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CLINICAL TRIAL REPORT

Effect of Oxycodone-Based Multimodal Analgesia on Visceral Pain After Major Laparoscopic Gastrointestinal Surgery: A Randomised, Double-Blind, Controlled Trial

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Purpose: Oxycodone is a potent μ- and κ-opioid receptor agonist that can relieve both somatic and visceral pain. We assessed oxycodone- vs sufentanil-based multimodal analgesia on postoperative pain following major laparoscopic gastrointestinal surgery.

Methods: In this randomised double-blind controlled trial, 40 adult patients were randomised (1:1, stratified by type of surgery) to receive oxycodone- or sufentanil-based multimodal analgesia, comprising bilateral transverse abdominis plane blocks, intraoperative dexmedetomidine infusion, flurbiprofen axetil, and oxycodone- or sufentanil-based patient-controlled analgesia. The co-primary outcomes were time-weighted average (TWA) of visceral pain (defined as intra-abdominal deep and dull pain) at rest and on coughing during 0–24 h postoperatively, assessed using the numerical rating scale (0–10) with a minimal clinically important difference of 1.

Results: All patients completed the study (median age, 64 years; 65% male) and had adequate postoperative pain control. The mean (SD) 24-h TWA of visceral pain at rest was 1.40 (0.77) in the oxycodone group vs 2.00 (0.98) in the sufentanil group (mean difference=−0.60, 95% CI, −1.16 to −0.03; *P*=0.039). Patients in the oxycodone group had a significantly lower 24-h TWA of visceral pain on coughing (2.00 [0.83] vs 2.98 [1.26]; mean difference=−0.98, 95% CI, −1.66 to −0.30; *P*=0.006). In the subgroup analyses, the treatment effect of oxycodone vs sufentanil on the co-primary outcomes did not differ in terms of age (18–65 years or >65 years), sex (female or male), or type of surgery (colorectal or gastric). Secondary outcomes (24-h TWA of incisional and shoulder pain, postoperative analgesic usage, rescue analgesia, adverse events, and patient satisfaction) were comparable between groups.

Conclusion: For patients undergoing major laparoscopic gastrointestinal surgery, oxycodone-based multimodal analgesia reduced postoperative visceral pain in a statistically significant but not clinically important manner.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR2100052085).

Keywords: laparoscopic gastrointestinal surgery, oxycodone, patient-controlled analgesia, visceral pain

Introduction

Laparoscopic gastrointestinal surgery is a widely performed procedure, with comparable safety and long-term outcomes to conventional open laparotomy.[1–3] Patients undergoing major laparoscopic gastrointestinal surgery often experience moderate to severe postoperative pain, especially visceral pain. Visceral pain is deep and dull pain inside the abdomen, which cannot be accurately localized. The pathological mechanisms of visceral pain are very complex, involving surgical manipulations, peritoneal inflammation, visceral ischemia, and visceral hypersensitivity due to peripheral and central pathway sensitization.[4] Visceral pain can trigger autonomic nerve reflexes, such as nausea, vomiting, sweating, and

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cardiovascular and respiratory changes,[5,6] and may provoke negative emotional responses.[7] Early postoperative visceral pain is also related to chronic pain following surgery.[8]

Opioids are the cornerstones of postoperative analgesia but are associated with adverse effects. Multimodal analgesic strategy with opioids, non-opioid analgesics, and local anaesthetics has been used to enhance analgesia and reduce opioid-related adverse events.[9–11] Oxycodone, a semisynthetic μ- and κ-opioid receptor agonist may provide a better treatment for both somatic and visceral pain after laparoscopic surgery than other opioids (morphine, fentanyl, sufentanil, or alfentanil).[12–14] Oxycodone has been shown to be effective for postoperative pain control and well-tolerated across a variety of surgical procedures and patient populations. Compared with morphine, oxycodone is associated with a reduced incidence of side effects including hallucinations, nightmares, and histamine-related symptoms (such as itching and hypotension).[15] In the context of multimodal analgesia provision, the effects of oxycodone administration on postoperative pain outcomes after laparoscopic surgery are not fully understood.

Therefore, we designed this randomised controlled trial comparing oxycodone-based with sufentanil-based multimodal analgesia among patients undergoing major laparoscopic gastrointestinal surgery. We hypothesized that the use of oxycodone-based analgesic regimen would be superior to sufentanil-based analgesia in terms of early visceral pain relief in these patients.

Methods

Study Design

This researcher-initiated, prospective, randomised, double-blind, controlled study was approved by the Institutional Review Board of First Affiliated Hospital of Soochow University (no. 2021–920) on September 23, 2021. The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (Registration no: ChiCTR2100052085; Principal investigator: Ke Peng; Date of registration: October 16, 2021; Accessible via https://www.chictr.org.cn/showproj.html?proj=135273). This study complied with the Declaration of Helsinki. Written informed consent was obtained from all patients. The implementation and reporting of this trial conformed to the Consolidated Standards of Reporting Trials guidelines (Supplementary material).

