ORIGINAL RESEARCH

Effect of butorphanol on opioid-induced cough: a meta-analysis of randomized controlled trials

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Objective: The aim of this study was to assess the effect of butorphanol on the prevention of opioid-induced cough by a meta-analysis.

Materials and methods: We searched PubMed, Embase, The Cochrane Library, and the China National Knowledge Infrastructure database for relevant randomized controlled trials (RCTs) to demonstrate the efficacy of butorphanol on the prevention of opioid-induced cough. We used RevMan 5.3 to conduct a meta-analysis on each outcome.

Results: Eight RCTs comparing 942 patients were included in this study. The pooled meta-analysis showed that the incidence of opioid-induced cough in the butorphanol group was significantly decreased compared with that of the control group (risk ratio [RR]=0.17, 95% CI [0.09, 0.33], $P<0.00001$). Incidences of opioid-induced cough in the butorphanol group resulting in mild cough (RR=0.30, 95% CI [0.11, 0.78], $P=0.01$), moderate cough (RR=0.08, 95% CI [0.03, 0.22], $P<0.00001$), or severe cough (RR=0.08, 95% CI [0.02, 0.30], $P=0.0001$) were significantly lower than those of the control group.

Conclusion: This meta-analysis suggested that butorphanol can effectively prevent the incidence of opioid-induced cough and reduce the severity of opioid-induced cough.

Keywords: butorphanol, opioid, cough, meta-analysis, randomized controlled trial

Introduction

Opioids are commonly used intravenous anesthetic drugs during the induction of anesthesia for their analgesic effect, inhibition of metabolism, and reduction in the cardiovascular response. However, during the induction of anesthesia, opioids can cause cough, and the incidence of opioid-induced cough can be as high as 65%.[1] Cough can lead to increased intracranial, intraocular, and intra-abdominal pressures.[2] Meanwhile, opioid-induced cough is a risk factor for postoperative nausea and vomiting.[3] Although opioid-induced cough is light and self-limiting, it is extremely harmful to patients undergoing neurosurgery, ophthalmology, or thoracic surgery. The mechanism of opioid-induced cough is still unclear, and many interventions for preventing opioid-induced cough have been demonstrated, for example, changing opioid administration, such as priming with fentanyl.[4,5] Additionally, lidocaine, as well as dezocine and dexmedetomidine, has been proven to be efficacious in preventing opioid-induced cough, as well as dezocine and dexmedetomidine.[3,6,7]

Butorphanol, an agonist–antagonist opioid, has an in vitro affinity for opioid receptors of 25:4:1 (κ:δ:μ) and is extensively used in clinical practice due to a potent analgesic effect and a desirable pharmaceutical formulation. To date, there have been several studies regarding the prevention of opioid-induced cough by butorphanol. Therefore, we reviewed available randomized controlled trials (RCTs) and conducted

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a meta-analysis to evaluate the effect of butorphanol on preventing opioid-induced cough.

Materials and methods
Inclusion and exclusion criteria
Studies were included if they were RCTs using butorphanol for the prevention of opioid-induced cough while the control group received an equal volume of saline. Studies were excluded for the following reasons: 1) non-RCTs, 2) retrospective studies, 3) review and case reports, and 4) no target outcomes. The primary outcome was the incidence of opioid-induced cough, and the secondary outcomes were incidence of cough at various degrees.

Search strategy
We searched PubMed, Embase, The Cochrane Library, and the China National Knowledge Infrastructure database for relevant RCTs from inception to June 2018, without language restriction. The references of the identified studies were also searched to identify any further relevant studies. The search terms included butorphanol, fentanyl, sufentanil, remifentanil, and cough.

Quality assessment
Two authors independently assessed the quality of the included studies according to the Jadad scale. The following items were evaluated for each study: 1) whether randomization was performed and whether the method was correct, 2) whether allocation concealment was used and whether the method was correct, 3) whether blinding was performed and in whom the method was used, and 4) whether there were withdrawals or dropouts. Articles with 1–3 points were classified as low quality, and those with 4–7 points were classified as high quality.

Data extraction
Two authors independently extracted the following data using standard data tables: 1) first author and year of publication, 2) country, 3) sample size, 4) outcomes, and 5) intervention details.

Statistical analyses
We used RevMan 5.3 to conduct all statistical analyses. The incidence of opioid-induced cough and its degrees were reported by the risk ratio (RR) and 95% CI. Heterogeneity of those included studies was assessed with the I^2 statistic, and $I^2 > 50\%$ was regarded as significant. A fixed effects model was used to conduct the meta-analysis if significant heterogeneity had been found, and a random effects model was adopted to perform the meta-analysis when I^2 was $\geq 50\%$.

