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ORIGINAL ARTICLE

The impact of prophylactic intravenous lidocaine on opioid-induced cough: a meta-analysis of randomized controlled trials

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Abstract
Background Opioids are commonly used for general anesthesia, but reflex cough can occur after an intravenous injection. We have performed a meta-analysis of randomized controlled trials (RCTs) that evaluated the effectiveness and safety of prophylactic lidocaine administered intravenously (IV) on opioid-induced cough (OIC) during induction in patients undergoing general anesthesia.
Methods We searched three bibliographic databases (PubMed, Embase, and the Cochrane Central Register of Controlled Trials) to identify studies meeting a priori inclusion criteria and also conducted a secondary reference review. The information used to calculate the relationship between lidocaine prophylaxis and the risk and severity of OIC was extracted by two principal investigators, respectively.
Results Six RCTs with a total of 1,740 participants were included in this meta-analysis. Overall, prophylactic lidocaine administered IV reduced both the risk of OIC [pooled risk ratio (RR) 0.471; 95 % confidence interval (CI) 0.355–0.625; $P = 0.074$; heterogeneity test, $I^2 = 50.3$ %] and its severity (weighed mean difference −0.316; 95 % CI −0.480 to −0.151; $P = 0.038$; heterogeneity test, $I^2 = 60.5$ %). Sub-group analysis indicated a significant reduction in the incidence of both fentanyl-induced cough (FIC) and remifentanil-induced cough (RIC), but it appeared that lidocaine only alleviated the severity of FIC. Further sub-group analysis indicated that the lowest effect dose of lidocaine for preventing the prevalence of OIC was 0.5 mg/kg. No severe adverse effects were reported.
Conclusions Our meta-analysis establishes the effectiveness of prophylactic lidocaine administered IV for the prevention of OIC during induction. The lowest effective dose of lidocaine on the risk of OIC appeared to be 0.5 mg/kg.

Keywords Lidocaine · Opioid-induced cough · Fentanyl-induced cough · Remifentanil-induced cough · Meta-analysis

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Introduction

Bohrer et al. [1] were the first to report that the injection of fentanyl through a central venous catheter induces the cough reflex, and since then opioid-induced cough (OIC) has been well-recognized as a common phenomenon after opioid (especially remifentanil and fentanyl) administration during the induction of general anaesthesia. The incidence of OIC has been reported to be approximately 26–31 % after remifentanil infusion [2–4] and 18–65 % after fentanyl injection [1, 5–7].

Opioid-induced cough has been independently associated with aging, body weight, smoking, a prior epidural injection of lidocaine, injection time of opioid, and a priming dose of vecuronium. It has been reported to be unaffected by gender, the presence of either bronchial asthma or chronic obstructive pulmonary disease, or prior use of atropine [4, 7, 8]. OIC is usually transient, self-limiting, and benign in clinical settings, but during the

induction of anesthesia coughing can increase intracranial, intraocular, and intra-abdominal pressures and therefore be a risk factor in patients with high ocular or intracranial pressure or a full stomach [6]. Furthermore, the injection of opioid may sometimes be spasmodic or explosive [9] and lead to life-threatening situations [10], all of which require immediate intervention.

Although there have been reports of reducing coughs by limiting the peak plasma concentration of fentanil and remifentanil [6, 11–13] or by a huffing maneuver [14] before inducing anesthesia, many drugs are currently available that will reduce OIC according to specific mechanisms. In this context, it has been reported that terbutaline [15], salbutamol [16], ephedrine [7], clonidine [17], ketamine [18], dexamethasone [19], and lidocaine [3, 5, 7, 20, 21] are effective in reducing fentanyl-induced cough (FIC) or remifentanil-induced cough (RIC).

Lidocaine is a widely used drug in clinical practice with minimal side effects when given at the recommended dose and may have the potential of reducing the incidence of OIC. However, its impact on OIC remains unclear since the results from different studies have been inconsistent. [3–5, 7, 20, 21]. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) in order to evaluate the efficacy of lidocaine on OIC, as well as its safety.

Materials and methods

Search strategy

We performed a systematic search of Pubmed, Embase, and the Cochrane Central Register of Controlled Trials through March 2013 for relevant studies of association between prophylactic lidocaine administered intravenously (IV) and OIC. Search strategies for subject headings and key words are as follows: (1) lidocaine; (2) opioid, fentanyl, remifentanil, sufentanil, alfentanil, and all variations of these terms; (3) cough. A secondary reference review was also conducted.

Selection criteria

The titles, abstracts, and full-texts of extracted articles were reviewed. The eligible studies met the following criteria: (1) prospective RCTs published in English; (2) the association of lidocaine with OIC was evaluated in the study as the number of patients with the outcome event or risk ratio (RR) with the corresponding confidence interval (CI) or severity of OIC using a standard method.

