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REVIEW ARTICLE

Pharmacological prevention of rocuronium-induced injection pain or withdrawal movements: a meta-analysis

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Abstract Rocuronium is reported to be associated with injection pain or withdrawal movement (IPWM). This meta-analysis assessed the efficacy of different pharmacological treatments used to decrease the incidence of the rocuronium-induced IPWM. We searched the Cochrane Library, Embase and PubMed for randomized controlled trials comparing a pharmacological drug with a placebo to prevent the rocuronium-induced IPWM and found 37 studies with 5,595 patients. Overall incidence of rocuronium-induced IPWM was 74 %. Pretreatment with opioids [risk ratio (RR) 0.16; 95 % confidence interval (95 % CI) 0.09—0.29], lidocaine (0.47; 0.35–0.64), and ketamine (0.41; 0.22–0.77) were effective in decreasing IPWM. Lidocaine pretreatment with venous occlusion (0.40; 0.32–0.49) and opioids pretreatment with venous occlusion (0.77; 0.61–0.96) were also effective. Mixing sodium bicarbonate ($NaHCO_3$) with rocuronium (0.15; 0.06–0.34) was also efficacious in reducing IPWM. Indirect comparison shows that the RR of $NaHCO_3$ admixture and pretreatment with opioids were lower than that of the other four interventions (pretreatments of ketamine or lidocaine, and lidocaine or opioids with venous occlusion). This meta-analysis suggests that opioids, lidocaine, ketamine, and $NaHCO_3$ are effective in decreasing rocuronium-induced IPWM. Considering the efficacy and convenience, pretreatment with opioids without venous occlusion is recommended for reducing rocuronium-induced IPWM.

Keywords Anesthesia · Meta-analysis · Rocuronium · Pain · Injection · Prevention

Introduction

Rocuronium-induced injection pain or withdrawal movement (IPWM) is well known, and its incidence varies between 50 and 80 % [1–3]. Severe and burning pain occurred sometimes during rocuronium injection [1, 4]. In anesthetized patients, injection pain may cause withdrawal movement of the arm, which may extend to a generalized movement presumably secondary to its injection pain [3, 5]. The withdrawal movements occur more frequently in young patients. Extreme movements during induction can cause injury, and pulmonary aspiration due to gastric regurgitation has been reported in children [6]. Various pharmacological or nonpharmacological strategies have been applied to reduce the incidence and intensity of rocuronium-induced IPWM, with varying results. Pharmacological interventions include pretreatment with various drugs (with and without venous occlusion) and mixing drugs with rocuronium, but systematic review regarding the efficacy of the interventions has not been addressed. We assessed the efficacy of pharmacological treatments used to eliminate or decrease rocuronium-induced IPWM by performing a meta-analysis.

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Methods

This study was conducted using systemic review guidelines: Cochrane Collaboration recommendation and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7, 8]. Databases searched comprised the Cochrane Library, Embase, and PubMed. We searched the following terms: "rocuronium" AND ("injection pain" OR "withdrawal"). The search included clinical and randomized controlled trials comparing the use of pharmacological drug with control patients receiving no treatment to prevent IPWM by rocuronium injection and articles written in English. To identify all available evidence, we hand searched the references cited in selected articles for additional studies. The last computer search date was April 2012. We included studies in which two or more interventions were used in the same patient to prevent IPWM by rocuronium injection. We included both pediatric and adults in awake or anesthetized states. Reviews, abstracts, protocols, and letters were excluded. When an article met the selection criteria, its quality was assessed before data extraction by two independent reviewers, both anesthetists. Any conflicting results were resolved by the two reviewers' discussion. A five-point Oxford scale was used to score article quality [9]. Extracted data included patients' characteristics; dose, timing, and administration route of pretreatment drugs; intervention strategy of administration; rocuronium dose; and hypnotic agents. The number of patients reporting any rocuronium-induced IPWM was primary outcome in this meta-analysis. The meta-analyses of pain or withdrawal scores were not performed.

Statistical analysis

Review Manager 5.1 software (RevMan 5.1, The Cochrane Collaboration, Oxford, UK) was used for statistical analysis. Response rate of IPWM was summarized using risk ratio (RR) with 95 % confidence interval (CI), with point estimates and 95 % CIs derived from a random-effects Mantel–Haenszel method. Forest plots were used to graphically represent and evaluate treatment effect. $P < 0.05$ and RRs not including the identity line were considered statistically significant. For studies with more than two treatment groups, to reduce unit of analysis issues, the number of patients in the control group and IPWM number were divided into more than two control groups within each meta-analysis. Statistical heterogeneity was assessed with the I^2 value. To examine bias related to unpublished results, funnel plots and the Begg–Mazumdar test were used for interventions involving ten or more studies. Sensitivity analysis was done considering the quality of the included trials by restricting the analysis to studies with an Oxford score ≥ 4.