Results
Characteristics of the included studies
Initially, 114 articles were found, and 8 of them[8–15] were eventually included in the meta-analysis based on the inclusion and exclusion criteria. Figure 1 shows the screening process and results. The basic characteristics of the included studies are shown in Table 1.

Incidence of opioid-induced cough
All RCTs were included in this meta-analysis. Heterogeneity was found among the studies ($I^2 = 72\%$). Therefore, a random effects model was applied to conduct this meta-analysis. The results showed that butorphanol could significantly prevent opioid-induced cough compared with placebo (RR=0.17, 95% CI [0.09, 0.33], $P < 0.00001$; Figure 2).

Severity of opioid-induced cough
Mild cough
Five RCTs including 592 patients reported the degree of mild cough that was induced by opioids. Statistical heterogeneity ($I^2 = 57\%$) was found, and a random effects model was employed for the meta-analysis. The results showed that there was a significant difference between the butorphanol group and the control group in the incidence of opioid-induced mild cough (RR=0.30, 95% CI [0.11, 0.78], $P=0.01$) (Figure 3).

Moderate cough
Five RCTs including 592 patients reported the degree of opioid-induced moderate cough. No statistical heterogeneity was found among the study results ($I^2=0\%$); thus, a fixed effects model was used to perform the meta-analysis. There was a significant difference between the butorphanol group and the control group in the incidence of opioid-induced moderate cough (RR=0.08, 95% CI [0.03, 0.22], $P < 0.00001$) (Figure 4).