Data extraction

We collected the following information from each study: first author, year of publication, country of origin, sample size, age, gender, weight, smoking, American Society of Anaesthesiologists Class (ASA) classification, interventions, outcomes, and adverse events. These data are presented in Tables 1 and 2. In extracting the data from three-arm studies with continuous data, we combined two of the reported groups into a single group. The sample size, mean and standard deviation (SD) of the combined group were calculated according to the formula described in the Cochrane Handbook of Systematic Reviews of interventions [22]. Independent investigators calculated and tabulated the data, respectively, with a standard extraction

Table 1 Characteristics of individual studies

Study	Sample size	Opioid	Interventions	Jadad score
Bang et al. 2010 [4] (Japan)	158	Remifentanil: 5 ng/ml by TCI (target concentration, within 1 min)	Lidocaine at 0.5 mg/kg IV 1 min prior to remifentanil infusion vs. normal saline	3
Guler et al. 2010 [5] (Turkey)	200	Fentanyl: 1.5 μg/kg injection (>2 s)	Lidocaine at 1.0 mg/kg IV 1 min before fentanyl injection vs. normal saline	5
Kim et al. 2008 [3] (Korea)	500	Remifentanil: 4 ng/ml by TCI (target concentration, >10 s)	Lidocaine at 0.5 mg/kg IV 1 min before remifentanil infusion vs. normal saline	4
Pandey et al. 2005 [20] (India)	320	Fentanyl: 3 μg/kg injection	Lidocaine at 0.5, 1.0, 1.5 mg/kg IV 1 min before fentanyl injection vs. normal saline	4
Lin et al. 2004 [7] (Taiwan, China)	60	Fentanyl: 2.5 μg/kg injection (within 2 s)	Lidocaine at 2.0 mg/kg IV 1 min before fentanyl injection vs. normal saline	3
Pandey et al. 2004 [21] (India)	502	Fentanyl: 3 μg/kg injection	Lidocaine at 1.5 mg/kg IV 1 min before fentanyl injection vs. normal saline	4

IV intravenously, *TCI* target controlled infusion

Table 2 Baseline patient characteristics

Study	Age (years), mean (SD)	Female (%)	Weight (kg), mean (SD)	ASA I/II (*n*)	Smoking (%)
Bang et al. 2010 [4] (Japan)	39.65 (13.06)	50.6	65.1 (11.95)	127/31	24.7
Guler et al. 2010 [5] (Turkey)	34.7 (9.8)	50.5	70.15 (11.63)	166/34	NA
Kim et al. 2008 [3] (Korea)	39.75 (12.46)	38.2	65.5 (10.66)	396/104	31.6
Pandey et al. 2005 [20] (India)	41.73 (12.49)	34.1	56.22 (6.63)	NA	NA
Lin et al. 2004 [7] (Taiwan, China)	40.28 (13.26)	68.3	59.12 (9.81)	37/23	NA
Pandey et al. 2004 [21] (India)	41.97 (13.89)	32.9	60.45 (8.81)	NA	NA

ASA American Society of Anesthesiologists Class, *SD* standard deviation, *NA* not available

formula. Discrepancies were resolved via review of the original articles and group discussion.

Quality assessment

A medical specialist evaluated the methodological quality of the included studies using the Jadad score scale [23], as shown in Table 1. The quality scale ranges from 0 to 5 points, with higher scores indicating better reporting. The studies are said to be of low quality if the Jadad score is ≤ 2 and of high quality if the score is ≥ 3 [24]. A different specialist verified the evaluation accuracy determined by the first specialist.

Statistical analysis

We pooled data across studies and calculated the RR and associated 95 % CI for each dichotomous outcome. For the severity of OIC, all of the studies used the standard method (coughing was graded as none, mild, moderate, or severe by counting coughs: mild 1–2, moderate 3–4, and severe ≥ 5). We therefore adopted the 4-point rating scale (none = 0, mild = 1, moderate = 2, severe = 3) to facilitate further comparisons and used the weighted mean differences (WMDs) as effect measures.

Heterogeneity across studies was tested by using the I^2 statistic, which is a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of 25–50 % are considered to have a low heterogeneity, those with an I^2 statistic of 50–75 % to have a moderate heterogeneity, and those with an I^2 statistic of >75 % to have a high degree of heterogeneity [25]. An I^2 value of >50 % indicates significant heterogeneity [26]. A fixed-effects model was used in the case of low heterogeneity, and a random-effects model was used in the case of significant heterogeneity ($I^2 > 50$ %).

