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Analgesic Efficacy and Safety of Butorphanol vs. Morphine in Adults: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Morphine, a reference analgesic, has been widely used for a long time, but its safety profile is unsatisfactory. Butorphanol, a partial agonist and antagonist of the mu-opioid receptor and agonist of the kappa-opioid receptor, may offer a better safety profile than morphine. Therefore, the present meta-analysis was conducted to compare the analgesic efficacy and safety of butorphanol with that of morphine.

Methods: Three electronic databases, MEDLINE, EMBASE, and Cochrane CENTRAL, were systematically searched to identify studies comparing the analgesic efficacy and safety of butorphanol with that of morphine. If heterogeneity tests revealed statistical heterogeneity, pooled analysis was conducted using a random-effects model; otherwise, a fixed-effects model was adopted. Sensitivity analysis was applied to assess the robustness of the results, and publication bias was evaluated using funnel plots and Begg's test.

Results: Nine studies, comprising 246 patients in the butorphanol groups and 245 patients in the morphine groups, were included in the meta-analysis. Pooled analysis revealed no significant difference between the analgesic efficacy of butorphanol and morphine (risk ratio [RR]=0.96, 95% confidence interval [CI] 0.79–1.17; P=.664). However, compared with morphine, butorphanol was associated with a lower incidence of pruritus (RR=0.05, 95% CI 0.01, 0.17, P=.000), nausea (RR=0.33, 95% CI 0.15–0.75, P=.008), and vomiting (RR=0.33, 95% CI 0.12–0.95, P=.039). In contrast, the incidence of drowsiness/somnolence/sedation with butorphanol which was used was significantly higher than that with morphine (RR=2.46, 95% CI 1.14–5.31, P=.022).

Conclusion: The analgesic efficacy of butorphanol was comparable to that of morphine. However, butorphanol offered a better safety profile than morphine in terms of pruritus, nausea, and vomiting, but was associated with a higher incidence of drowsiness/somnolence/sedation. Thus, butorphanol may be an appropriate substitute for morphine for patients with risk factors of pruritus and postoperative nausea and vomiting, and patients requiring both analgesia and sedation. Because of the limited number of the studies currently available, more research is needed.

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Keywords

Butorphanol; Morphine; Meta-analysis; Efficacy; Safety

Abbreviations: PONV: Postoperative Nausea and Vomiting; CI: Confidence Interval; RR: Risk Ratio; VAS: Visual Analog Scale; VRS: Verbal Rating Score; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Rcts: Randomized Controlled Trials; ERAS: Enhanced Recovery after Surgery.

Introduction

Most people undergo surgery at some point during their lives over 51 million operations are performed each year in the USA, and surgical care in England results in 4.6 million hospital admissions per year [1]. Postoperative pain causes not only psychological and physical harm, but also cardiovascular and pulmonary complications, prolongation of hospital stay and increase in medical expenditure [2,3]. Effective analgesia accelerates patient recovery and rehabilitation after surgery [4]. Opioids are widely used to treat moderate and severe pain [5]. Morphine, a classic opioid analgesic, remains the gold standard for postoperative pain treatment [6]. However, many patients treated with morphine experience undesired side effects such as pruritus, nausea, vomiting, and respiratory depression [6,7]. Therefore, a need exists for alternative efficacious analgesics with a better safety profile.

Butorphanol, a completely synthetic opioid, exhibits partial agonist and antagonist activity at the mu-opioid receptor and agonist activity at the kappa-opioid receptor [8,9]. It was first approved by the US Food and Drug Administration in 1978, and its use in the treatment of acute postoperative pain and chronic pain has been reported as early as in the 1970s [10,11]. It is reported to have several advantages, including a low incidence of side effects, minimal potential for abuse, and low toxicity [12,13], suggesting that it may be a good alternative for treating postoperative pain (Table 1). Even though many studies have suggested that butorphanol could be a viable alternative analgesic, the effects of butorphanol have mostly been investigated in studies with small sample sizes and low statistical power, leading to conflicting conclusions. This makes it difficult to judge which agent provides better analgesic efficacy and safety. Therefore, we performed a meta-analysis of available studies to compare the analgesic efficacy and safety of butorphanol with that of morphine [14-18].

Materials and Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for the meta-analysis of intervention trials [19]. Because we analyzed data from the existing published literature, ethical approval was not required for this meta-analysis.

Search strategy

Three electronic databases, MEDLINE, EMBASE, and Cochrane CENTRAL, were systematically searched from their respective inceptions to May 3, 2016. We applied the search strategy of the Cochrane Collaboration by using combined free text words and controlled vocabulary MeSH terms, with no language restriction.

Table 1: Characteristics of the included studies.

