

Oxycodone versus other opioids analgesia after laparoscopic surgery: a meta-analysis

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Research

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Abstract

Background

Intravenous opioids are administered for management of visceral pain after laparoscopic surgery. Whether oxycodone has an advantage over other opioids in the treatment of visceral pain is not yet clear.

Methods

This article evaluates the analgesic efficiency and adverse events of oxycodone and other opioids including alfentanil, sufentanil, fentanyl and morphine for the treatment of post laparoscopic surgery visceral pain. This review was conducted according to the methodological standards described in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. The PubMed, Embase and Cochrane libraries were searched in December 2019.

Results

Ten studies were included in this review. The sample size was 815 participants. The results showed that compared with morphine and fentanyl, oxycodone had a more potent analgesic efficacy at the first day after laparoscopic surgery, especially during the first 0.5h. There was no significant difference in sedation between the two groups. Compared to morphine and fentanyl, oxycodone was more likely to increase the risk of dizziness and drowsiness. The overall patients satisfaction had no significant difference between oxycodone versus other opioids.

Conclusions

Oxycodone is a superior analgesic within 24h after laparoscopic surgery with careful regards to its adverse effects.

Background

Visceral pain is one of the most frequent reasons for patients to seek medical attention after laparoscopic surgery[1]. Opioids are the most common means for the treatment of postoperative visceral pain, whether they can be used prior to the completion of the operation or in the patient controlled analgesia (PCA) pump after surgery[1]. However, it is still controversial that which kind of opioids is most appropriate.

Oxycodone is a semisynthetic drug that is derived from thebaine, an opium alkaloid, which acts as a μ -opioid receptor agonist exerting its effects in the central nervous system. Experiments in rodents suggest that oxycodone also has an effect at the κ -opioid receptor, which in visceral nervous system was believed to inhibit visceral pain[2]. In animal experiments and clinical observations have shown that oxycodone may occasionally be superior to, e.g., morphine and fentanyl in the treatment of visceral pain[2]. However, by utilizing a meta-analysis, one can detect treatment effects with greater power and estimate these effects with greater precision[11]. To allow an indirect comparison with existing evidence on the efficacy of oxycodone and other opioids options used in postoperative pain management after laparoscopic surgery a meta-analysis was performed.

Methods

Design

Meta-analysis was performed in this study.

Information Source

The PubMed, Excerpta Medica (EMBASE), Cochrane Library databases were searched for trials published from inception to December, 2019, with no language restrictions. Hand searches of the reference lists of the included studies or relevant reviews were also employed. The search method included relevant text and medical subject headings related to oxycodone, laparoscopic surgery and randomized controlled trials (RCTs).

The search strategy for each database were presented in Appendix 1.

Inclusion Criteria

Type of study: RCTs

Participants: The participants must be patients with clinical diagnosis of visceral pain after laparoscopic surgery.

Type of interventions: oxycodone versus other opioids including alfentanil, sufentanil, fentanyl and morphine.

Outcomes: Pain intensity measured by Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS), Sedation status, adverse event and patient satisfaction that measured by validated scales.

Study Records

All retrieved studies were imported into Endnote X7. To ensure a high level of confidence between researchers, we conducted a pilot-test on literature screening. Two researchers independently reviewed the titles and abstracts of the literatures and selected studies that met the eligibility criteria. Then, the full text of all the literatures that meet the requirements were obtained.

Data Items

Using a standardized data sheet in Microsoft Excel 2013 (Microsoft Corp, Redmond, WA,), two investigators independently extracted data for study characteristics (eg, first author's name, publication year, region where the study was conducted), characteristics of study subjects (eg, number of participants, gender distribution), interventions details (eg, treatment and comparison), outcome variables (eg, adverse event). Any discrepancies observed between the data extracted by the two extractors were resolved by consensus.

Risk Of Bias Individual Studies

The risk of bias of included RCTs was assessed according to the Cochrane Handbook version 5.1.0 including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other bias. We evaluated risk of bias as low, high, or unclear. The risk of bias assessment was completed by two independent reviewers, and conflicts were resolved by a third reviewer.

Meta-analysis

Meta-analysis was conducted by using Revman 5.3 software. Calculate the combined risk ratio (RR) for the 95% confidence interval (CI) for the dichotomous results. The heterogeneity of the therapeutic effects in the trials was assessed by χ^2 and I^2 . If there was no statistical heterogeneity (the p value was ≥ 0.1 and $I^2 \leq 50\%$), the Mantel-Haenszel fixed effect model was used for meta-analysis. Otherwise, we explored the potential causes of heterogeneity through subgroup analysis and meta-regression. If no clinical heterogeneity is determined, a meta-analysis was performed using the Mantel-Haenszel random effects model.