We further conducted sub-group analyses and sensitivity analyses to explore possible explanations for heterogeneity. The possibility of publication bias was assessed using the Begg and Egger test [27, 28]. All analyses were performed using STATA ver. 11.2 (Stata Corp LP, College Station, TX). A P value of < 0.05 was considered to be statistically significant.

Results

Literature search

We initially retrieved 400 articles from the PubMed and Embase databases and the Cochrane Central Register of Controlled Trials (39 from Pubmed, 346 from Embase, and 15 from the Cochrane Central). The majority of references were excluded as they did not meet the inclusion criteria. Six independent studies that met the inclusion criteria were ultimately included in our final meta-analysis. [3–5, 7, 20, 21]. The detailed steps of our literature search and the study selection are described in Fig. 1.

Study characteristics

The characteristics of the six RCTs included in the meta-analysis, all published between 2004 and 2010, are presented in Table 1. All of the studies were conducted in Asia {1 in China (Taiwan) [7], 1 in Japan [4], 1 in Korea [3], 1 in Turkey [5], 2 in India [20, 21]}. Remifentanil infusion was examined in two studies [3, 4], and fentanyl injection was investigated in the other four studies [5, 7, 20, 21]. The incidence of OIC was reported in all six studies, and the severity of OIC was investigated in five studies [3–5, 20, 21]. The number of subjects in the RCTs ranged from 60 to 502 (total 1,740). The dose range of fentanyl and remifentanil was 1.5–3.0 and 4.0–5.0 μg/kg, respectively. The dose of lidocaine ranged from 0.5 to 2.0 mg/kg, and lidocaine was always injected 1 min before administration of the opioid.