Study	Location	No of patients (B/M)	Age (B/M)	Procedure	Route	Dose (B)	Dose (M)
Abboud TK et al. [20]	USA	31/32	27 /27	Cesarean section	Epidurally	1mg	5mg
Abboud TK et al. [25]	USA	10/10	25/22	Cesarean section	Epidurally	1mg	2mg
Aldrete JA et al. [22]	USA	42/40	54/56	Coronary bypass surgery	Intravenously	1mg	5mg
Del PA et al. [11]	USA	25/25	54/51	NR	Intravenously	2mg	10mg
Hu DH et al. [23]	CHINA	30/30	NR	Hip replacement	Epidurally	4mg/100ml	4mg/100ml
Mok and sai [25]	USA	20/20	NR	Upper abdominal surgery	Epidurally	4mg	5mg
Palacios QT et al. [21]	USA	22/23	24/23	Cesarean section	Epidurally	1mg	5mg
Parikh GP et al. [26]	INDIA	40/40	52/50	Open nephrectomy	Epidurally	0.04mg/kg	0.06mg/kg
Tavakoli M et al. [10]	USA	26/25	33/31	Hysterectomy, Laparotomy, Hernia and Arthroplasty	Intramuscularly	1mg	5mg

NR = not reported, B = butorphanol, M = morphine

MeSH and entry terms of "butorphanol" and "morphine" were searched. We also identified potential eligible trials by searching the reference lists of the relevant reports.

Inclusion criteria and study selection

Randomized controlled trials were included in the meta-analysis if they met both of the following criteria: (1) At least one group was treated with only butorphanol and one group treated with only morphine. (2) Outcomes included analgesic effects and/or safety of butorphanol and morphine in adults. Two investigators (CMZ and CW) independently performed the initial search, screened titles, abstracts, and full texts according to the above criteria. Any discrepancy between the two authors was resolved by discussion with another author (JLS) until a consensus was achieved.

Data extraction and quality assessment

Two authors (CMZ and CW) independently extracted the following data from the included studies: the first author, year of publication, location, number of patients, age, procedure, route of administration, and dosage. Analgesic effects can be described using pain score systems such as the visual analog scale (VAS), verbal rating score (VRS), or the verbal category scale. However, the primary information was whether patients needed supplemental analgesics during the observation period. Therefore, our primary outcome of pain relief was defined as no supplemental medication or a VAS score ≤ 40 during the observation period, or no painful response during surgery. The secondary outcome was the incidence of side effects. As the included studies reported various side effects, we only adopted the side effects reported by at least four studies.

The quality of the included studies was evaluated using the "Cochrane assessment tool." The Cochrane assessment system included random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, selective reporting, and other biases. Data extraction and quality assessment were performed independently by two authors (CMZ and CW). Any discrepancy between the two authors was resolved by discussion with another author (JLS) until a consensus was achieved.

Statistical analysis

All data were processed with the Stata software, version 14.0 (Stata Corp., College Station, TX, USA) and RevMan 5.30 software (The Cochrane Collaboration, Oxford, UK). Dichotomous data are presented as risk ratios (RR) with 95% confidence intervals (95% CI). Q and I^2 statistics were used to evaluate the heterogeneity among the included studies, and statistical heterogeneity was defined as $p<0.1$ for the Q statistics and $I^2>50\%$. A random-effects model was applied when the heterogeneity tests revealed statistical heterogeneity; otherwise, a fixed-effects model was adopted. Sensitivity analysis was performed to find the source of heterogeneity. Funnel plots and Begg's test were used to assess publication bias, which was considered to be present if the shape of funnel plot was asymmetrical and the p-value of Begg's test was less than .05.

Results

Search results

The database searches performed yielded 106 studies and the reference searches yielded two additional studies. Among these 108 studies, 59 were identified as duplicated reports and were excluded. After applying the inclusion criteria, screening the titles, and reading the abstracts and full-text articles, we included nine randomized controlled trials [10,11,20-26] in the present meta-analysis, comprising 246 patients in the butorphanol groups and 245 patients in the morphine groups (Figure 1).

Study characteristics

The characteristics of the nine included studies [10,11,20-26] are presented in Figure 2. Six studies [10,11,20-23] compared the analgesic effects of butorphanol with that of morphine, and four [10,11,20,21] of these reported the number of patients needing supplemental analgesics during the observation period. In addition, one study [22] reported the number of patients without painful response during surgery, and another [23] reported the number of patients with a VAS score of ≤ 40. Three other studies [24-26] were included for safety assessment. Eight studies [10,11,20,21,23-26] compared the safety of butorphanol with that of morphine. The side effects of pruritus, nausea, and vomiting were reported in five studies each and somnolence/drowsiness/sedation was reported in four studies.

Quality assessment

In terms of bias, five trials [10,11,20,21,25] were categorized as low risk and four were categorized as unclear [22-24,26]. An adequate randomized sequence was generated in three trials [11,21,26], and appropriate allocation concealment was reported in five [10,11,20,21,25]. None of the studies had incomplete outcome data or selective reporting (Figure 3).

Results of the meta-analysis

Pain relief: Six studies [10,11,20-23] that included 351 patients (176 butorphanol, 175 morphine) investigated the pain relief provided