In addition to direct comparisons between intervention and control, indirect comparisons of individually significant interventions were also performed. For indirect comparison, we performed mixed-effects metaregression [10]; when a direct intervention was compared with three or more studies, only those interventions that reduced injection pain significantly were selected. The summary statistic values were presented as the RR (95 % CI). The control group was the common comparator. In the mixed-effects models, the moderators were the interventions, which were entered as categorical covariates. In this analysis, the following points were assumed: sufficient homogeneity in different trials; normal distribution of treatment effects (log-RR) around a typical value; and the same residual heterogeneity (τ^2) among different moderators. R package metafor using restricted maximum likelihood estimation was used for data analysis. Knapp and Hartung [11] (t and F distributions) method was used to adjust the test statistics of individual estimates of moderator variables as well as omnibus hypotheses of all moderators. The chi-square test was used to examine residual heterogeneity.

Results

Three hundred and twenty-eight articles were found using our search criteria, and 51 articles were considered as potential clinical trials to be included (Fig. 1). This review analyzed a 37 articles including 3,145 patients with pharmacological interventions and 2,450 patients with no intervention. Twenty-two agents were used to reduce

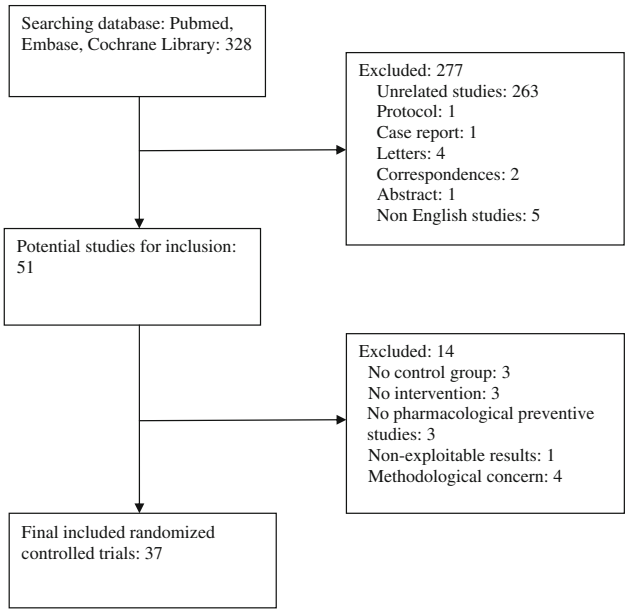

Fig. 1 Study diagram

rocuronium-induced IPWM: opioids (remifentanil, fentanyl, alfentanil, sufentanil, hydromorphone, tramadol), lidocaine, sodium bicarbonate ($NaHCO_3$), ketamine, magnesium sulfate ($MgSO_4$), dexmedetomidine, esmolol, ketorolac, pheniramine, ondansetron, metoclopramide, acetaminophen, sodium chloride (NaCl), nitrous oxide, gabapentin, thiopental, nafamostat (Table 1). Intervention techniques were pretreatment of study drugs before rocuronium administration, pretreatment of study drugs with venous occlusion (manual or tourniquet), and mixing study drugs with rocuronium. Eleven studies assessed pain on rocuronium injection, and 22 assessed withdrawal movements. Four studies assessed both pain and withdrawal response induced by rocuronium [16, 31, 36, 39]. Approximately 74 % of patients in the control group showed rocuronium-induced injection or withdrawal pain.

Opioids were the most commonly studied intervention of the pretreatment drugs: remifentanil (six studies), fentanyl (five), alfentanil (two), hydromorphone (one). Pretreatment with opioids reduced rocuronium-induced IPWM [RR (95 % CI) = 0.16 (0.09–0.29)] (Fig. 2). Lidocaine [0.47 (0.35–0.64)] (Fig. 3) and ketamine [0.41 (0.22–0.77)] pretreatment both reduced rocuronium-induced IPWM. Lidocaine was the most frequently used agent in conjunction with venous occlusion techniques and was effective in reducing rocuronium-induced IPWM [0.40 (0.32–0.49)] (Fig. 4). Opioid pretreatment with venous occlusion was the least effective [0.77 (0.61–0.96)] (Fig. 5). Mixing $NaHCO_3$ with rocuronium was the most effective method to decrease rocuronium-induced IPWM [0.15 (0.06–0.34)] (Fig. 6).