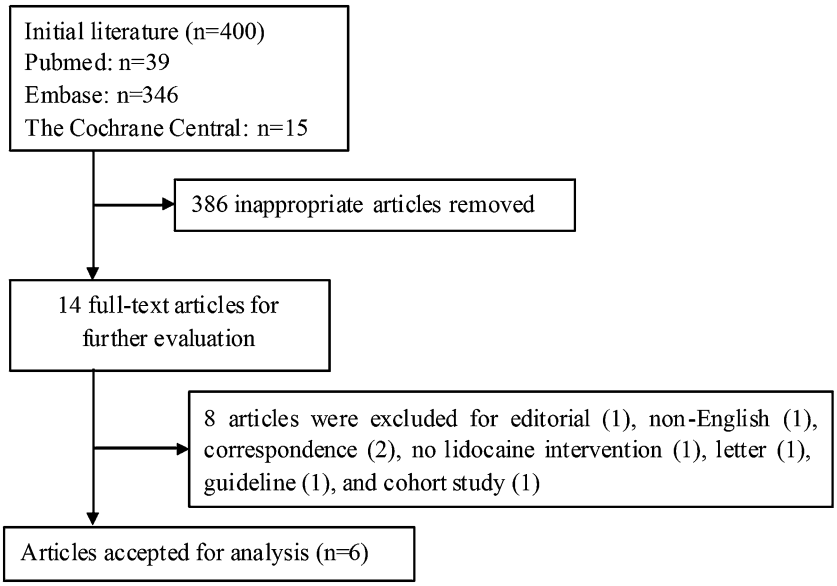

Fig. 1 Flow chart of study selection

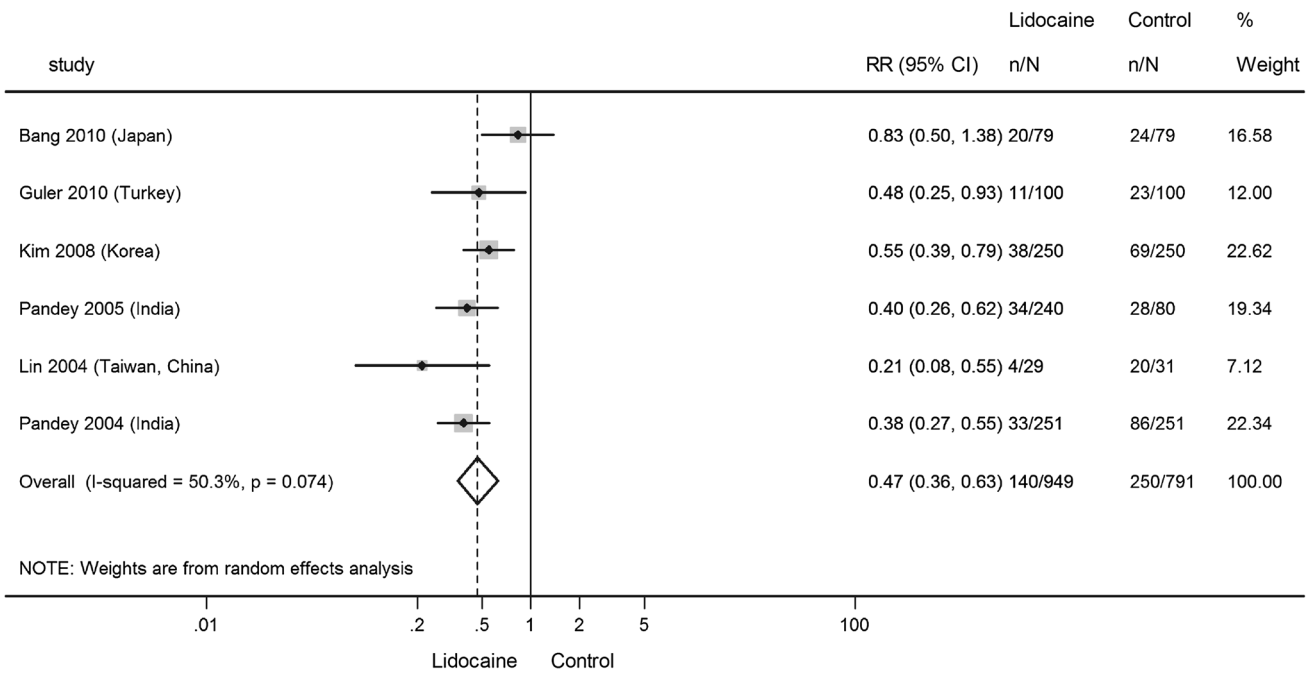

Fig. 2 Lidocaine on the incidence of opioid-induced cough (OIC) (random-effects model). *RR* risk ratio, *CI* confidence interval

Association of lidocaine with the incidence and severity of OIC

Among the six selected articles, five [3, 5, 7, 20, 21] reported positive associations between prophylactic lidocaine and a decreased incidence and severity of OIC; one study [4] did not find any positive results.

Lidocaine administered IV was associated with a decreased risk of OIC; the pooled RR was 0.471 (95 % CI 0.355–0.625), although with moderate heterogeneity ($P = 0.074$; $I^2 = 50.3$ %), as shown in Fig. 2. Lidocaine also alleviated the severity of OIC; the WMD was −0.316 (95 % CI −0.480 to −0.151), an effect was statistically significant, but with moderate heterogeneity ($P = 0.038$; $I^2 = 60.5$ %), as shown in Fig. 5.

Adverse effect and safety of lidocaine

The potential occurrence of adverse effects of lidocaine, such as allergic reaction, injection pain, nausea and/or vomiting, dizziness, unconsciousness, convulsion, coma, respiratory arrest, and cardiovascular system depression,