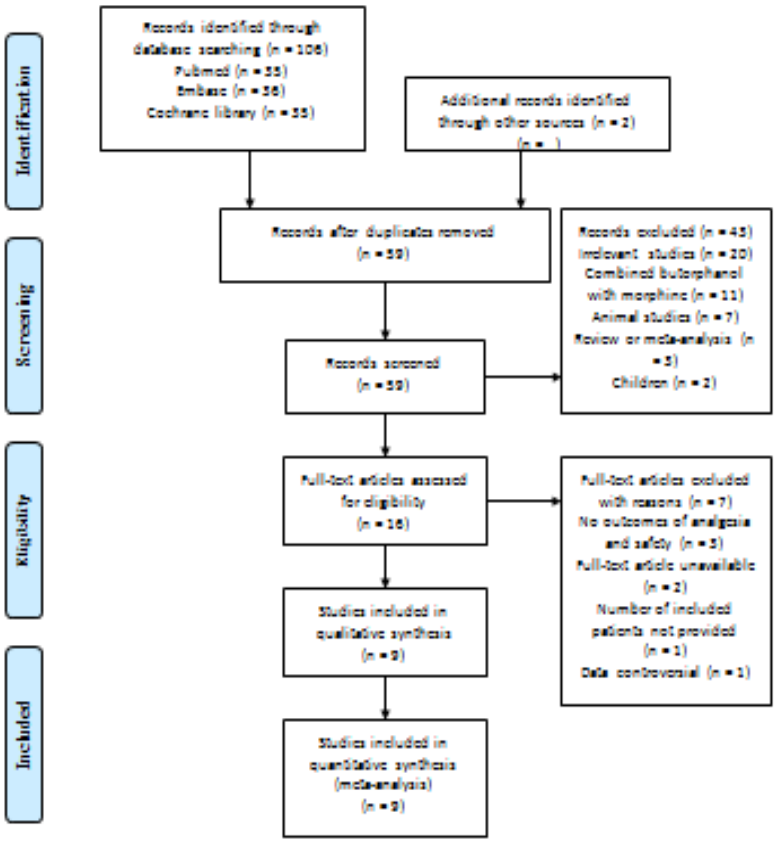


Figure 1: Flow chart of the literature search.

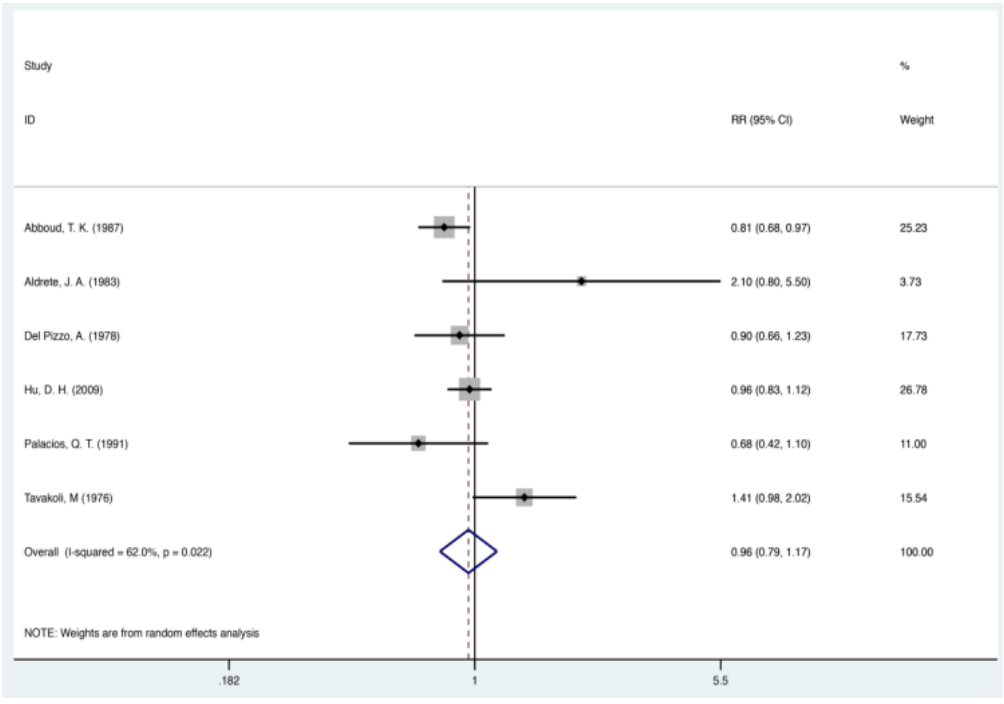


Figure 2: Forest plot diagram showing the pain relief provided by butorphanol vs. morphine.

*RR: Risk Ratio; CI: Confidence Interval.

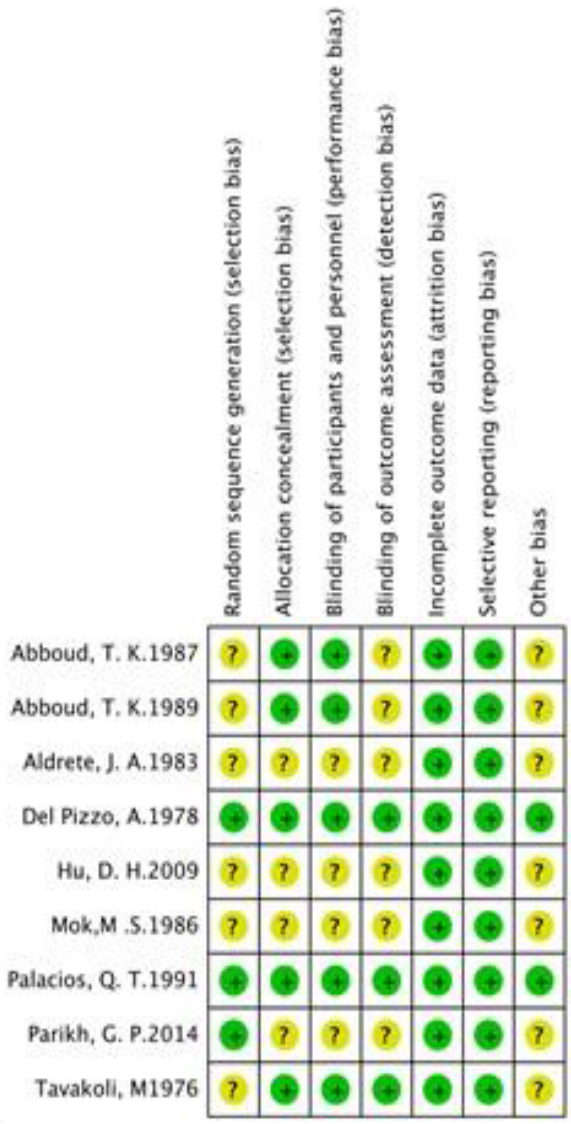


Figure 3: Methodological quality of the randomized controlled trials.