Severe cough
Five RCTs including 592 patients reported the degree of opioid-induced severe cough. No statistical heterogeneity ($I^2=0\%$) was found, and a fixed effects model was adopted for meta-analysis. The results showed that there was a significant difference between the butorphanol group and the control group in the incidence of opioid-induced severe cough (RR=0.08, 95% CI [0.02, 0.30], $P=0.0001$) (Figure 5).
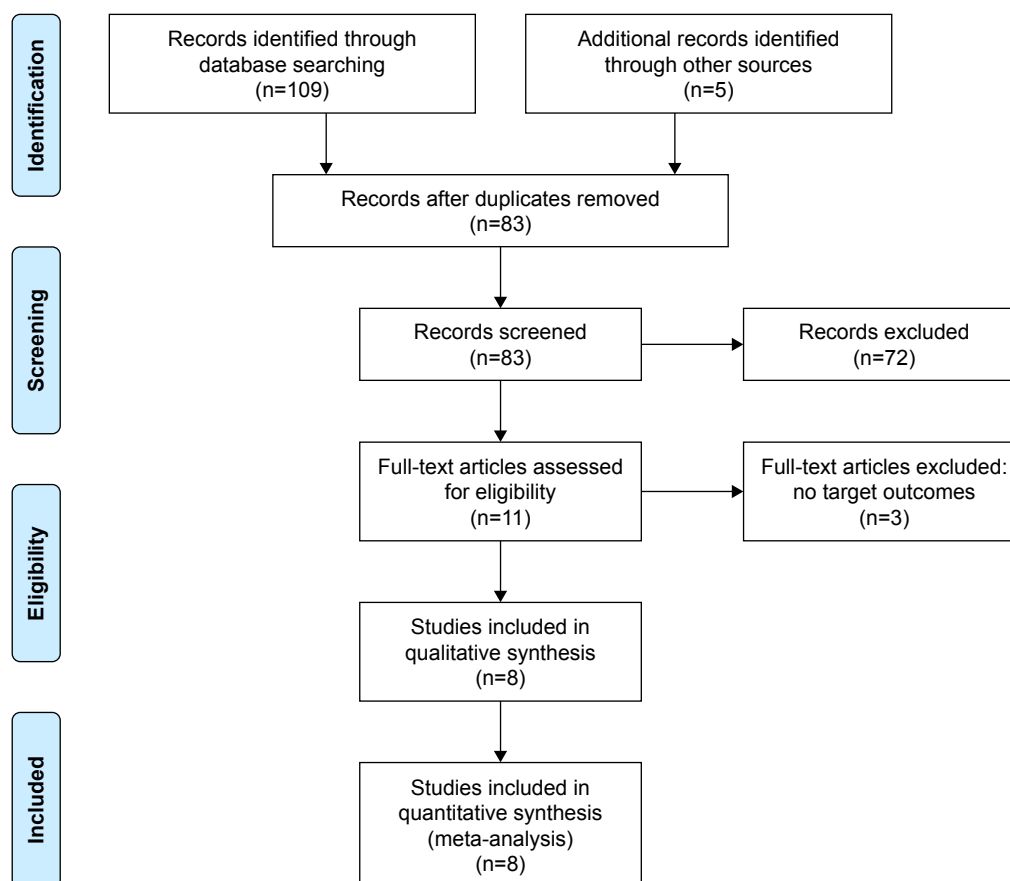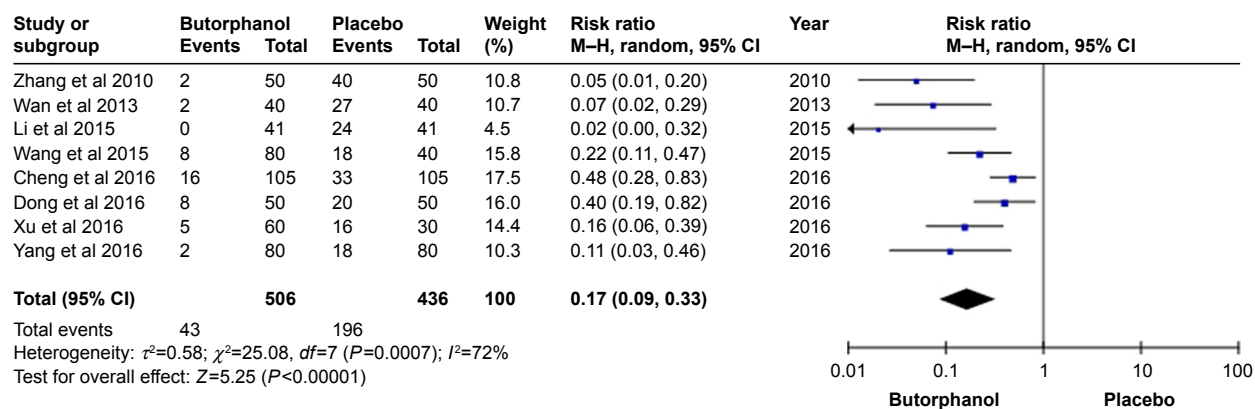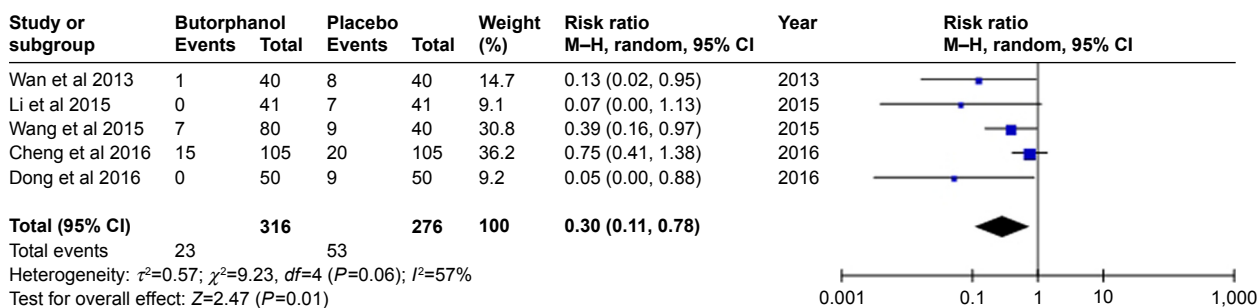
Figure 1 PRISMA flowchart of the included studies.

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year of publishing	Country	Sample	Grouping	Incidence of cough				Jadad score
					Total	Mild	Moderate	Severe	
Zhang et al	2010	China	100	Butorphanol 1 mg	2	NA	NA	NA	6
				Normal saline	40	NA	NA	NA	
Wan et al	2013	China	80	Butorphanol 1 mg	2	1	1	0	4
				Normal saline	27	8	15	4	
Wang et al	2015	China	160	Butorphanol 10 µg/kg	6	5	1	0	3
				Butorphanol 20 µg/kg	1	1	0	0	
				Butorphanol 25 µg/kg	1	1	0	0	
				Normal saline	18	9	6	3	
Li et al	2015	China	82	Butorphanol 1 mg	0	0	0	0	3
				Normal saline	24	7	9	8	
Cheng et al	2016	China	315	Butorphanol 15 µg/kg	12	11	1	0	7
				Butorphanol 30 µg/kg	4	4	0	0	
				Normal saline	33	20	7	6	
Dong et al	2016	China	150	Butorphanol 0.5 mg	8	8	0	0	3
				Butorphanol 1 mg	0	0	0	0	
				Normal saline	20	9	7	4	
Xu et al	2016	China	120	Butorphanol 10 µg/kg	5	NA	NA	NA	3
				Butorphanol 20 µg/kg	0	NA	NA	NA	
				Butorphanol 30 µg/kg	0	NA	NA	NA	
				Normal saline	16	NA	NA	NA	
Yang et al	2016	China	160	Butorphanol 1 mg	2	NA	NA	NA	2
				Normal saline	18	NA	NA	NA	