Patients

Adult patients with ASA physical status I–III undergoing major laparoscopic gastrointestinal surgery (defined as surgical time ≥90 min, involving at least partial resection of stomach or intestine) were recruited. Exclusion criteria included emergency surgery; body mass index ≥35 kg m^{-2}; allergy to medications in this study; severe cardiopulmonary disease (myocardial infarction, heart failure, or respiratory failure); severe cerebrovascular disease (hemorrhagic or ischemic stroke); severe liver (Child-Pugh class C) or renal failure (requiring renal replacement therapy); cognitive impairment, use of antipsychotics, alcoholism, long-term use of opioids or other analgesics; inability to understand the rating scales or refusal for participation.

Randomisation

A researcher who was not involved in the other parts of the study performed the randomisation in a ratio of 1:1 and stratified by type of surgery (gastric or colorectal). Randomisation results were concealed in sealed opaque envelopes. A research nurse assigned eligible patients to an oxycodone group or a sufentanil group. Both oxycodone and sufentanil were colorless solutions constituted with normal saline in identical syringes and patient-controlled analgesia (PCA) containers. All patients, anaesthesiologists, perioperative care team, and researchers who collected postoperative outcome data were blinded throughout the study.

Anaesthesia and Interventions

The baseline mean blood pressure (MBP) and heart rate (HR) values were obtained in surgical wards preoperatively. Patients received the ASA standard monitoring during surgery. For patients in both groups, anaesthesia was induced with i.v. propofol 1.5–2 mg kg^{-1}, sufentanil 0.2 μg kg^{-1}, and cisatracurium 0.2 mg kg^{-1}. Anaesthesia was maintained with

sevoflurane, titrated to a minimal alveolar concentration at 0.7–1.2. Patients received remifentanil infusion of 0.05–0.2 μg kg^{-1} min^{-1} and cisatracurium 0.1 mg kg^{-1} as required. The ventilation was adjusted to maintain the end-tidal carbon dioxide at 35–45 mmHg. Dexamethasone 8 mg and ondansetron 4 mg were administered for prophylaxis of nausea and vomiting. Hypotension (a reduction in MBP >30% of baseline), hypertension (an increase in MBP >30% of baseline), bradycardia (HR <45 beats min^{-1}), and tachycardia (HR >100 beats min^{-1}) were treated.

Patients in both groups received a multimodal analgesia consisting of the following aspects: (1) transverse abdominis plane (TAP) blocks were conducted before skin incision using a subcostal approach in laparoscopic gastric surgery or a lateral approach at the level of the umbilicus in colorectal surgery. With patients in the supine position, the rectus abdominis, external oblique, internal oblique, and transversus abdominis muscles were identified by ultrasonography. A 22G 8-cm block needle was advanced using the in-plane technique until the needle tip reached the fascia above the transversus abdominis muscle. After negative aspiration, 0.375% ropivacaine 20 mL was injected at both sides; (2) intraoperative dexmedetomidine infusion at 0.4 μg kg^{-1} h^{-1} until 30 min before skin closure; (3) i.v. flurbiprofen axetil 50 mg at the end of surgery; and (4) a loading dose of oxycodone 0.2 mg kg^{-1} or sufentanil 0.2 μg kg^{-1}, followed by oxycodone- or sufentanil-based PCA until 48 h after surgery. The PCA system contained oxycodone 100 mg or sufentanil 100 μg diluted with normal saline to a volume of 100 mL (no background infusion, bolus of 1 mL, lockout time of 5 min). Rescue analgesia with additional oxycodone 5 mg (the oxycodone group) or sufentanil 5 μg (the sufentanil group) could be given to treat moderate to severe pain, defined as a score ≥4 on a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (the worst pain imaginable). To standardize the doses of sufentanil and oxycodone, equivalent milligrams of morphine was calculated according to the literature: i.v. sufentanil 1 μg = i.v. oxycodone 1 mg = i.v. morphine 1 mg.[16,17] The conversion ratio between parenteral morphine and oxycodone ranged from 0.65 to 1.5, and we selected a ratio of 1.0 in our study based on the previous studies.[18,19]

A researcher who was blinded to the allocation assessed postoperative pain (visceral, incisional, and shoulder pain) on the NRS at 1, 3, 6, 18, 24, and 48 h postoperatively. The three types of pain were defined as previously reported: visceral pain was intra-abdominal deep and dull pain; incisional pain was pain located at the abdominal wall; and shoulder pain was pain referred to the shoulder.[20,21]

Study Outcomes

The co-primary outcomes were visceral pain at rest and on coughing during the first 24 h after surgery. The 24-h overall pain was expressed as time-weighted average (TWA) which was calculated by plotting the area under the curve of NRS pain scores during 24 h and dividing that number by 24.[22]

The secondary outcomes included incisional and shoulder pain at rest and on coughing during 24 h postoperatively; PCA usage during 24 and 48 h; need for rescue analgesia; sedation in PACU and ward (defined as ≥2 on a 5-point level of sedation scale);[23] nausea and vomiting; use of antiemetics; respiratory depression, constipation, and dizziness; patient satisfaction (very satisfied, satisfied, neutral, or dissatisfied). The exploratory outcomes were quality of recovery (QoR)-15 scores on postoperative days 1, 2, 3, and 30; 30-d post-surgical pain (defined as NRS scores ≥1);[24] and 30-d death.