Bias was assessed for pretreatment with opioids (ten studies). Figure 7 shows results for pretreatment with

Table 1 Summary of drug interventions

	No. of studies	No. of patients	Relative risk (Mantel–Haenszel, random) (95 % CI)	Heterogeneity *P* value	References
Pretreatment					
Opioids	10	1049	0.16 (0.09–0.29)	<0.001	[5, 19, 22–28, 43]
Lidocaine	6	620	0.47 (0.35–0.64)	0.01	[26, 28, 30, 31, 36, 40]
Ketamine	3	407	0.41 (0.22–0.77)	<0.001	[31–33]
Magnesium sulfate	1	200	0.60 (0.35–1.01)	0.008	[35]
Dexmedetomidine	1	90	0.68 (0.31–1.50)	0.004	[34]
Esmolol	1	160	0.19 (0.03–1.16)	0.07	[36]
Ketorolac	1	50	0.33 (0.10–1.09)	NA	[28]
Pheniramine	1	120	0.58 (0.23–1.44)	NA	[38]
Nitrous oxide	1	160	0.24 (0.12–0.50)	0.25	[39]
Gabapentin	1	82	0.52 (0.30–0.90)	NA	[37]
Drugs with venous occlusion					
Lidocaine	9	662	0.40 (0.32–0.49)	0.20	[3, 12–18, 44]
Opioids	5	418	0.77 (0.61–0.96)	<0.001	[13, 15, 16, 18, 19]
Ondansetron	2	140	0.65 (0.46–0.93)	0.1	[12, 13]
Metoclopramide	1	44	0.43 (0.20–0.91)	0.71	[16]
Acetaminophen	1	79	0.47 (0.30–0.75)	NA	[14]
Ketamine	1	54	0.16 (0.04–0.59)	NA	[45]
Thiopental	1	80	0.30 (0.19–0.47)	NA	[20]
Dexmedetomidine	1	60	0.69 (0.50–0.96)	NA	[17]
Dexmedetomidine + lidocaine	1	90	0.53 (0.38–0.72)	0.49	[17]
Magnesium sulfate	1	100	0.33 (0.20–0.54)	NA	[15]
Sodium bicarbonate	1	100	0.44 (0.29–0.66)	NA	[15]
Nafamostat	1	90	0.35 (0.20–0.61)	NA	[21]
Admixture					
Sodium bicarbonate	4	300	0.15 (0.06–0.34)	0.01	[40–42, 46]
Lidocaine	2	190	0.61 (0.39–0.95)	0.002	[41, 46]
Sodium chloride	1	150	0.09 (0.00–19.61)	<0.001	[47]
Fentanyl	1	100	0.74 (0.59–0.94)	NA	[41]