Study or subgroup	Butorphanol Events	Total	Placebo Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Year	Risk ratio M–H, random, 95% CI
Zhang et al 2010	2	50	40	50	10.8	0.05 (0.01, 0.20)	2010	
Wan et al 2013	2	40	27	40	10.7	0.07 (0.02, 0.29)	2013	
Li et al 2015	0	41	24	41	4.5	0.02 (0.00, 0.32)	2015	
Wang et al 2015	8	80	18	40	15.8	0.22 (0.11, 0.47)	2015	
Cheng et al 2016	16	105	33	105	17.5	0.48 (0.28, 0.83)	2016	
Dong et al 2016	8	50	20	50	16.0	0.40 (0.19, 0.82)	2016	
Xu et al 2016	5	60	16	30	14.4	0.16 (0.06, 0.39)	2016	
Yang et al 2016	2	80	18	80	10.3	0.11 (0.03, 0.46)	2016	
Total (95% CI)		**506**		**436**	**100**	**0.17 (0.09, 0.33)**		
Total events	43		196					

Heterogeneity: $\tau^2=0.58$; $\chi^2=25.08$, $df=7$ ($P=0.0007$); $I^2=72\%$
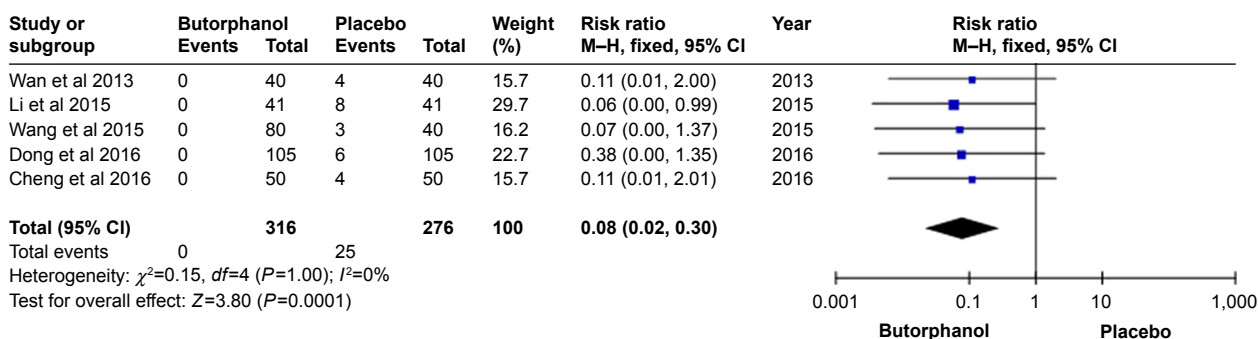Test for overall effect: $Z=5.25$ ($P<0.00001$)

Figure 2 Butorphanol reduced the incidence of opioid-induced cough.
Abbreviation: M-H, Mantel-Haenszel.

Study or subgroup	Butorphanol Events	Total	Placebo Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Year	Risk ratio M–H, random, 95% CI
Wan et al 2013	1	40	8	40	14.7	0.13 (0.02, 0.95)	2013	
Li et al 2015	0	41	7	41	9.1	0.07 (0.00, 1.13)	2015	
Wang et al 2015	7	80	9	40	30.8	0.39 (0.16, 0.97)	2015	
Cheng et al 2016	15	105	20	105	36.2	0.75 (0.41, 1.38)	2016	
Dong et al 2016	0	50	9	50	9.2	0.05 (0.00, 0.88)	2016	
Total (95% CI)		**316**		**276**	**100**	**0.30 (0.11, 0.78)**		
Total events	23		53					

Heterogeneity: $\tau^2=0.57$; $\chi^2=9.23$, $df=4$ ($P=0.06$); $I^2=57\%$
Test for overall effect: $Z=2.47$ ($P=0.01$)

Figure 3 Butorphanol reduced the intensity of opioid-induced cough: mild cough.
Abbreviation: M-H, Mantel-Haenszel.