by butorphanol and morphine. High heterogeneity existed between the included studies (I^2=62.0%, P=.022; Figure 4), and therefore, a random-effects model was applied. No significant difference in pain relief was found between butorphanol and morphine (RR=0.96, 95% CI 0.79–1.17, P=.664; Figure 4). The shape of the funnel plot (Figure 5A) and results of Begg's test (P=.466; Figure 5B) indicate that publication bias was not present among the included studies.

Subgroup analyses were performed according to the route of administration. The RRs were 0.86 (95% CI 0.71–1.03, P=.110; I^2=52.1%, P=.124) for epidural administration, 1.25 (95% CI 0.48–3.28, P=.644; I^2=73.4%, P=.052) for intravenous administration, and 1.41 (95% CI 0.98–2.02, P=.061) for intramuscular administration, indicating that the route of administration might not be the source of heterogeneity (Figure 5C). Sensitivity analysis revealed that the study by Tavakoli et al. [10] contributed the most to the variance. When this study was omitted, the I^2 decreased from 62% to 39%, indicating that this study was one of the main sources of heterogeneity (Figure 5D).

Side effects: ***Pruritus:*** Five studies [20,23-26] that included 263 patients (butorphanol 131, morphine 132) compared the incidence of pruritus between butorphanol and morphine. A low heterogeneity existed between the included studies (I^2=0, P=.875), and therefore, a fixed-effects model was applied. The results (RR=0.05, 95% CI 0.01–0.17, P=.000) showed that the incidence of pruritus in the butorphanol groups was significantly lower than that in the morphine groups (Figure 6).

Nausea: Five studies [11,20,23,24,26] that included 293 patients (butorphanol 146, morphine 147) compared the incidence of nausea between butorphanol and morphine. A low heterogeneity existed between the included studies (I^2=0, P=.660), and therefore, a fixed-effects model was applied. The results (RR=0.33, 95% CI 0.15–0.75, P=.008) showed that the incidence of nausea in the butorphanol groups was significantly lower than that in the morphine groups (Figure 7).

Vomiting: Five studies [11,20,23,24,26] that included 243 patients (butorphanol 121, morphine 122) compared the incidence of vomiting between butorphanol and morphine. A low heterogeneity existed between the included studies (I^2=0, P=.600), and therefore, a fixed-effects model was applied. The results (RR=0.33, 95% CI 0.12–0.95, P=.039) showed that the incidence of vomiting in the butorphanol groups was significantly lower than that in the morphine groups (Figure 8).

Drowsiness/Somnolence/Sedation: Four studies [11,20,24,26] that included 234 patients (butorphanol 117, morphine 117) compared the incidence of drowsiness/somnolence/sedation between butorphanol and morphine. A significant heterogeneity existed between the included studies (I^2=74.6%, P=.008), and therefore, a random-effects model was applied. The results (RR=2.46, 95% CI 1.14–5.31, P=.022) showed that the incidence of drowsiness/somnolence/sedation in the butorphanol groups was significantly higher than that in the morphine groups (Figure 9A). Sensitivity analysis performed to analyze the origin of heterogeneity revealed that the study by Parikh et al. [26] caused the heterogeneity (Figure 9B).

Discussion and Conclusion

To our knowledge, this is the first meta-analysis to compare the analgesic efficacy and safety of butorphanol with that of morphine. Our results indicated that (1) the analgesic efficacy of butorphanol is comparable to that of morphine, and (2) butorphanol has advantages over morphine with respect to side effects such as pruritus, nausea, and vomiting, but not drowsiness/somnolence/sedation.

We found two randomized controlled trials of children treated with butorphanol or morphine [27,28]. The trial by Lawhorn et al. [27] evaluated 15 patients aged 4-12 years treated with 15-20 μg/kg butorphanol or 50-60 μg/kg morphine, and reported adequate analgesia in all patients, with no reports of side effects. The trial by Splinter et al. [28] evaluated 156 patients aged 1.5–13 years treated with 30 μg/kg butorphanol (B-patients, N=78) or 150 μg/kg morphine (M-patients, N=78). Of the 156 patients, 48 B-patients and 38 M-patients required additional analgesia, and 11 B-patients and 22 M-patients experienced vomiting. Inclusion of the results of the trial by Splinter et al. [28] in the present meta-analysis did not significantly change the results of pain relief (RR=0.92, 95% CI 0.78–1.10, P=.362; I^2=55.2%, P=.037) and vomiting (RR=0.44, 95% CI 0.25–0.76, P=.003; I^2=0.0%, P=.690). Because of the limited amount of data currently available, it is difficult to clarify if the analgesic effects and safety of butorphanol in children are the same as that in the adults.