Results

Literature selection

The derivation of the databases and published articles was described in Figure 1. There were 145 studies by searching database. Of them, 121 articles were excluded by screening the title and abstract. The remaining 24 studies concerning the oxycodone for visceral pain after laparoscopic surgery were identified. Among them, 14 studies were excluded due to non-randomized controlled trials (n=1), ineligible patients (n=2), ineligible comparator (n=9), and absent of eligible outcome reporting (n=2). Therefore, 10 studies [13,6,31,7,6,10,6,4,2] met our inclusion criteria.

Characteristics Of Included Studies

A total of 815 participants (including 410 oxycodone subjects and 405 controls) matched the inclusion criteria and were selected for the data analysis; study design and location, characteristics of patients (diagnose, duration of surgery, duration of anesthesia, ASA (American Society of Anesthesiologists) physical status I/II), details about interventions and measured outcomes were presented in Table 1.

Table 1
Characteristic of included studies

Study	Study design and country	Participants Age (Mean/SD, years)	Intervention and sample size(M/F/N)		Duration of surgery (mean/SD,min)	Duration of anesthesia (mean/SD,min)	ASA physical status I/II	Outcomes
			Oxycodone	Other Opioid				
Choi 2015 (7)	RCT Korea	Age 55.1/11.3; undergoing elective laparoscopic cholecystectomy	Twenty minutes before the end of surgery, the patients received 0.08 mg/kg oxycodone; 19/9/28	Twenty minutes before the end of surgery, the patients received 1 ug/kg fentanyl; 12/14/26	52.3/20.0	67.8/17.4	29/25	Postoperative pain intensity (VAS); Sedation score; Dizziness; Nausea; Vomiting
Choi 2018(15)	RCT Korea	Age 46/11.8; elective laparoscopic cholecystectomy	Ten minutes prior to the completion of the operation, the patients received a 2 mL mixture of oxycodone (0.08 mg/kg) in isotonic saline intravenously; 14/16/30	Ten minutes prior to the completion of the operation, the patients received a 2 mL mixture of fentanyl (1 ug/kg) in isotonic saline intravenously; 10/20/30	36/12.1	61/15	NR	Postoperative Pain intensity (NRS) ; Nausea; Vomiting; Dizziness; Respiratory Depression
Han 2018(16)	RCT China	Aged 50.12/10.54; elective abdominal surgery (laparotomy or endoscopy)	Oxycodone (0.1 mg/kg for endoscopy procedures; 0.15 mg/kg for laparotomy procedures) or was administrated intravenously at the end of surgery. PCA was given to the patients immediately at the end of surgery; 55/8/63	Sufentanil (0.1 mg/kg for endoscopy procedures; 0.15 mg/kg for laparotomy procedures) was administrated intravenously at the end of surgery. PCA was given to the patients immediately at the end of surgery; 49/8/57	NR	158.2/65.85	NR	Nausea and vomiting; Pruritus; Respiratory depression
HWang 2014(8)	RCT Korea	Age 54.5/13.8; scheduled for laparoscopic cholecystectomy	Oxycodone (1 mg oxycodone and 1.5 mg ketorolac); NR/NR/41	Fentanyl (10 mcg fentanyl and 1.5 mg ketorolac); NR/NR/40	NR	NR	NR	Pain intensity (NRS); Sedation levels (Ramsey sedation scores); Nausea; Vomiting; Headache; Pruritus; Respiratory depression; Patient satisfaction

Notes: M = number of male patients; F = number of female patients; N = number of total patients; NR = not reported; PCA = patient controlled analgesia