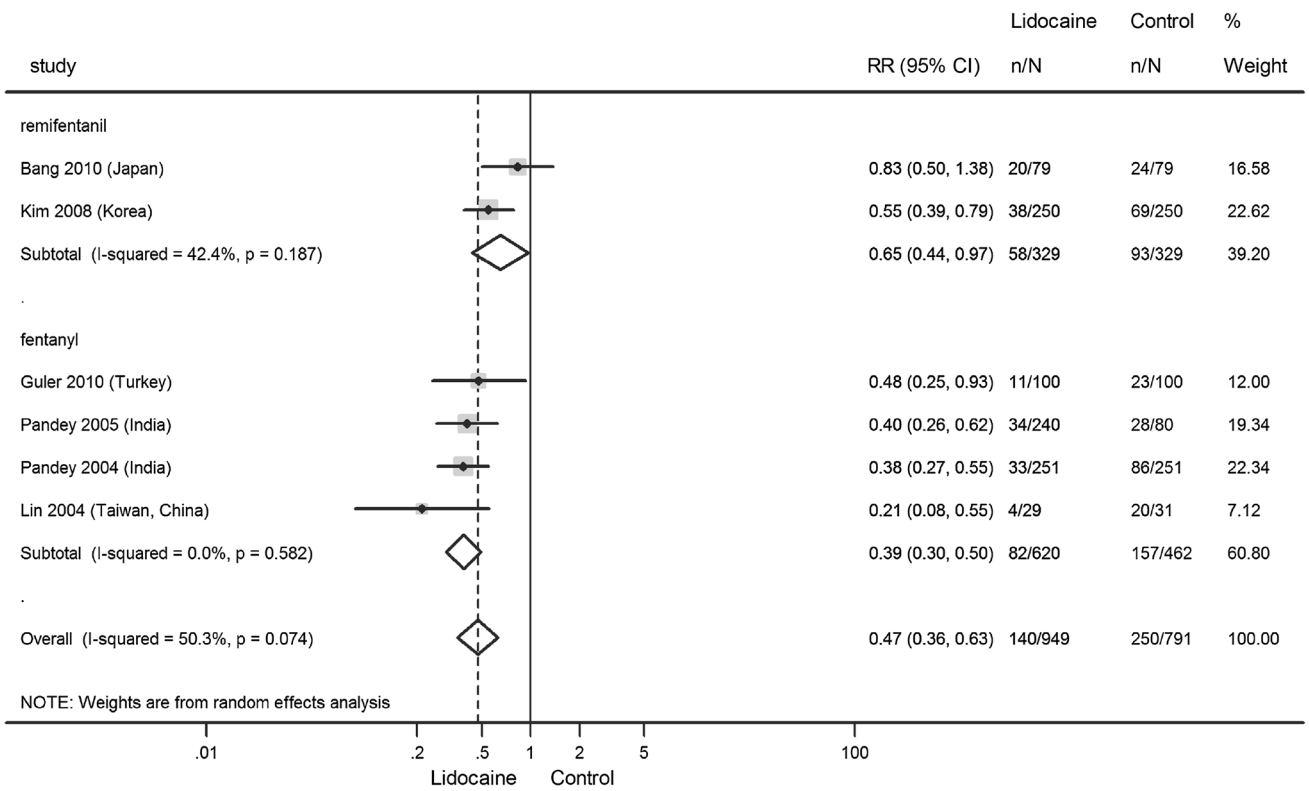

Fig. 3 Effect of lidocaine on the incidence of OIC (grouped by opioid type; random-effects model)

were not found or tested for in most of the studies. One study [7] did report there was one patient each who suffered injection pain, nausea/vomiting, and dizziness in the lidocaine group, but that there were no significant differences between this group and the placebo group.

Sub-group analyses

To explore the study heterogeneity and dose effect of lidocaine for preventing OIC, we also performed stratified analyses.

After dividing the study population into two groups, namely, the remifentanil group and the fentanyl group, we found that the incidence of OIC was significantly reduced in two groups but that lidocaine only alleviated the severity of FIC [pooled RR 0.651 (95 % CI 0.437–0.970) vs. 0.387 (95 % CI 0.302–0.495), respectively], with a WMD of −0.124 (95 % CI −0.531 to 0.282) and −0.431 (95 % CI −0.560 to −0.302), respectively, as shown in Figs. 3 and 6.

For analyzing the dose effect of lidocaine, we divided the dose into four groups: 0.5, 1.0, 1.5, and 2.0 mg/kg. It appeared that lidocaine was able to significantly reduce the incidence of OIC in all groups, with moderate heterogeneity only at the 0.5 mg/kg dose ($P = 0.168$; $I^2 = 44.0$ %), as shown in Fig. 4. That is to say, the lowest effective dose of lidocaine for preventing the risk of OIC was 0.5 mg/kg.

Sensitivity analyses

Sensitivity analyses were also conducted to explore potential sources of heterogeneity in the association between lidocaine and OIC.

As for the incidence and severity of OIC, after excluding 2 studies [3, 4] involved the remifentanil administration, the pooled RR was 0.387 (95 % CI 0.302–0.495) and the pooled WMD of the severity of OIC was −0.431 (95 % CI −0.560 to −0.302), with no heterogeneity any more ($P = 0.582$; $I^2 = 0$ % and $P = 0.853$; $I^2 = 0$ %, respectively).

Publication bias

Visual inspection of the Begg funnel plot did not indicate any substantial asymmetry. The Begg rank correlation test and Egger linear regression test also did not support the presence of publication bias.

Discussion

The relationship between prophylactic lidocaine and OIC remains controversial. To our knowledge, this is the first meta-analysis that has investigated the association of lidocaine with OIC. Our results strongly suggest that