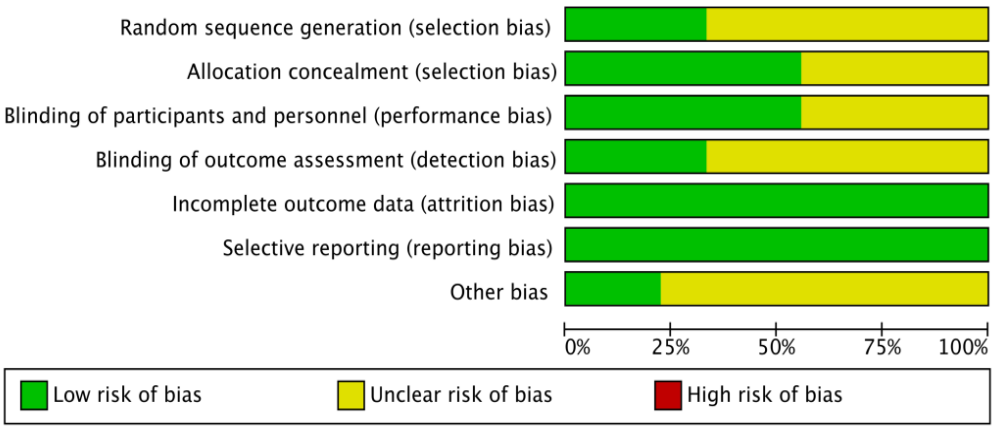
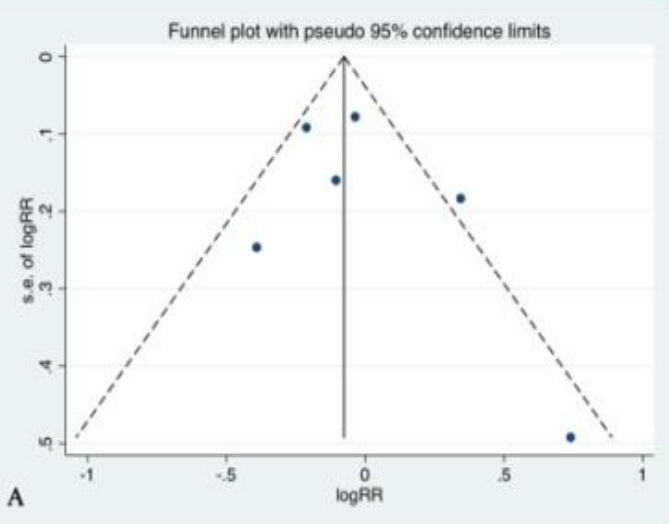
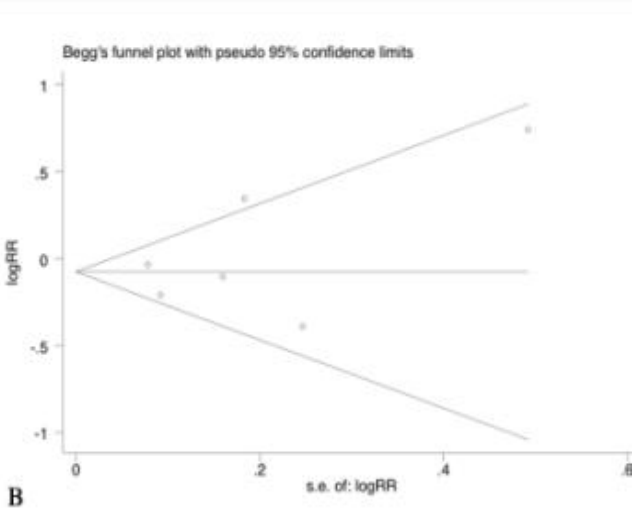
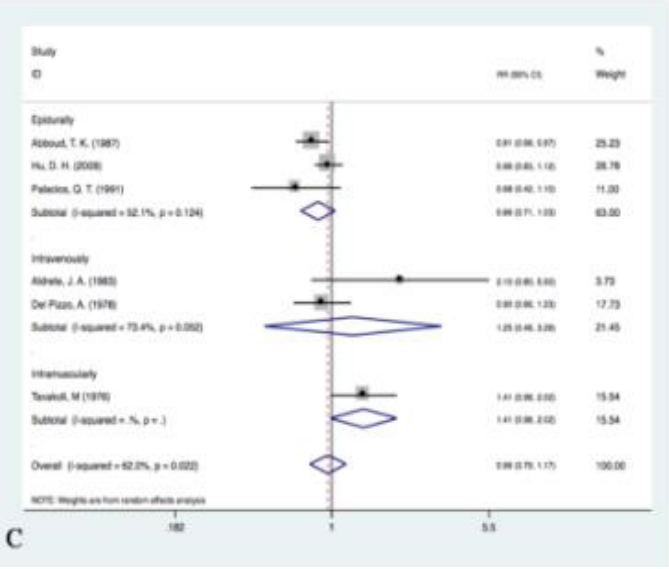


Figure 4: Risk of bias of the randomized controlled trials.