Study or subgroup	Butorphanol Events	Total	Placebo Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year	Risk ratio M–H, fixed, 95% CI
Wan et al 2013	1	40	15	40	31.9	0.07 (0.01, 0.48)	2013	
Li et al 2015	0	41	9	41	20.2	0.05 (0.00, 0.88)	2015	
Wang et al 2015	1	80	6	40	17.0	0.08 (0.01, 0.67)	2015	
Dong et al 2016	0	50	7	50	16.0	0.07 (0.00, 1.14)	2016	
Cheng et al 2016	1	105	7	105	14.9	0.14 (0.02, 1.14)	2016	
Total (95% CI)		**316**		**276**	**100**	**0.08 (0.03, 0.22)**		
Total events	3		44					

Heterogeneity: $\chi^2=0.44$, $df=4$ ($P=0.98$); $I^2=0\%$
Test for overall effect: $Z=4.90$ ($P<0.00001$)

Figure 4 Butorphanol reduced the intensity of opioid-induced cough: moderate cough.
Abbreviation: M-H, Mantel-Haenszel.

Study or subgroup	Butorphanol Events	Total	Placebo Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year	Risk ratio M–H, fixed, 95% CI
Wan et al 2013	0	40	4	40	15.7	0.11 (0.01, 2.00)	2013	
Li et al 2015	0	41	8	41	29.7	0.06 (0.00, 0.99)	2015	
Wang et al 2015	0	80	3	40	16.2	0.07 (0.00, 1.37)	2015	
Dong et al 2016	0	105	6	105	22.7	0.38 (0.00, 1.35)	2016	
Cheng et al 2016	0	50	4	50	15.7	0.11 (0.01, 2.01)	2016	
Total (95% CI)		**316**		**276**	**100**	**0.08 (0.02, 0.30)**		
Total events	0		25					

Heterogeneity: $\chi^2=0.15$, $df=4$ ($P=1.00$); $I^2=0\%$
Test for overall effect: $Z=3.80$ ($P=0.0001$)

Figure 5 Butorphanol reduced the intensity of opioid-induced cough: severe cough.
Abbreviation: M-H, Mantel-Haenszel.

Sensitivity analysis

Significant heterogeneity was found in the incidence of opioid-induced cough and mild cough; therefore, sensitivity analysis was performed. By removing one study at a time, the sensitivity analysis had no effect on the results.

Discussion

The present meta-analysis aimed to estimate the efficacy of butorphanol in preventing opioid-induced cough. The meta-analysis indicated that butorphanol can effectively prevent the incidence of opioid-induced cough and decrease the incidence of opioid-induced mild, moderate, and severe cough.

Numerous studies have been conducted to estimate the mechanisms of opioid-induced cough; however, the exact mechanism remains unclear. The following mechanisms may be some of the reasons for the occurrence of opioid-induced cough. Opioids could activate the vagus nerve by inhibiting central sympathetic outflow, which is a possible reason for cough and bronchoconstriction.[16] Another possible mechanism is the pulmonary chemoreflex, which is mediated by rapidly adapting receptors (irritant receptors) or vagal C-fiber receptors close to pulmonary vessels.[17] Opioid-induced tracheal smooth muscle constriction may contribute to cough by simulating opioid receptors in the upper pulmonary mucosa. Substances such as histamine released from lung mast cells and the sudden adduction of the vocal cords or supraglottic obstruction caused by opioid-induced muscle rigidity also play important roles in the occurrence of opioid-induced cough.[18] Among the different interventions used to prevent opioid-induced cough,[19–21] agonist–antagonist opioid analgesic agents, such as dezocine and pentazocine, could reduce the incidence of opioid-induced cough, and there were no obvious adverse effects.[7,22,23] Butorphanol, an agonist–antagonist opioid, can antagonize the μ receptor to prevent the cough reflex while acting on the C-fiber receptor to inhibit the afferent pathway of the cough reflex. This meta-analysis found that the incidence of opioid-induced cough was significantly lower in the butorphanol group than in the control group. Similar results were found with severe cough. Our findings were consistent with the previous studies. However, significant heterogeneity was found in the results, which may have affected the rigor of those findings. The heterogeneity may be explained by the different doses of butorphanol administered to prevent opioid-induced cough, such as 10, 20, and 25 μg/kg.

Several limitations may affect the objectivity of the meta-analysis. First, the overall sample size was small. Second, the patients included in this meta-analysis were all from China. Third, significant heterogeneity was found in the results. Therefore, high-quality, large-sample studies involving different races are still needed to confirm the results. In summary, this study showed that butorphanol can reduce the incidence of opioid-induced cough and can mitigate the severity of cough.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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