Study	Study design and country	Participants Age (Mean/SD, years)	Intervention and sample size(M/F/N)		Duration of surgery (mean/SD,min)	Duration of anesthesia (mean/SD,min)	ASA physical status I/II	Outcomes
			Oxycodone	Other Opioid				
Kim 2015(9)	RCT Korea	Age 48.1/5.3; scheduled for laparoscopic hysterectomy	Oxycodone (10 mg); NR/NR/24	Fentanyl (100 mg fentanyl with 30-mg ketorolac); NR/NR/24	73.3/23.0	NA	46/14	Pain intensity (NRS); Dizziness; headache; nausea; vomiting; pruritis; respiratory depression; Patient satisfaction
Kim 2017(10)	RCT Korea	Age 46.3/5.2; Scheduled for laparoscopic supracervical hysterectomy	52.5 mg of oxycodone, 150 mg of ketorolac, and 0.6 mg of ramosetron were mixed with saline to a total volume of 100 mL; NR/NR/64	700 mg of fentanyl, 150 mg of ketorolac, and 0.6 mg of ramosetron were mixed with saline to a total volume of 100 mL; NR/NR/63	70.8/ 22.1	70.8/ 22.1	93/34	Pain intensity (NRS); Nausea; Vomiting; Dizziness; Drowsiness; Headache; Pruritis; Respiratory Depression; Patient satisfaction
Koch 2008(11)	RCT Denmark	Age 43.4/11; scheduled for elective outpatient laparoscopic cholecystectomy	Patients received 10 mg oxycodone at end of surgery; 12/24/36	Patients received 100 ug fentanyl at end of surgery; 9/28/37	82.4/28.5	NA	47/26	Pain intensity; Sedation; Nausea; Vomiting.
Kwon 2016(12)	RCT Korea	Age 46.2/12.8; underwent laparoscopic cholecystectomy	Patients received IV PCA with 100 mg of oxycodone, 0.6 mg of ramosetron, and 86 mL of normal saline; 14/27/41	Patients received IV PCA with 10 mg of alfentanil, 0.6 mg of ramosetron, and 76 mL of normal saline; 16/25/41	42.8/16.7	NA	NA	Pain intensity (VAS); Nausea; vomiting; dizziness; headache; respiratory; pruritus; Patient satisfaction;
Lens 2009(13)	RCT Norway	Age 46/6.9; underwent laparoscopic cholecystectomy	Patients received oxycodone 0.07 mg /kg 10–15 min before the end of surgery; After emergence, patients received PCA oxycodone 0.015 mg /kg; NR/NR/46	Patients received morphine 0.07 mg /kg 10–15 min before the end of surgery; After emergence, patients received PCA morphine 0.015 mg /kg; NR/NR/45	100/29	123/32	33/58	Pain intensity (VAS), Sedation level; Nausea; Vomiting; Itching.
Park 2015(14)	RCT Korea	Age 46.5/8.6 undergo either elective total laparoscopic hysterectomy (TLH) or laparoscopic myomectomy	Oxycodone (a basal infusion of 0.9 mg/h, bolus dose of 0.9 mg, and lockout interval of 15 minutes); 37 females	Fentanyl (a basal infusion of 15 µg/h, bolus dose of 15 µg, and lockout interval of 15 minutes); 32 females	NA	NA	46/23	Pain intensity (VAS); Dizziness; headache; nausea; vomiting; Patients satisfaction

Notes: M = number of male patients; F = number of female patients; N = number of total patients; NR = not reported; PCA = patient controlled analgesia

Results Of Risk Of Bias Individual Studies

Risk of bias of included studies according to the Cochrane Risk of Bias tool was provided in Fig. 2. Of the included 10 studies, seven studies were rated as low risk of bias on randomization, as they used computer-generated random number sequence. Three studies[7, 6, 2] did not describe the method of randomization. Most studies stated that the allocation concealment was conducted, however four studies[7, 6, 2] did not report the information. Only half of the included studies stated that the participants and personnel were blinded. The other five studies[7, 6, 4, 2] did not report the information. For blinding of outcome assessor, one study[6] stated that partial of the outcome assessor knew the group assignment during treatment, so it was rated as high risk of bias on this domain. One study[4] did not report data for some measured outcomes including nausea, vomiting, or itching, therefore was rated as high risk of selective reporting.

Meta-analysis

Pain intensity

Nine studies[13, 6, 7, 6, 10, 6, 4, 2] measured pain intensity by VAS or NRS scale. However, only four of them[7, 10, 4] contributed data for meta-analysis. Result showed that oxycodone can significantly reduce the pain intensity than other opioids (fentanyl, alfentanil or morphine) in 30 minutes (2 RCTs, N = 218, MD -11.9, 95% CI -16.16 to -7.63), 4 hours (3 RCTs, N = 290, MD -4.73, 95% CI -8.9 to -0.57), and 24 hours post operation (2 RCTs, N = 208, MD -3.00, 95% CI -4.02 to -1.98), but not for 48 hours post operation (2 RCTs, N = 208, MD -0.62, 95% CI -3.00 to 1.76) (Fig. 3). The data of the other five studies are not available to do meta-analysis as their data were skewed. Kim 2015[6] also found a similar results as above. Choi 2018[13] and Park 2015[2] concluded that oxycodone and fentanyl have equal effectiveness in relieving postoperative pain. Choi 2015[6] found that the pain intensity in oxycodone is significantly lower than fentanyl group in half hours post operation, but this effect did not last longer than 0.5 hours. Koch 2008[6] stated that the intensity of deep abdominal pain was significantly lower in the oxycodone group at arrival, after 30, 60 and 90 min and at discharge from the PACU.