Statistical Analysis

According to our institutional data, the mean (standard deviation [SD]) 24-h NRS visceral pain on coughing was 3.5 (1.0) in patients undergoing major laparoscopic gastrointestinal surgery with sufentanil-based PCA. For patients with postoperative acute pain, the established minimum clinically important difference is 1 (on a 0–10 scale).[25] We hypothesized that the oxycodone-based analgesia would reduce the visceral pain score to 2.5 (1.0). To detect this difference at a significance level of 0.05 and a power of 80%, 17 patients were required in each group. After accounting for possible dropouts, we enrolled a total of 40 patients (n = 20 in each group). The sample size calculation was conducted using the PASS 15.0 (NCSS, LCC, Kaysville, UT, USA).

Data normality was assessed using the Shapiro–Wilk test. Continuous data were presented as mean (SD) if they were normally distributed and as median (interquartile range [IQR]) if not. Categorical data were presented as n (%). Data

were analysed using the unpaired *t* test, Mann–Whitney *U*-test, $\chi 2$ test, or Fisher exact test, as appropriate. For pain scores at several postoperative timepoints, multiple unpaired *t* test was used with corrections for multiple comparisons using the false discovery rate and a two-stage step-up method of Benjamini, Krieger, and Yekutieli. The interventional effects of oxycodone vs sufentanil were evaluated using the mean/median difference or odds ratios (OR) with the 95% confidence interval (CI). Additionally, subgroup analyses of the co-primary outcomes were conducted in terms of age (18–65 years or >65 years), sex (female or male), and type of surgery (colorectal or gastric).

The outcome data were analysed in the intention-to-treat population (including all randomised patients who had surgery). For the two co-primary outcomes, a two-sided P <0.025 indicates a statistically significant difference (Bonferroni correction, 0.05/2). For the perioperative data and secondary and exploratory outcomes, no multiple comparison correction was applied. All analyses were done using the SPSS 25.0 (IBM SPSS, Chicago, IL, USA).

Results

Patient Characteristics

A total of 60 patients were screened from December 1, 2021 to May 31, 2022 (Figure 1). Of them, 12 were excluded, 8 declined to participate, and 40 were randomised and included in the intention-to-treat analysis. All patients had available data on the primary outcomes.

Table 1 shows the characteristics of patients. The median (IQR) age was 67.5 (61.3–71.8) years in the oxycodone group and 62 (57.3–70) years in the sufentanil group. Overall, 26 of 40 (65%) patients were male. In both groups, 95% of patients were at ASA classification I or II, 35% underwent laparoscopic gastric surgery, and 65% had laparoscopic colorectal surgery. Table 2 shows that the two groups are comparable in terms of perioperative values of MBP and HR, haemodynamic events, use of anaesthetics and analgesics, use of other medications, duration of surgery, duration of anaesthesia, and length of postoperative hospital stay. The mean (SD) length of PACU stay was 51.7 (21.2) min in the oxycodone group and 69.6 (29.6) min in the sufentanil group.

Primary Outcomes

The mean (SD) TWA of visceral pain score at rest during the first 24 h postoperatively was 1.40 (0.77) in the oxycodone group vs 2.00 (0.98) in the sufentanil group (difference=−0.60, 95% CI, −1.16 to −0.03; P=0.039), which was not statistically significant (Table 3).

The 24-h TWA of visceral pain score on coughing was significantly lower in the oxycodone group compared with the sufentanil group (mean [SD], 2.00 [0.83] vs 2.98 [1.26]; difference=−0.98, 95% CI, −1.66 to −0.30; P=0.006) (Table 3); however, this difference did not reach the minimum clinically important difference of 1.

Additionally, the treatment effect of oxycodone vs sufentanil did not differ in terms of age (18–65 years or >65 years), sex (female or male), or type of surgery (colorectal or gastric) in the subgroup analyses of 24-h visceral pain at rest (Figure 2A) and on coughing (Figure 2B).

Secondary and Exploratory Outcomes

Patients in the oxycodone group had lower visceral pain scores at rest at 3 h (mean [SD], 0.95 [0.76] vs 1.60 [0.88]; P=0.043) and 6 h postoperatively (mean [SD], 1.10 [0.85] vs 2.05 [0.89]; P=0.007) (Figure 3A), and lower visceral pain scores on coughing from 3 h (mean [SD], 1.35 [0.88] vs 2.35 [1.09]; P=0.006) to 48 h after surgery (mean [SD], 1.80 [0.89] vs 2.70 [1.13]; P=0.011) (Figure 3B). The two groups had comparable incisional pain scores at rest and on coughing (Figure 3C and D). The median shoulder pain scores were 0 in both groups (Table 3).

