO_2 (%)	99.6 ± 1.0	99.39 ± 1.9	0.671
Respiratory rate (intra-procedural)	11.7 ± 1.5	10.5 ± 1.5	0.020
Ramsay sedation score	2.5 ± 0.7	2.4 ± 0.6	0.603
Adverse events			
Respiratory depression	1 (5.0)	4 (22.2)	0.170
Body movement	2 (10.0)	8 (44.4)	0.027
Dizziness	9 (45.0)	2 (11.1)	0.033
Nausea	6 (30.0)	2 (11.1)	0.238
Vomiting	1 (5.0)	0 (0.0)	1.000

Values are presented as the mean ± SD. Values in parentheses are percentages

increased vestibular sensitivity, secondary to opioid activation of mu opioid receptors on the vestibular epithelium [17].

No differences in respiratory depression were observed between the two groups in the present study, but the respiratory rate was lower in the F group than in the O group during non-intubated general anaesthesia. However, Xie et al. [18] reported that fentanyl was more prone to respiratory depression and hypoxaemia than oxycodone for painless anaesthesia under the same dose of propofol. The potency ratio of fentanyl to oxycodone was 1:100 in the current study [19–21], but several studies demonstrated that the appropriate dose conversion ratio should be 1:75 [15, 16], which indicated that a lower dose of oxycodone was sufficient to control post-operative acute pain. Opioids induce dose-dependent respiratory depression via direct action on respiratory centres in the brainstem [22, 23], and the respiratory rate is generally drastically slower following opioid overdose [23]. Reducing the dose of oxycodone may prevent respiratory depression in more patients, but the efficacy of low-dose oxycodone must be verified. Haji's study in decerebrate cats demonstrated that kappa receptor activation depressed central respiratory activity and opposed mu receptor-mediated respiratory depression [24]. This differential activation may explain the lower rate of respiratory depression with oxycodone use compared to fentanyl. However, oxycodone hydrochloride does exhibit respiratory depression, but it leads to lower exhibit respiratory depression than fentanyl.

This study has several limitations. First, the potency ratio of fentanyl to oxycodone was 1:100 in the current study. A study using various potency ratios may be needed to determine the adequate potency ratio. Second, oxycodone or fentanyl was administered at a fixed intravenous injection rate. Adjustments to the infusion rate according to the patient's condition may reduce the side effects of opioids. Third, prior to the procedure, we explained to patients that oxycodone may be superior to fentanyl in analgesia, which may have produced a subjective bias in the reporting of pain using NRS.

In conclusion, oxycodone was safely and effectively used in percutaneous MWA of hepatic subcapsular tumours. Oxycodone exhibited better performance than fentanyl in reducing intra-procedural body movement incidence and relieving post-procedural pain. However, the optimized oxycodone–fentanyl dose conversion ratio should be verified in future research.

Compliance with Ethical Standards

Conflict of interest All of the authors declare that they have no conflicts of interest.

Ethical Approval All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all of the individual participants included in the study.

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