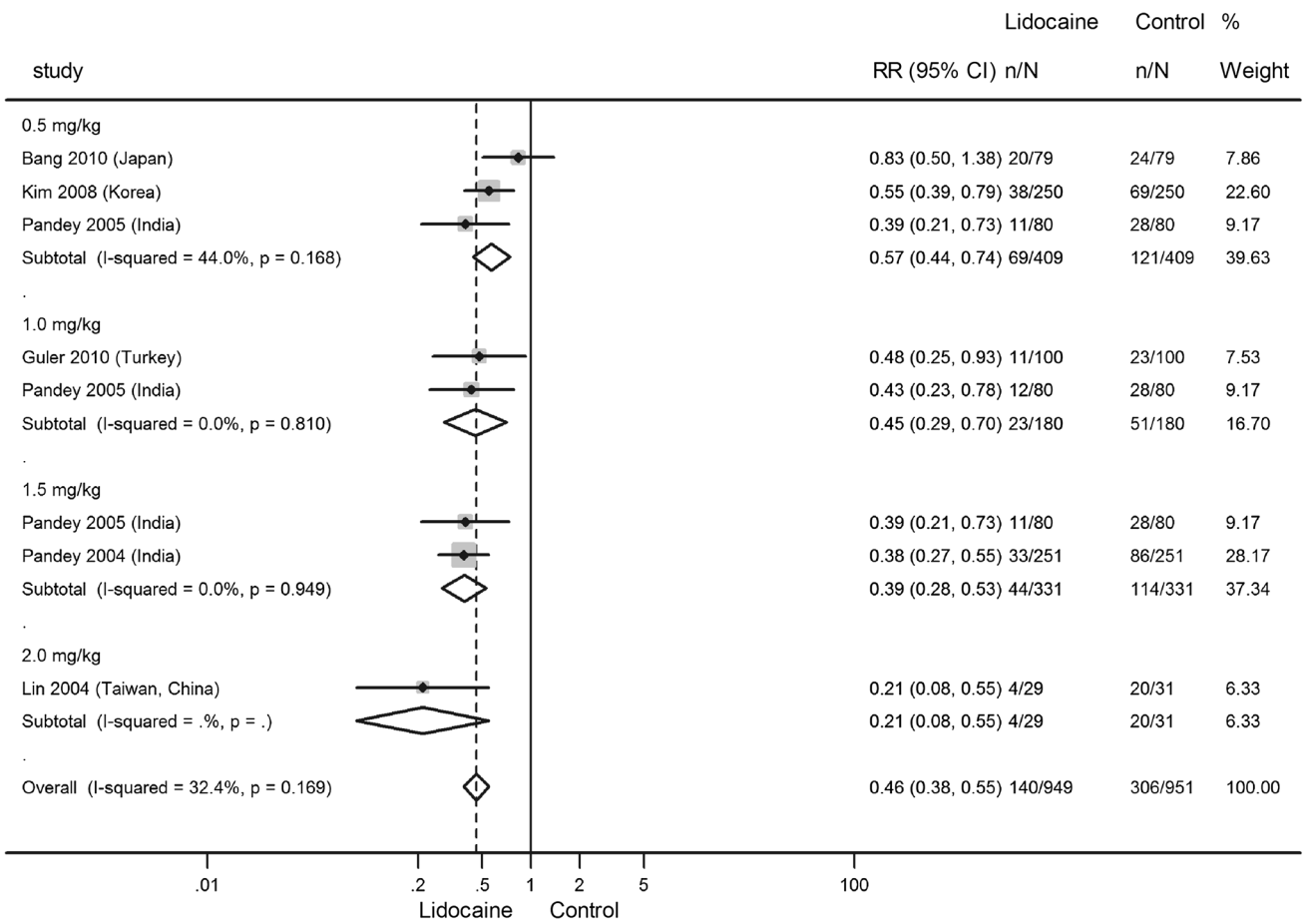

Fig. 4 Effect of lidocaine on the incidence of OIC (grouped by dosage; fixed-effects model)