There were no significant between-group differences in PCA usage, need for rescue analgesia, postoperative sedation, nausea and vomiting, use of antiemetics, dizziness, patient satisfaction, i.v. morphine equivalent doses, QoR-15 scores, and 30-d post-surgical pain (Table 3). No patients developed respiratory depression or constipation. No death event occurred within 30 days after surgery.

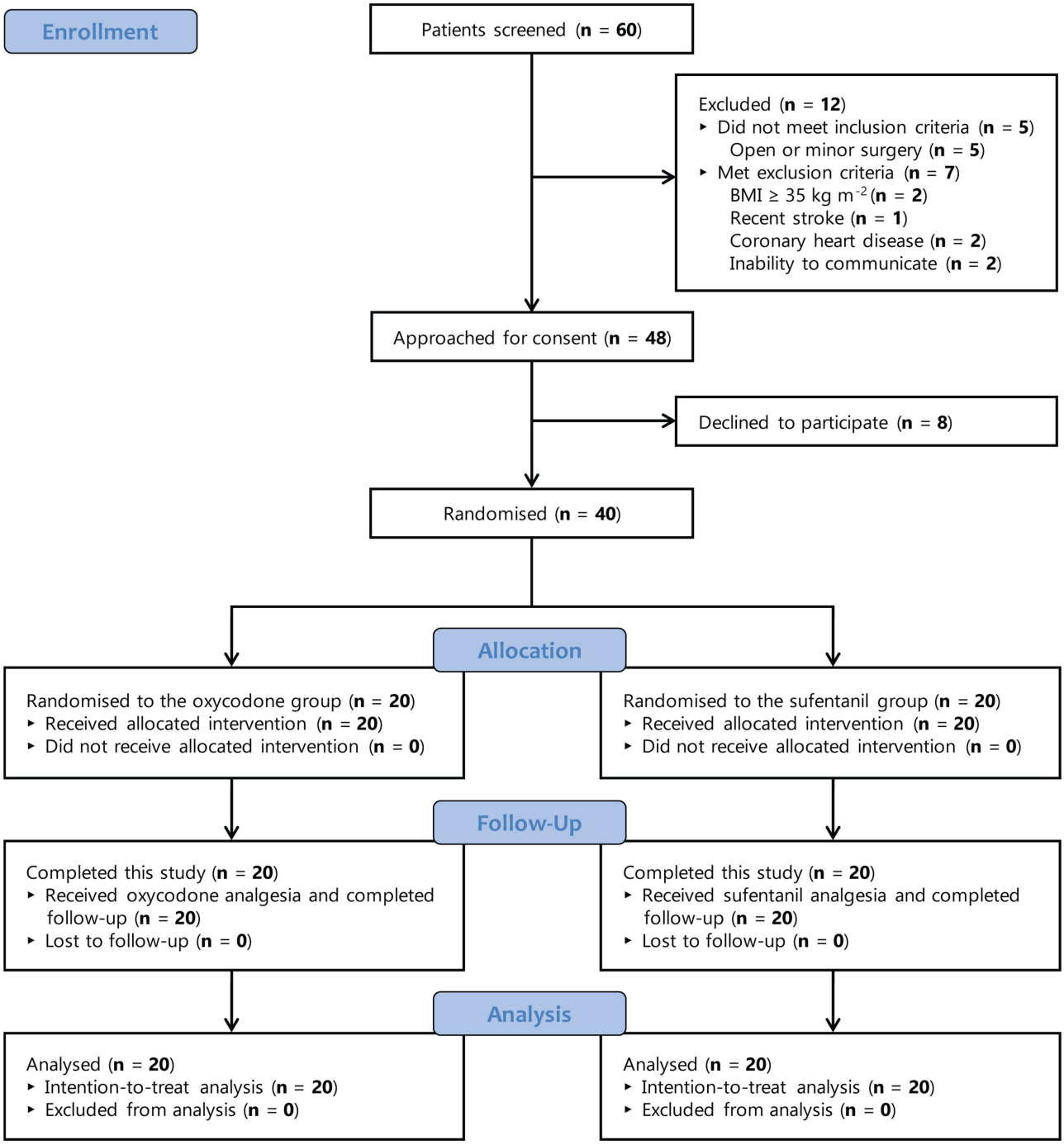

Figure 1 Trial flow diagram. PCA, patient-controlled analgesia.

Discussion

This study suggested that in the context of multimodal analgesia, oxycodone- vs sufentanil-based postoperative analgesia reduced 24-h visceral pain on coughing in patients undergoing major laparoscopic gastrointestinal surgery; however, this reduction in pain scores did not achieve the minimum clinically important difference. Meanwhile, both analgesic regimens provided adequate postoperative pain control, with a good safety profile and high patient satisfaction.