Sedation

Four studies[6, 7, 6, 4] reported this outcome. Choi 2015[6] and Koch 2008[6] used the following methods to assess sedation: "S, asleep, easily aroused; 1, awake and alert; 2, occasionally drowsy, easily aroused; 3, frequently drowsy, falls asleep during conversation; 4, somnolent, minimal or no response to stimulation". Meta-analysis showed that no difference between oxycodone and fentanyl for sedation score at 2 (2RCTs, N = 127, RR 2.06, 95% CI 0.56 to 7.60, Fig. 4). Both studies reported that no patient had a sedation score at 3 or 4. Hwang 2014[7] also concluded that the sedation level was similar between oxycodone and fentanyl group. However, Lenz 2009[4] found a different result that sedation level was significantly less in oxycodone group compared with Morphine group (P = 0.006).

Adverse Event

All studies reported adverse events. Oxycodone may induce higher risk of dizziness (6 RCTs, N = 455, RR 2.31, 95% CI 1.64 to 3.27) and drowsiness (1 RCT, N = 127, RR 7.88, 95% CI 1.89 to 32.85). There is no difference between groups for the risk of headache, pruritus, respiratory depression, nausea, and vomiting (Fig. 5).

Patient Satisfaction

Patient satisfaction was classified into four levels: very satisfied, satisfied, neutral, dissatisfied. Meta-analysis was performed to assess the number of patients with satisfaction or very satisfaction in both groups. Result from four studies[7, 6, 10] showed that there are no significant difference between oxycodone versus other opioids for this outcome (4 RCTs, N = 350, RR 0.88, 95% CI 0.66 to 1.17, Fig. 6).

Discussion

Summary of findings

This meta-analysis identified 10 studies, including 815 patients, to compare the analgesic effect of oxycodone and other opioids including fentanyl, morphine, sulfentanil and alfentanil. Most of the included studies indicate the efficacy of oxycodone and support it as an superior analgesia to treat visceral pain within 24 hours after laparoscopic surgery[7, 6, 10, 4]. However, there was no significant difference in pain scores between either of the oxycodone group and other opioid groups at 48 hours after surgery. There appears to be no uniformity in the findings of sedation level adverse events and patient's satisfaction. However, it suggests that oxycodone may induce higher risk of dizziness and drowsiness than other opioids. We also found no significant difference in patient satisfaction among those other opioids versus oxycodone.

Quality Of The Evidence

The quality of the evidence was fair. As most studies were rated as low risk of bias in randomization, allocation concealment, blinding, attrition rates and selective reporting. Only two studies (Koch, Lenz) were rated as poor quality, owing to issues of imprecision (small sample size and a sparse number of events observed) and risk of bias (unclear reporting of allocation concealment and blinding).

Analgesic Efficacy

Postoperative pain after laparoscopic surgery consists of three components: incisional pain (somatic), deep abdominal pain (visceral) and inflammatory pain after carbon dioxide was absorbed by the peritoneum (can also be referred as visceral pain)[6]. This is an ideal clinical model to test the effectiveness of visceral pain treatment, where the somatic pain component is minimized.

Four of the included studies found that oxycodone is more potent in the treatment of visceral pain than morphine or fentanyl during the first 0.5 h after surgery. In these studies, the intensity of analgesic drugs has peaked at this time point. Fentanyl has a rapid onset of action (5–7 min), which is much faster than oxycodone (10–15 min)[49]. Although morphine is considered to be a slower-acting drug, it was given to patients 10–15 min before the end of surgery in Lenz's study[4]. Therefore, the onset time cannot be used to explain the difference in their initial pain relief.

It may have an analgesic mechanism explanation. Several recent studies have suggested that oxycodone attenuates visceral pain better than other opioids[3, 2, 2]. Oxycodone has a proposed effect at the κ -opioid receptor, that is a different pharmacological profile from other opioids. κ -opioid receptors on peripheral nerves in the gut have been suggested as an important feature for antinociception in the visceral pain system[1–2]. The analgesic effect of oxycodone correlated to plasma concentrations indicating an effect in the periphery perhaps mediated via κ -receptors[5].