Study omitted	Heterogeneity			RR(95%CI)	P
	tau2	I-squared	P		
Abboud, T. K.1987	0.04	58%	0.05	1.02(0.79,1.30)	0.90
Aldrete, J. A.1983	0.02	57%	0.05	0.93(0.78,1.11)	0.41
Del Pizzo, A.1978	0.05	70%	0.009	0.98(0.76,1.25)	0.86
Hu, D. H.2009	0.07	70%	0.010	0.98(0.72,1.32)	0.88
Palacios, Q. T.1991	0.04	70%	0.01	1.01(0.80,1.26)	0.96
Tavakoli, M.1976	0.01	39%	0.16	0.89(0.76,1.04)	0.15

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Figure 5: Statistical analysis of pain relief data (A) Funnel plot (B) Begg's test (C) Subgroup analysis (D) Sensitivity analysis.

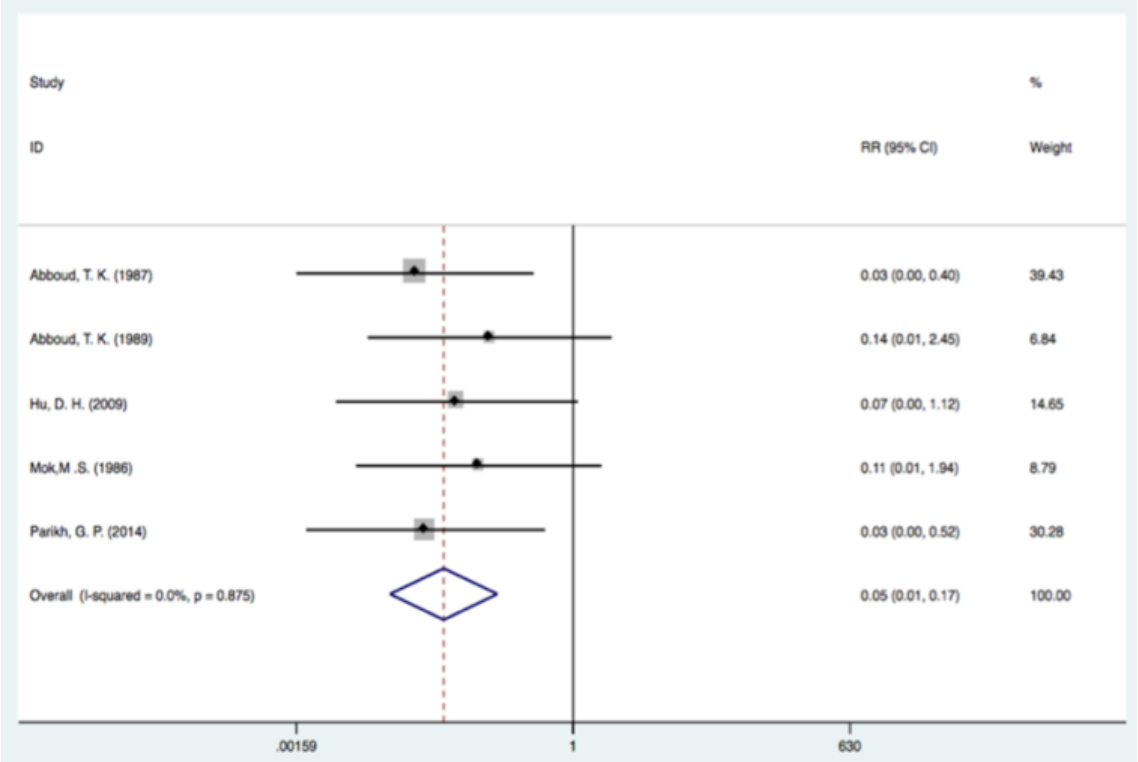


Figure 6: Forest plot diagram comparing the incidence of pruritus induced by butorphanol vs. morphine.