Visceral pain originates within internal organs, distinguishing it from somatic pain. Visceral pain tends to elicit significant discomfort and negative emotional responses,[26] which is attributed to the dual innervation and central

Table 1 Patient Characteristics

	Oxycodone (n=20)	Sufentanil (n=20)	*P* value
Age, yr	67.5 (61.3–71.8)	62 (57.3–70)	0.233
Sex			0.741
Male	12 (60%)	14 (70%)	
Female	8 (40%)	6 (30%)	
Height, cm	161.3 (7.6)	163.6 (9.0)	0.380
Weight, kg	58.6 (11.2)	59.6 (12.6)	0.793
BMI, kg m^{-2}	22.7 (3.2)	22.1 (3.2)	0.598
Current smoker	3 (15%)	9 (45%)	0.082
Educational level			>0.999
≤ Elementary school	12 (60%)	12 (60%)	
Secondary school	6 (30%)	6 (30%)	
Higher education	2 (10%)	2 (10%)	
ASA physical status			0.835
I	1 (5%)	2 (10%)	
II	18 (90%)	17 (85%)	
III	1 (5%)	1 (5%)	
Comorbidities			
Hypertension	9 (45%)	8 (40%)	>0.999
Diabetes	1 (5%)	4 (20%)	0.342
Cardiovascular disease	2 (10%)	0	0.487
Pulmonary disease	0	2 (10%)	0.487
Neurological disease	0	1 (5%)	>0.999
Anaemia	5 (25%)	5 (25%)	>0.999
Haemoglobin, g dL^{-1}	121.8 (19.9)	125.8 (19.1)	0.515
Albumin, g L^{-1}	38.8 (4.4)	39.4 (4.9)	0.697
Potassium, mmol L^{-1}	4.1 (0.4)	4.1 (0.4)	0.904
Serum creatinine, μmol L^{-1}	67.4 (60.5–73.9)	63.3 (55.5–72.5)	0.551
Type of surgery			>0.999
Gastric	7 (35%)	7 (35%)	
Colorectal	13 (65%)	13 (65%)	

Note: Data are mean (SD), median (IQR), or n (%).
Abbreviations: BMI, body mass index; ASA, American Society of Anaesthesiologists.

Table 2 Perioperative Data

	Oxycodone (n=20)	Sufentanil (n=20)	*P* value
Mean blood pressure, mmHg			
Baseline	105 (10)	105 (14)	0.950
After induction	88 (15)	88 (13)	0.894
Skin incision	92 (20)	86 (15)	0.331
End of surgery	85 (10)	89 (11)	0.243
Heart rate, beats min^{-1}			
Baseline	72 (11)	75 (11)	0.305
After induction	65 (12)	72 (11)	0.100
Skin incision	57 (11)	60 (9)	0.319
End of surgery	62 (8)	60 (6)	0.342

(*Continued*)

Table 2 (Continued).

	Oxycodone (n=20)	Sufentanil (n=20)	*P* value
Haemodynamic events			
Hypotension	16 (80%)	16 (80%)	>0.999
Bradycardia	5 (25%)	3 (15%)	0.695
Hypertension	3 (15%)	2 (10%)	>0.999
Tachycardia	1 (5%)	0	>0.999
Anaesthetics and analgesics			
Propofol, mg	119 (29.5)	123 (30.4)	0.714
Dexmedetomidine, μg	61.1 (29.9)	72.4 (31.4)	0.253
Sevoflurane, MAC			
0.5 h in surgery	0.7 (0.6–0.7)	0.7 (0.7–0.8)	0.629
End of surgery	0.3 (0.2–0.3)	0.3 (0.2–0.3)	0.949
Other medications			
Ephedrine	15 (75%)	15 (75%)	>0.999
Phenylephrine or metaraminol	6 (30%)	7 (35%)	0.736
Atropine	3 (15%)	0	0.231
Esmolol, nitroglycerin, or nicardipine	0	0	>0.999
Duration of surgery, min	161 (56)	184 (61)	0.214
Duration of anaesthesia, min	188 (60)	213 (65)	0.214
Length of PACU stay, min	51.7 (21.2)	69.6 (29.6)	0.035
Length of postoperative hospital stay, d	8 (7–11.5)	8 (6.3–12)	0.823

Note: Data are mean (SD), median (IQR), or n (%).
Abbreviations: MAC, minimal alveolar concentration; PACU, post-anaesthesia care unit.