This meta-analysis was also found that at 4 hours and 24 hours, the analgesic effect of oxycodone was also superior to other opioids, regardless of whether the administration method was a single dose at the end of the surgery or using a PCA pump. These contents indicated that oxycodone was more potent than other opioids in the treatment of postoperative visceral pain at the equivalent dose. However, the antalgic advantage of oxycodone did not last up to 48 hours after surgery, whether it was a single dose[7] or PCA[10]. A possible explanation is that the pain intensity 48 h after such minimal surgery may be too low to yield a significant difference in pain scores[3].

Safety Evaluation

Sedation is an important indicator for evaluating the safety of a drug for postoperative analgesia[8]. Although Lenz et al found that sedation level was significantly less in oxycodone group compared with Morphine group[4]. The meta-analysis found that the oxycodone groups had similar sedation levels compared with morphine and fentanyl and there was no incidence of excessive sedation or respiratory depression in either group.

According to previous studies, adverse effects associated with opioid use include constipation, nausea, vomiting, drowsiness, dizziness, and pruritus[1, 1]. The specific incidence varies greatly depending on the dosage. A higher incidence of dizziness was reported with oxycodone compared to fentanyl and morphine in our study. The precise mechanism of opioid-induced dizziness is unknown. Vestibular sensitivity caused by opioids activating on the μ receptors in the vestibular epithelium may be involved in[49]. Nevertheless, the potential causes of the different incidence in dizziness still need to be further explored. As with previous studies, the reported incidences of side effects differ widely, probably because most researches were powered to investigate analgesic efficacy and not differences in side effects.

Strength And Limitations

There are several strengths of this meta-analysis, first of all, our search strategy was developed by information specialist to avoid missing of any relevant trial. Secondly, two reviewers screened and extracted the data to reduce system error in the fabrication process. Like other studies, our meta-analysis also have some limitations: there were only a small number of clinical trials available, and that contributed a relatively small sample size for meta-analysis. Second, age may also alter the opioid pharmacokinetics and influence the pain, and the mean age was relatively high in the present patient population (40–69). Third, publication bias may have resulted in over-estimation of some outcomes, as positive results are more likely to be published than negative ones[12].

Conclusion

Choosing the best opioid for postoperative visceral pain treatment is complicated with no recommended "gold standard" choice globally. The results of this meta-analysis suggest that oxycodone is a superior analgesic within 24 h after laparoscopic surgery. However, in some cases, even if it is effective, its incidence of adverse reactions is higher, especially dizziness. Clinicians must choose appropriate opioids based on their clinical judgment and adjust the dose as needed. In order to obtain the best clinical evidence, it is necessary to do more in-depth research in this field.

Abbreviations

PCA, patient controlled analgesia

RCTs, randomized controlled trials

VAS, visual analogue scale

NRS, numeric rating scale

RR, risk ratio

CI, confidence interval

ASA, American Society of Anesthesiologists

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No conflict of interest exists in the submission of this manuscript.

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Authors' contributions

Yan Li and Zhi Dou are co-first authors who contributed equally to the statistical analysis and drafted the manuscript. Liqiang Yang helped to design the study and draft the manuscript. Qi Wang and Jiaxiang Ni participated in the design of the study and data collection. Jun Ma conceived of the study and helped to draft the manuscript.