*RR: Risk Ratio, CI: Confidence Interval

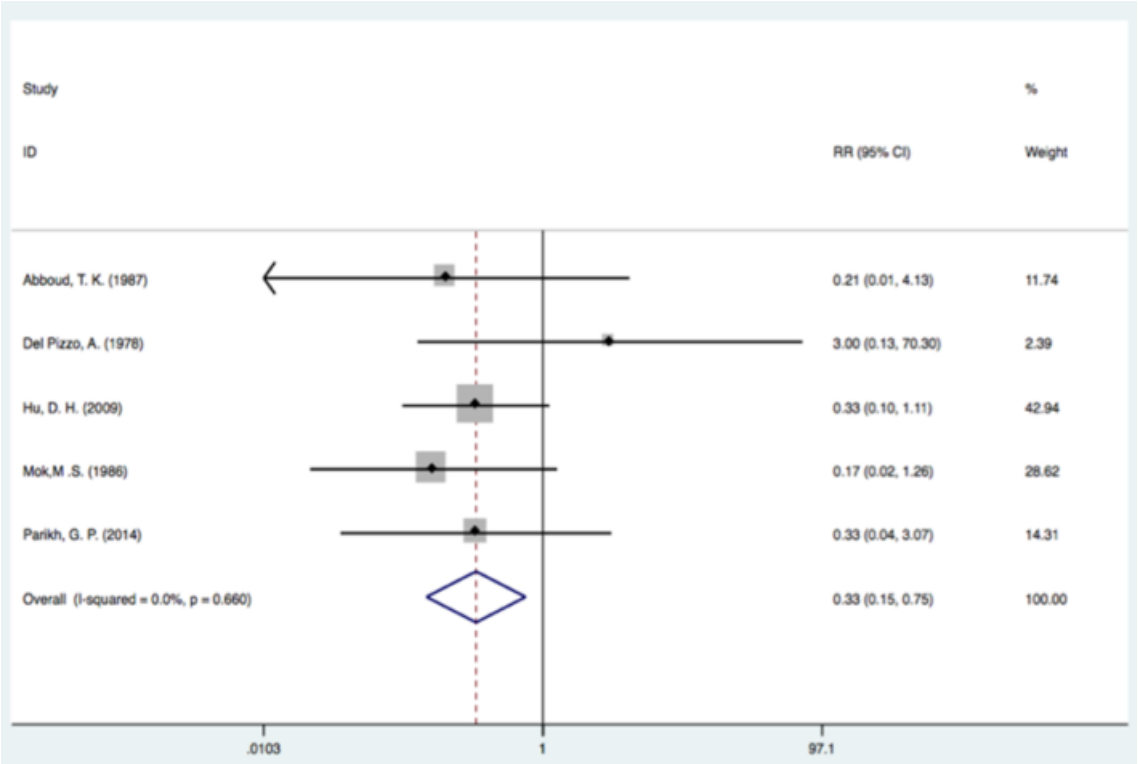


Figure 7: Forest plot diagram comparing the incidence of nausea induced by butorphanol vs. morphine.

*RR: Risk Ratio, CI: Confidence Interval

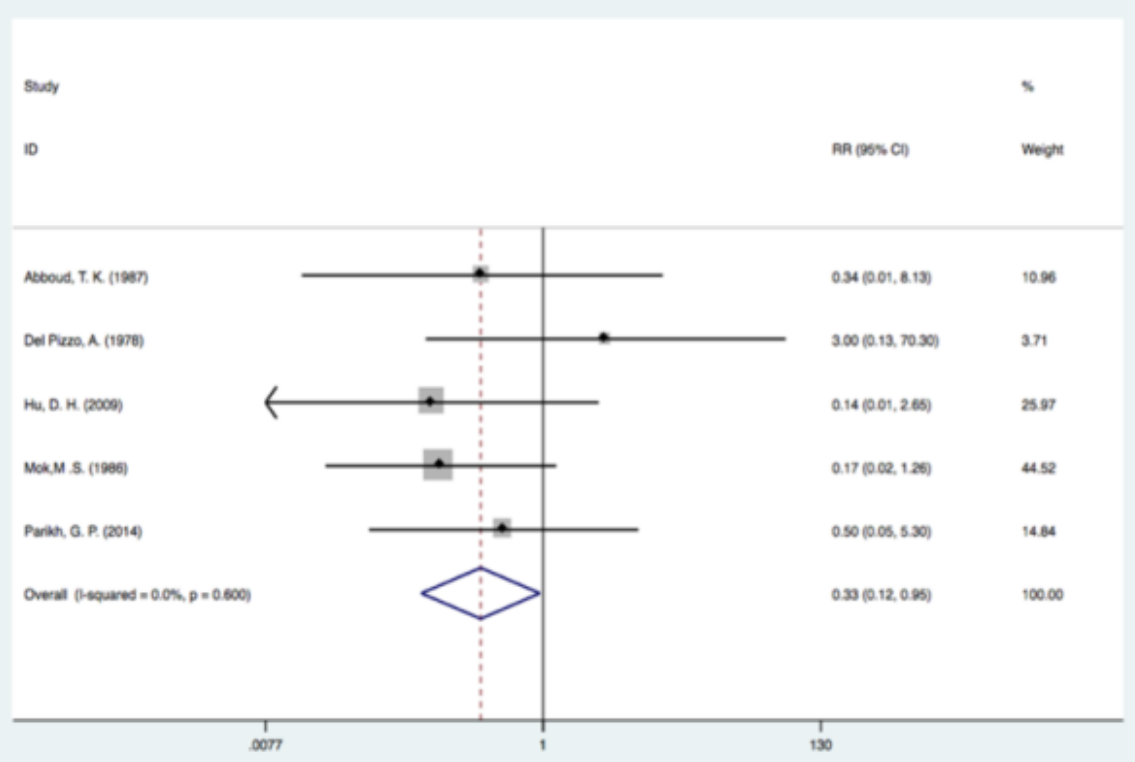
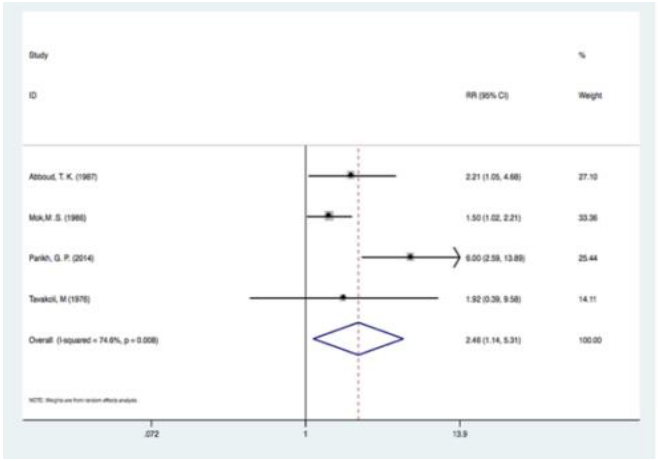


Figure 8: Forest plot diagram comparing the incidence of vomiting induced by butorphanol vs. morphine.