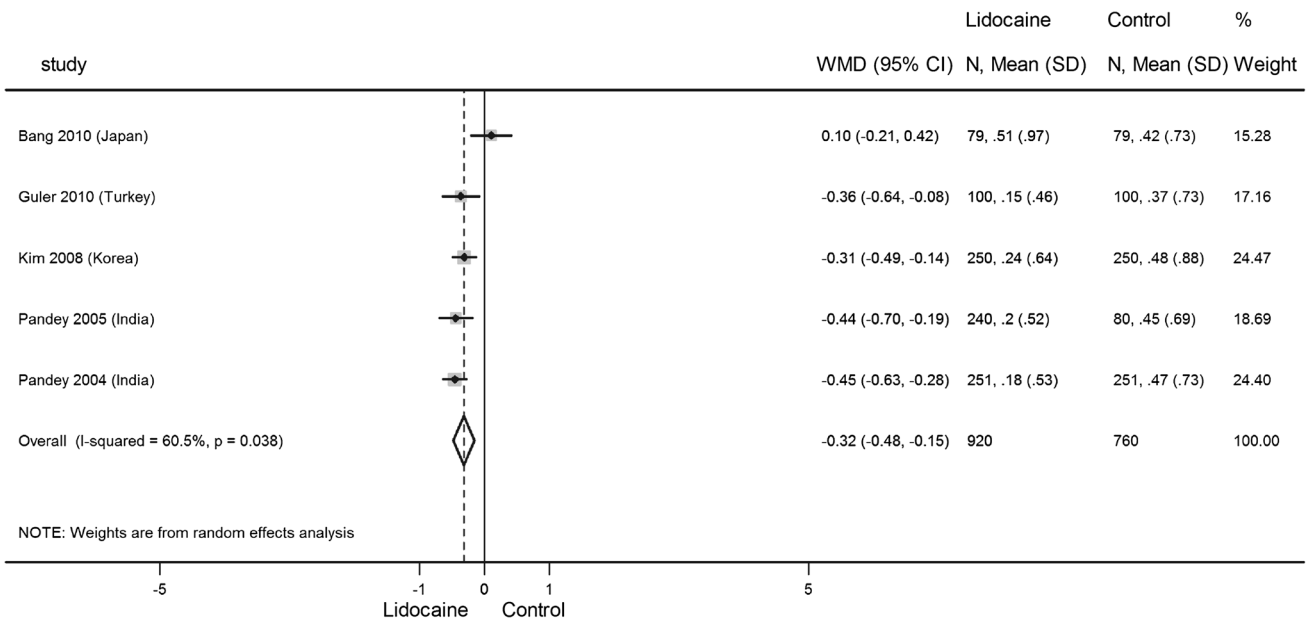

Fig. 5 Effect of lidocaine on the severity of OIC (random-effects model). *WMD* weighted mean difference, *SD* standard deviation

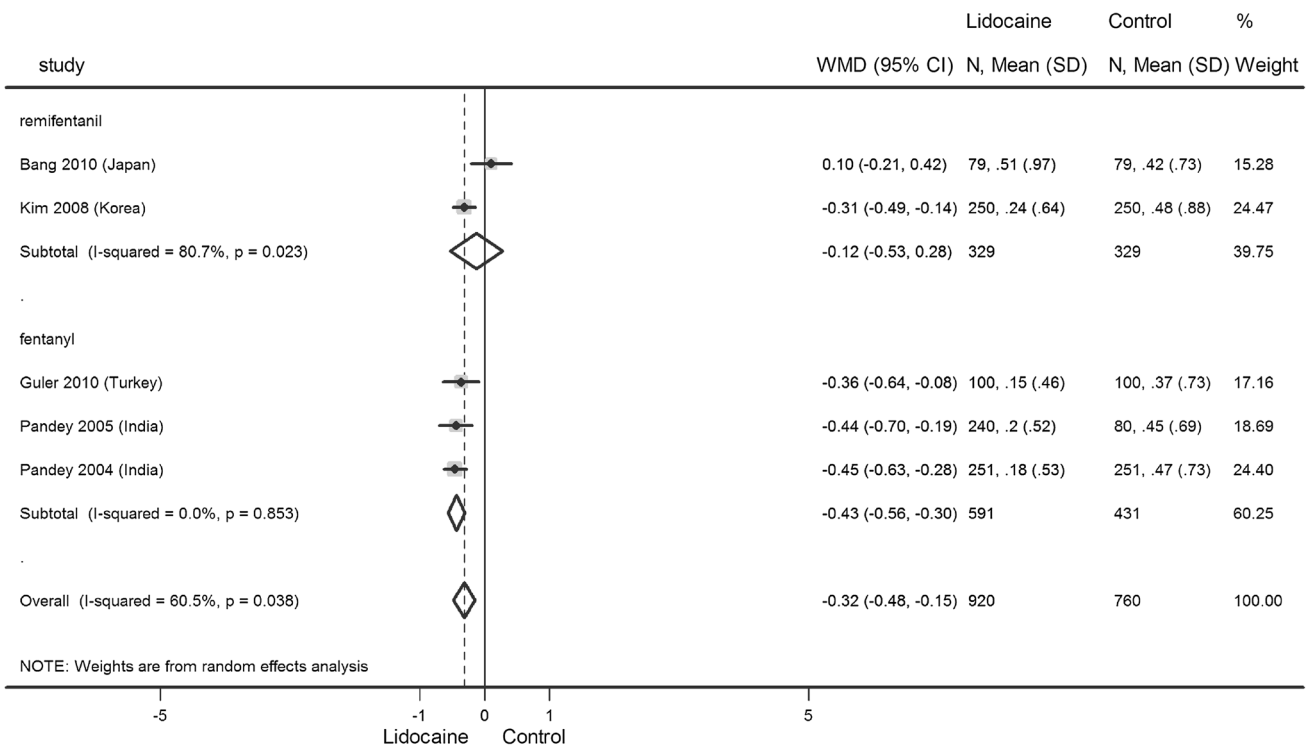

Fig. 6 Effect of lidocaine on the severity of OIC (grouped by opioid type; random-effects model)

lidocaine can significantly reduce the incidence of OIC, but only the severity of FIC—not RIC.

In order to reduce the bias of our meta-analysis, we selected only RCTs in which only a single dose of prophylactic lidocaine was administered IV. Our meta-analysis of these RCTS revealed that lidocaine therapy reduced the prevalence (Figs. 2, 3, 4) and severity (Figs. 5, 6) of OIC. Although the side effects of using lidocaine for the prevention of OIC were reported in only one of these six studies, most were minimal ones with no statistical difference with the placebo.