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Not applicable

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Figures

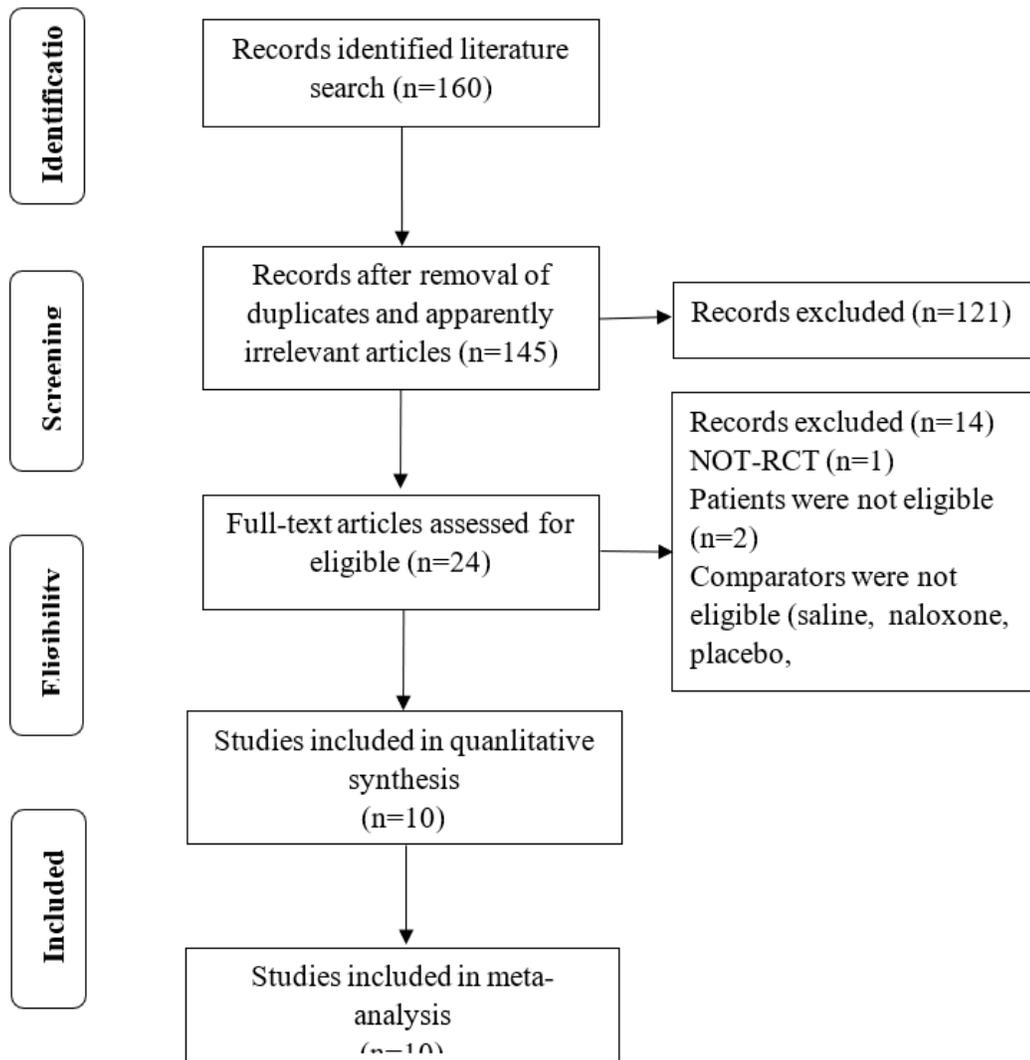


Figure 1
Study screening flow diagram.

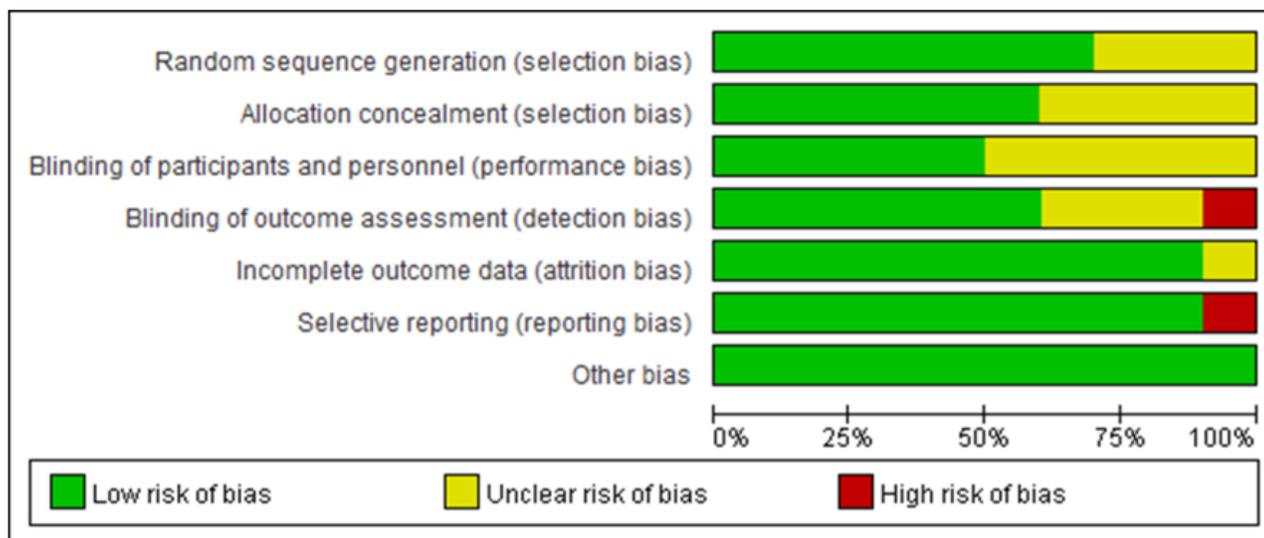


Figure 2

Risk of bias of included studies.