*RR: Risk Ratio, CI: Confidence Interval



Study omitted	Heterogeneity			RR(95%CI)	P
	tau2	I-squared	P		
Abboud, T. K.1987	0.94	84%	0.002	2.60(0.76,8.90)	0.13
Mok,M .S.1986	0.20	44%	0.17	3.20(1.50,6.81)	0.003
Parikh, G. P.2014	0.00	0	0.59	1.64(1.17,2.29)	0.004
Tavakoli, M.1976	0.55	84%	0.002	2.58(1.03,6.50)	0.04

Figure 9: (A) Forest plot diagram comparing the incidence of drowsiness/somnolence/sedation induced by butorphanol vs. morphine (B) Sensitivity analysis of drowsiness/somnolence/sedation incidence.

*RR: Risk Ratio, CI: Confidence Interval

Our analysis implicated the study conducted by Tavakoli et.al. [10] as one of the factors causing heterogeneity of pain relief. However, because of its acceptable quality, we could not find any reasons to exclude this study. In addition to pain relief, many characteristics can be evaluated for the assessment of analgesic effects, such as the onset and duration of drug action, and peak response. Parikh et al. [26] conducted a trial to compare the analgesic effects and safety of epidural butorphanol and epidural morphine for postoperative pain relief after open nephrectomy surgery. Their results indicated that butorphanol has a shorter duration of action but faster onset than morphine did [26].

Pruritus is a very common side effect of spinal morphine, and is often difficult to treat [29,30]. A meta-analysis conducted by Du et al. [31] which included sixteen trials (795 patients), revealed that continuous intravenous and epidural butorphanol reduced morphine-induced pruritus with a RR of 0.22 (95% CI 0.10–0.45) and 0.24 (95% CI 0.16–0.36), respectively. Thus, butorphanol may be recommended for preventing and treating morphine-induced pruritus during

the perioperative period. In this present meta-analysis, no pruritus occurred in the patients treated with butorphanol. However, Palacios et al. [21] did report that one patient treated with butorphanol developed pruritus, but they did not specify the butorphanol group (1, 2, and 4 mg groups) to which his patient belonged. In that study, the incidence rate of pruritus in the butorphanol group (1.44%, 1/69) was significantly lower than that in the morphine group (43.48%, 10/23).

Respiratory depression is the most serious opioid-related side effect [32]. In a previous study, increasing doses of morphine were associated with increased respiratory depression; in contrast, doubling the dose of butorphanol was not associated with a greater degree of respiratory depression [33]. Among the studies included in this meta-analysis, respiratory depression was reported in three studies [11,23,26], with incidence rates of 1.05% for butorphanol and 6.32% for morphine, which were consistent with earlier reports [33,34]. However, we did not include respiratory depression in this meta-analysis because the currently available data are too few to draw a firm conclusion.

Consistent with earlier reports [12,35], the present meta-analysis revealed that butorphanol usage resulted in lower incidence rates of pruritus, nausea, and vomiting, but significantly higher incidence rates of drowsiness/somnolence/sedation than morphine did. Nevertheless, the heterogeneity of drowsiness/somnolence/sedation among the studies was high, and the sensitivity analysis identified the study by Parikh et al. [26] as the cause of the heterogeneity. However, because this study was of high quality, there was no plausible reason to exclude it. Even if we excluded this study, the RR changed to 1.64 (95% CI 1.17–2.29), which still indicated that the incidence of drowsiness/somnolence/sedation in the butorphanol groups was significantly higher than that in the morphine groups. However, drowsiness/somnolence/sedation may be a positive side effect in some instances. For example, patients in the intensive care unit usually need both analgesia and sedation to relieve their anxiety, improve adaption to the endotracheal tube, and aid compliance with mechanical ventilation [36]. Simple analgesia is generally insufficient for young children experiencing pain, and sedative and tranquillizing effects are extremely desirable in such cases. In these circumstances, butorphanol may be a better choice than morphine, especially considering the better safety profile of butorphanol. However, the side effect of drowsiness/somnolence/sedation may delay recovery and discharge from the facility, especially for the patients receiving the enhanced recovery after surgery (ERAS). So, for the patients receiving ERAS, butorphanol may not be a good choice.

This meta-analysis has some limitations. First, since the data in the included studies was presented in different non-comparable formats, we found that only dichotomous data such as pain relief could be analyzed in this meta-analysis to obtain useful results. Moreover, because the dichotomous data of pain relief was indirect evidence, it was not as accurate as the direct evidence provided by continuous data of pain scores. Second, the limited number of small-sample trials included in this meta-analysis prevents the drawing of robust conclusions. Third, because this meta-analysis included studies with different types of surgery, patients of both sexes, and different routes of drug administration, the results may be biased and must be interpreted with caution [37].

In conclusion, the analgesic efficacy of butorphanol and morphine are comparable; however, butorphanol has a much better safety profile than morphine, with fewer instances of pruritus, nausea, and vomiting, but more instances of drowsiness/somnolence/sedation. Thus, butorphanol may be an appropriate substitute for morphine for patients with risk factors of pruritus and postoperative nausea and vomiting, and patients requiring both analgesia and sedation. Because the sample size and the number of included studies were limited, studies with a larger sample size are still needed to definitively compare the analgesic efficacy and safety of butorphanol with that of morphine.

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