A total of 1,740 patients were included in the RCTs of this meta-analysis, of whom 949 were allocated to lidocaine therapy and 791 to the control group. This relatively large sample size made it possible to identify a significant difference between lidocaine intervention and placebo. Because of our comprehensive search strategy, it is unlikely that any important trials were missed.

Confounding factors and the causes of heterogeneity between the studies included characteristics of the patients (age, gender, ASA classification, smoking), publication year, region, interventions, and methodology (components of validity assessment). We therefore performed sub-group analyses and sensitivity analyses to investigate potential bias from opioid type used and dose effect of lidocaine. The results of these analyses showed that opioid type was the source of heterogeneity; the sensitivity analyses confirmed this result.

The sub-group analyses investigating the effect of opioid type on OIC revealed that lidocaine can effectively prevent FIC. A subsequent sub-group analysis of the dose effect of lidocaine on OIC was conducted which showed that the lowest effect dosage of lidocaine on the risk of OIC was 0.5 mg/kg. Interestingly, our results revealed that lidocaine can only reduce the risk of RIC—and not its severity. We cannot explain this result although possible factors were examined. Therefore, the effect of lidocaine on RIC should be examined in more detail in future studies.

OIC is a common adverse event after opioid administration during general anesthesia. However, the mechanisms of OIC have not yet been elucidated. Various mechanisms proposed to explain OIC are: (1) inhibition of central sympathetic outflow causes vagal predominance and induces the cough reflex [15, 16, 29]; (2) pulmonary chemoreflex resulting from the stimulation of C-fiber receptors (Juxta-capillary receptors) [1] or irritant receptors (rapidly adapting receptors) from deformation of the trachea-bronchial wall by tracheal smooth muscle constriction [21, 30]; (3) histamine release from lung mast cells[16]; (4) the sudden adduction of the vocal cords or supraglottic obstruction by soft tissue caused by opioid-induced muscle rigidity [31, 32].

Based on these proposed mechanisms of OIC, many pharmacological measures have been conducted to prevent OIC, such as the administration of terbutaline, salbutamol, ephedrine, clonidine, ketamine, or dexamethasone.

Lidocaine is a commonly used drug in the treatment of wide-ranging problems in clinical settings, and it has the potential effect of reducing the incidence and severity of OIC. Although the bronchodilation effect of lidocaine has been questioned, [33] lidocaine administered IV has been found to suppress both mechanically and chemically induced airway reflexes, including the cough reflex [34, 35]. The mechanisms by which lidocaine suppresses cough are not known, but it has been proposed that the depression of brain-stem functions by lidocaine may be responsible for cough suppression. An alternative mechanism is that lidocaine may act by anesthetizing peripheral cough receptors in the trachea and hypopharynx [36]. In addition to the prevention of OIC through drug administration, various other methods with the aim of alleviating OIC have proven to be effective, including limiting the peak plasma concentration of opioid [6, 11, 13] and a huffing maneuver [14]. Such alternatives have led Han et al. [37] to suggest that researchers are focusing too much on how to prevent OIC by drug medication and that OIC can actually be prevented by non-drug therapy. Moreover, these authors asserted that OIC is usually benign in adults and that preventing OIC is therefore meaningless. However, for high-risk patients with increased intracranial pressure, intraocular, and intra-abdominal pressure, OIC may lead to severe consequences that may on occasion be life-threatening.

Therefore, we propose that preventing OIC using drugs is of great importance, not only in terms of patients' comfort and safety, but also so that anesthesiologists can continue to use opioids during the induction of anesthesia. Among these drugs, we recommend lidocaine as the first choice, given its effectiveness and other perioperative benefits [38–41]. With respect to lidocaine administered IV, a dose of 1.5 mg/kg has been found to be optimal to suppress OIC, as 2 mg/kg may be associated with possible systemic toxicity [35].

Further studies are needed due to a number of limitations to our meta-analysis. First, the number of included studies was limited, and data from some studies were not complete. Second, it is a controversial step to combine the results of different protocols in a pooled RR or WMD estimate. Third, as all of the data were from adults, we did not know the effectiveness of lidocaine on OIC in children.

In summary, we have illustrated the effectiveness of prophylactic lidocaine administered IV for the prevention the incidence and severity of OIC in this meta-analysis. The lowest effective dose of lidocaine appeared to be 0.5 mg/kg. The dosage of lidocaine for preventing OIC was safe.

Based on the results of this meta-analysis, high-quality RCTs of lidocaine on both children and adults and other kinds of drug therapies for OIC should be investigated in the future.

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Conflict of interest None declared.

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