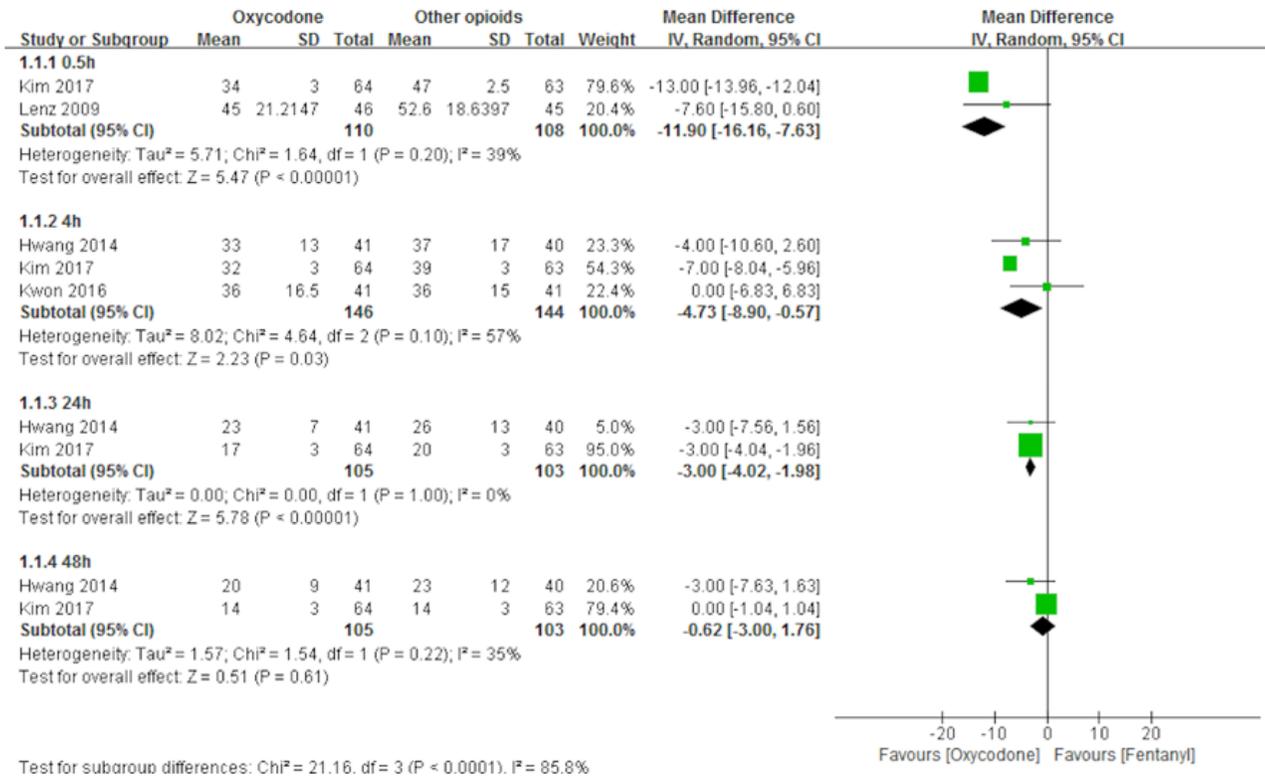


Figure 3

Meta-analysis of pain intensity. Notes: "CI" represents confidence interval.

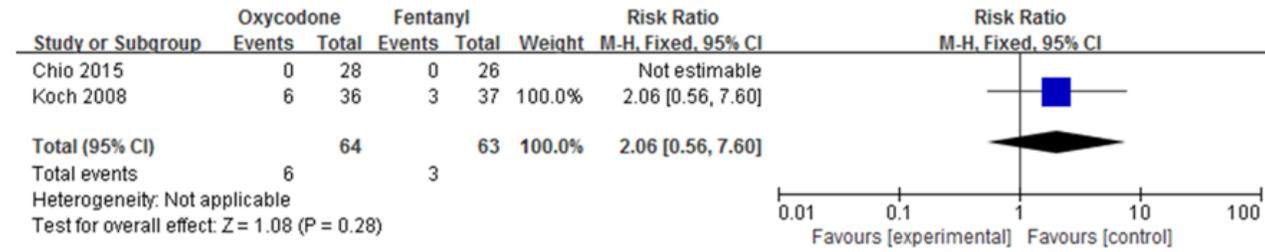


Figure 4

Meta-analysis of sedation score at 2 (occasionally drowsy, easily aroused). Notes: "CI" represents confidence interval.