Table 3 Study Outcomes

	Oxycodone (n=20)	Sufentanil (n=20)	Difference or OR (95% CI)	*P* value
Primary outcomes				
TWA visceral pain at rest 0–24 h	1.40 (0.77)	2.00 (0.98)	−0.60 (−1.16 to −0.03)	0.039
TWA visceral pain on coughing 0–24 h	2.00 (0.83)	2.98 (1.26)	−0.98 (−1.66 to −0.30)	0.006
Secondary outcomes				
TWA incisional pain at rest 0–24 h	1.53 (0.72)	1.94 (0.88)	−0.41 (−0.92 to 0.10)	0.115
TWA incisional pain on coughing 0–24 h	2.32 (1.13)	2.68 (1.27)	−0.36 (−1.13 to 0.42)	0.357
TWA shoulder pain at rest 0–24 h	0 (0–0.78)	0 (0–0.75)	0 (0 to 0)	0.880
TWA shoulder pain on coughing 0–24 h	0 (0–0.90)	0 (0–0.75)	0 (0 to 0)	0.938
PCA usage, mL				
0–24 h	28 (25–40.8)	33.5 (27.3–49.5)	−5.5 (−12 to 1)	0.146
0–48 h	63.5 (48.5–85)	68 (53.3–95.5)	−4.5 (−20 to 5)	0.301
Need for rescue analgesia	3 (15%)	4 (20%)	0.71 (0.16 to 3)	>0.999
Sedation				
In PACU	4 (20%)	4 (20%)	1.00 (0.25 to 3.93)	>0.999
In ward	2 (10%)	1 (5%)	2.11 (0.23 to 32)	>0.999
Nausea and vomiting	5 (25%)	3 (15%)	1.89 (0.37 to 7.97)	0.695
Use of antiemetics	1 (5%)	1 (5%)	1.00 (0.05 to 19.9)	>0.999
Respiratory depression	0	0	–	>0.999
Constipation	0	0	–	>0.999
Dizziness	4 (20%)	2 (10%)	2.25 (0.45 to 12.8)	0.661

(*Continued*)

Table 3 (Continued).

	Oxycodone (n=20)	Sufentanil (n=20)	Difference or OR (95% CI)	*P* value
Patient satisfaction				
Very satisfied	3 (15%)	2 (10%)	1.59 (0.29 to 9.69)	>0.999
Satisfied	14 (70%)	16 (80%)	0.58 (0.16 to 2.24)	0.716
Neutral	3 (15%)	2 (10%)	1.59 (0.29 to 9.69)	>0.999
Dissatisfied	0	0	–	>0.999
Exploratory outcomes				
IV morphine equivalent dose, mg				
Intraoperative	25 (20–30)	24 (20–29.5)	1 (−2 to 6)	0.510
Postoperative 0–48 h	63.5 (50–85)	68 (55.5–97.5)	−4.5 (−22 to 5)	0.316
Total	90 (71.8–119.3)	88.5 (76.8–124.5)	1.5 (−20 to 14)	0.597
QoR-15 scores				
Postoperative day 1	103 (96–110)	99 (96–106)	4 (−3 to 9)	0.330
Postoperative day 2	113 (103–115)	114 (105–118)	−1 (−6 to 7)	0.783
Postoperative day 3	125 (117–127)	126 (115–129)	−1 (−5 to 4)	0.606
Postoperative day 30	146 (142–149)	146 (141–149)	0 (−3 to 4)	0.930
30-d post-surgical pain	1 (5%)	1 (5%)	1.00 (0.05 to 19.9)	>0.999
30-d death	0	0	-	>0.999

Note: Data are mean (SD), median (IQR), or n (%).
Abbreviations: TWA, time-weighted average; PCA, patient-controlled analgesia; PACU, post-anaesthesia care unit; OR, odds ratio; CI, confidence interval.

projection to emotion-controlling areas.[7] Currently, postoperative pain after laparoscopic surgical procedures is often treated with the combined use of opioid medications and nonsteroidal anti-inflammatory drugs, but sometimes the pain can be difficult to treat, especially the visceral components.

Oxycodone produces effective postoperative analgesia through acting on both opioid μ and κ receptors.[14,20,27–30] The κ-opioid receptors locate within the gastrointestinal tract are significant factors for anti-nociception in the visceral pain system.[31] The analgesic efficacy of oxycodone is associated with its plasma concentration, suggesting a peripheral effect mediated through κ-receptors.[32] With the activation of κ-opioid receptors, oxycodone presents a distinct pharmacological profile compared to other opioids such as morphine and fentanyl in which analgesia is mediated by μ receptors located mainly in the central nervous system.

A recent meta-analysis showed that oxycodone led to better analgesia than other opioids (morphine, fentanyl, sufentanil, and alfentanil) in laparoscopic surgery.[12] In that meta-analysis, the majority of included studies were conducted in patients undergoing laparoscopic cholecystectomy and gynecological surgery. However, it is still unclear to what extent oxycodone-based postoperative analgesia compared with sufentanil-based analgesia would affect post-operative pain, especially visceral pain, in patients who had major laparoscopic gastrointestinal surgery.

Many multimodal analgesia strategies are currently being investigated to reduce opioid-related adverse effects. In our study, the multimodal analgesia strategy comprised bilateral TAP blocks after anaesthesia induction, intraoperative dexmedetomidine infusion, flurbiprofen axetil administration at the end of surgery, and postoperative analgesia with oxycodone or sufentanil. Owing to the use of these analgesic techniques, postoperative pain was successfully treated in all patients, with a mean NRS score ranging from 1.4 to 3.1.

Adverse effects associated with postoperative oxycodone or sufentanil analgesia include nausea, vomiting, constipation, dizziness, and respiratory depression. In our study, all patients received the prophylactic use of dexamethasone and ondansetron. Postoperative nausea and vomiting occurred in 5 patients (25%) in the oxycodone group and 3 (15%) in the sufentanil group; of them, only 1 patient in each group needed rescue antiemetics. Four patients (20%) in the oxycodone group and 2 (10%) in the sufentanil group experienced dizziness. No patients developed respiratory depression or constipation. The two multimodal analgesia strategies showed similar clinical efficacy and safety, without significant adverse events.