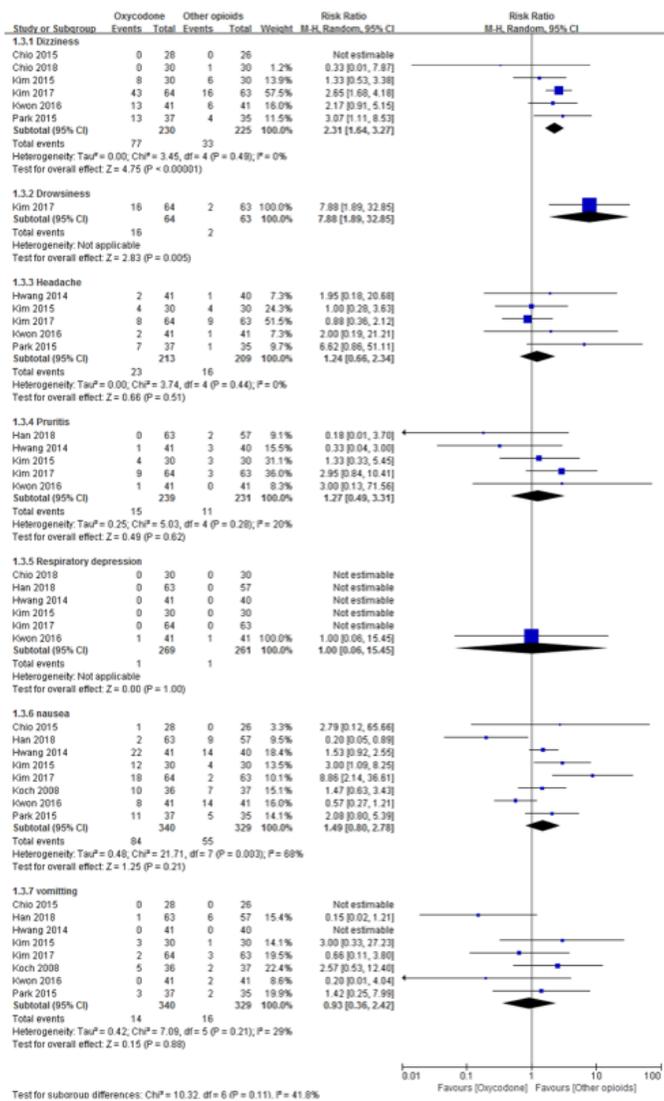


Figure 5

Meta-analysis of adverse events. Notes: "CI" represents confidence interval.

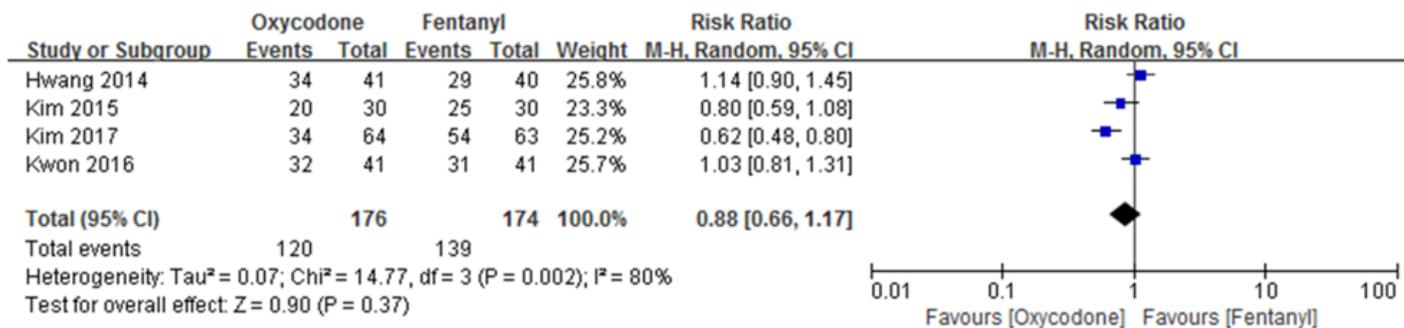


Figure 6

Meta-analysis of patient satisfaction. Notes: "CI" represents confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix1.docx](#)