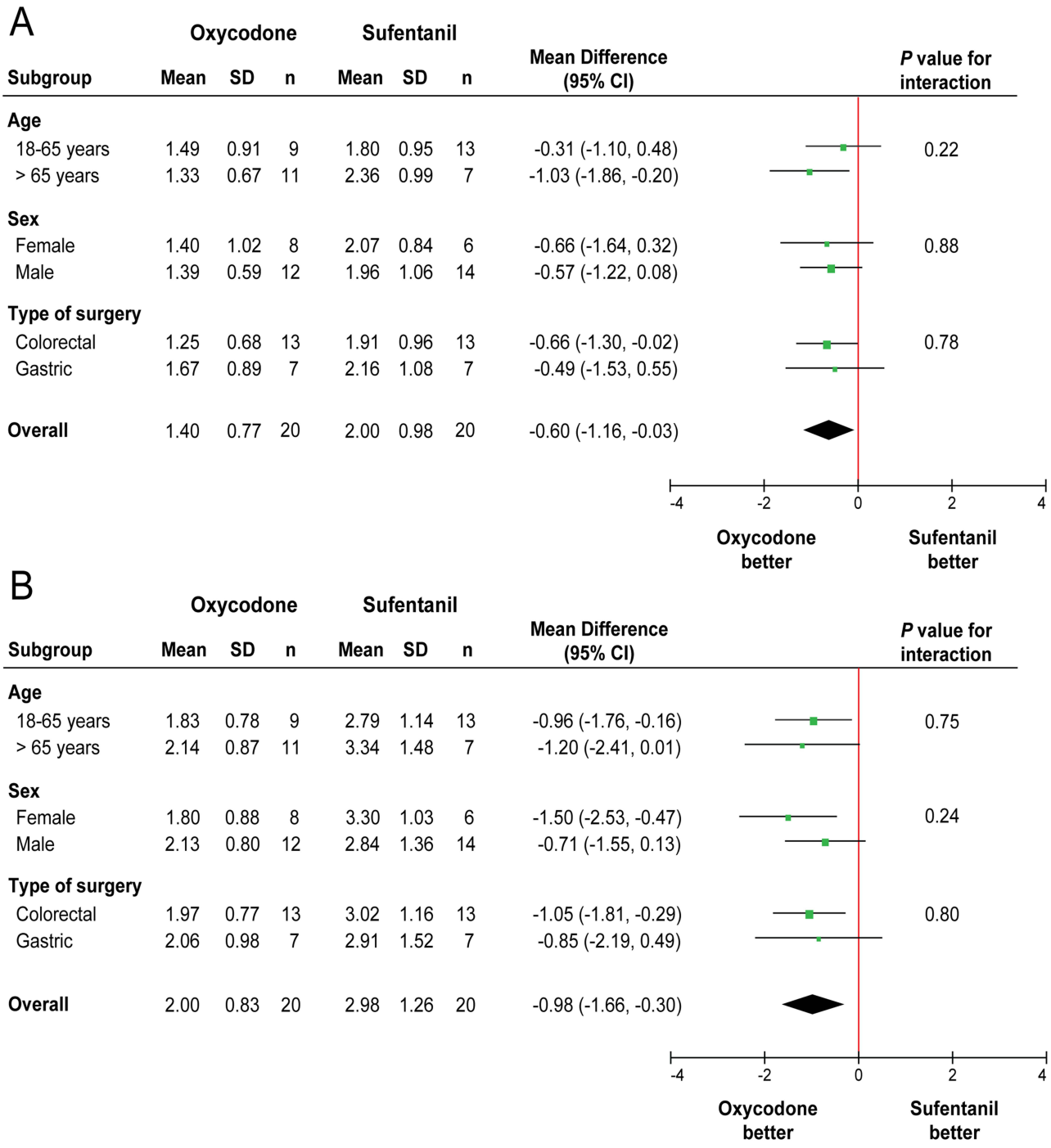

Figure 2 Subgroup analyses of the co-primary outcomes based on age, sex, and type of surgery. (**A**) 24-h visceral pain at rest. (**B**) 24-h visceral pain on coughing. SD, standard deviation; CI, confidence interval.

The strengths of this trial include (1) the prospective, randomised, double-blind, controlled study design; (2) the primary focus on oxycodone-based analgesia and visceral pain in patients undergoing major laparoscopic gastrointestinal surgery; (3) the rigorous consideration of stratified randomisation by the type of surgery; and (4) the implementation of multimodal pain management (TAP blocks, dexmedetomidine, flurbiprofen axetil, and PCA) for patients in both groups.

Nonetheless, this study is limited by the small sample size, relatively healthy patients (95% at ASA status I or II), and lack of postoperative gastrointestinal function assessment (such as time to first flatus and time to first oral feeding).

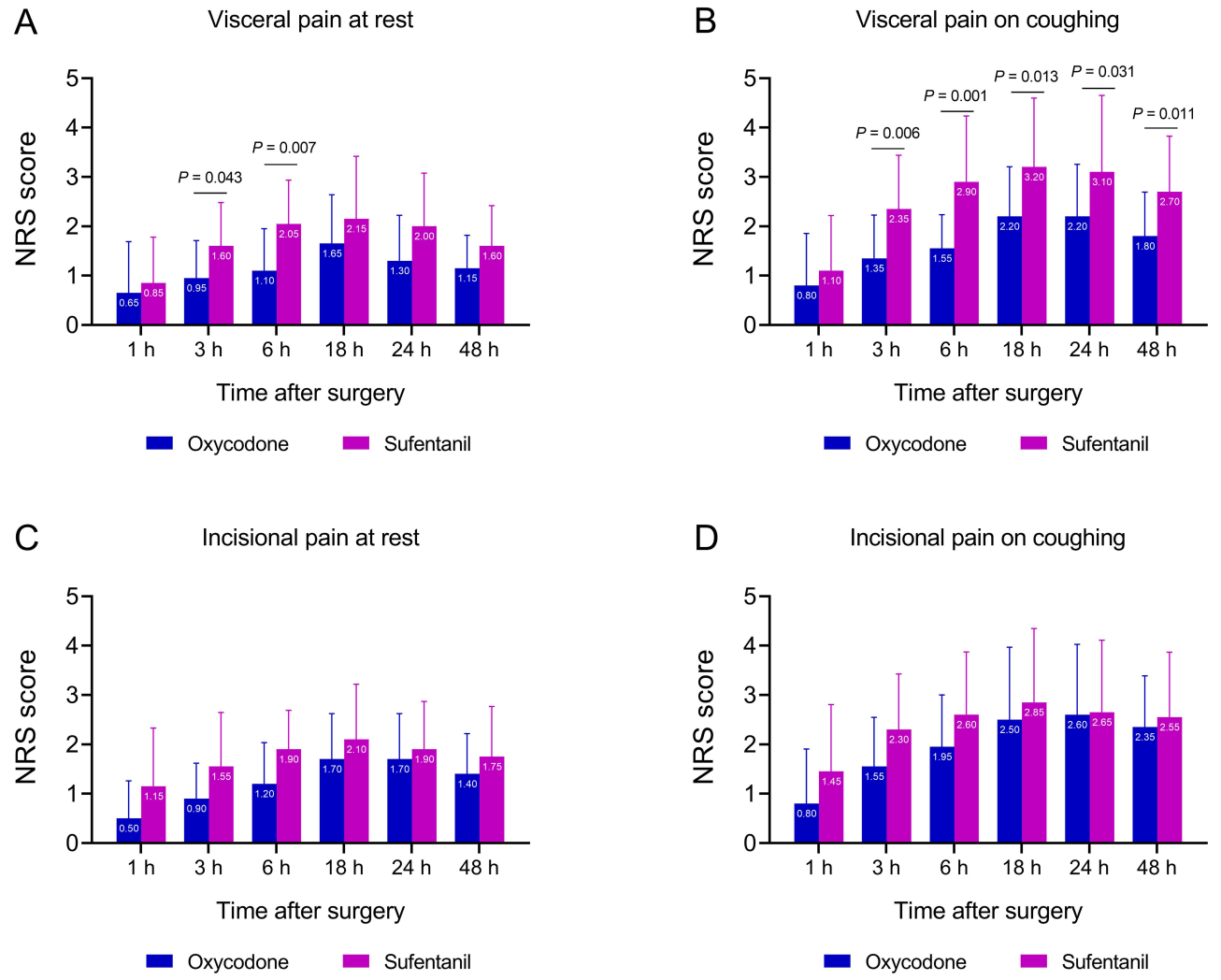

Figure 3 Visceral pain and incisional pain during the first 48 h postoperatively. (**A**) Visceral pain at rest. (**B**) Visceral pain on coughing. (**C**) Incisional pain at rest. (**D**) Incisional pain on coughing. NRS, numerical rating scale.

Additionally, the reduced visceral pain in the oxycodone group did not translate into higher QoR-15 scores in this pilot study. Last, we showed that only 1 patient in each group had 30-d post-surgical pain, but we did not evaluate chronic pain (eg pain at 3 months or later after surgery). A larger multicentre trial is required to ascertain the optimal multimodal analgesic strategy on postoperative pain and quality of recovery in this patient population.

In conclusion, our results suggest that for patients undergoing major laparoscopic gastrointestinal surgery, the oxycodone-based multimodal analgesia decreased postoperative visceral pain in a statistically but not clinically meaningful manner. For these surgical patients, postoperative pain can be satisfactorily treated using the multimodal analgesic strategy with either oxycodone or sufentanil.

Data Sharing Statement

All data and materials generated or used in this study (including individual deidentified participant data, Case Report Form, and Informed Consent Form) are available upon reasonable request to the corresponding author. Data can be accessible after the publication of this article without time limit.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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