NA not applicable

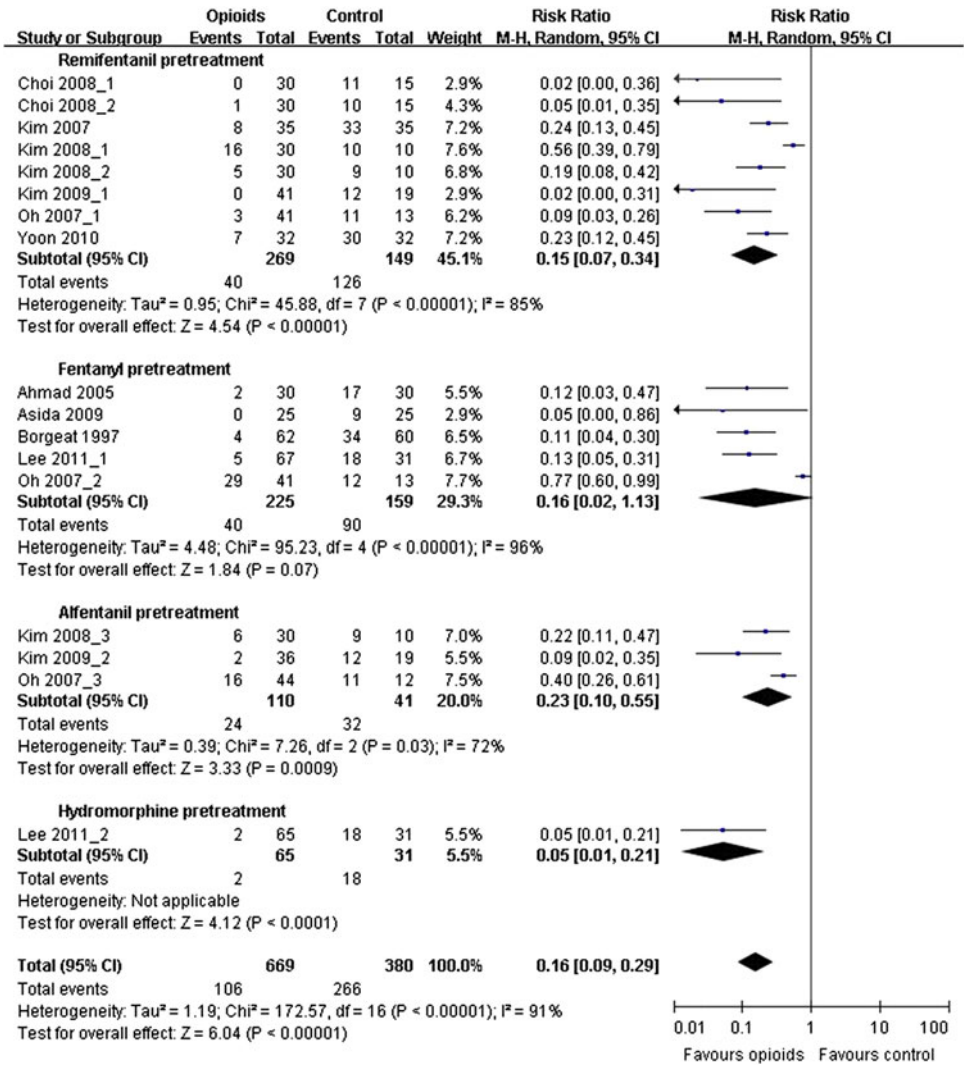

Fig. 2 Effect of pretreatment with opioids for rocuronium-induced injection pain or withdrawal

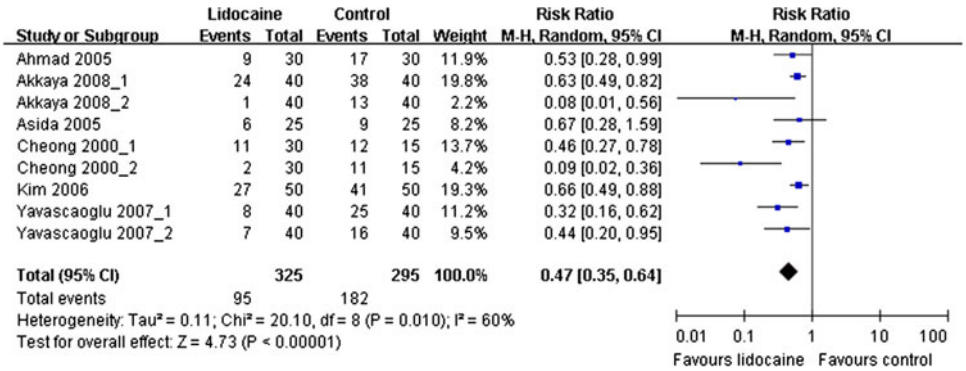

Fig. 3 Effect of pretreatment with lidocaine for rocuronium-induced injection pain or withdrawal

opioids with asymmetrical funnel plot and a Begg–Mazumdar Kendall's $\tau = -0.43$ ($P = 0.0075$), indicating the possibility of bias. Sensitivity analysis indicated that when studies with an Oxford score ≥ 4 only were included, meta-analysis results were not changed.

To rank interventions, indirect comparisons among effective interventions were performed using a network approach. Indirect treatment comparisons were carried out for six statistically significant interventions: pairwise (intervention vs. control); $NaHCO_3$ admixture; pretreatment with opioids, ketamine, and lidocaine; and lidocaine and opioids in conjunction with venous occlusion (Table 2). In a mixed-effects metaregression, the moderators were these six interventions. The RR of $NaHCO_3$

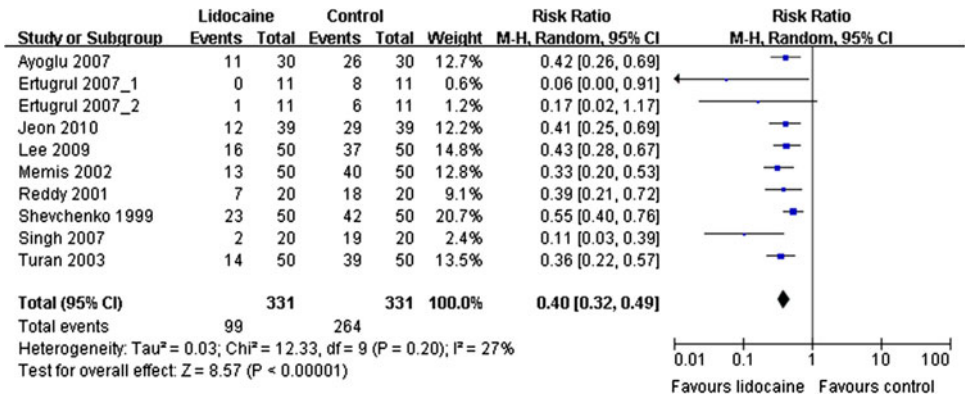

Fig. 4 Effect of lidocaine with venous occlusion for rocuronium-induced injection pain or withdrawal

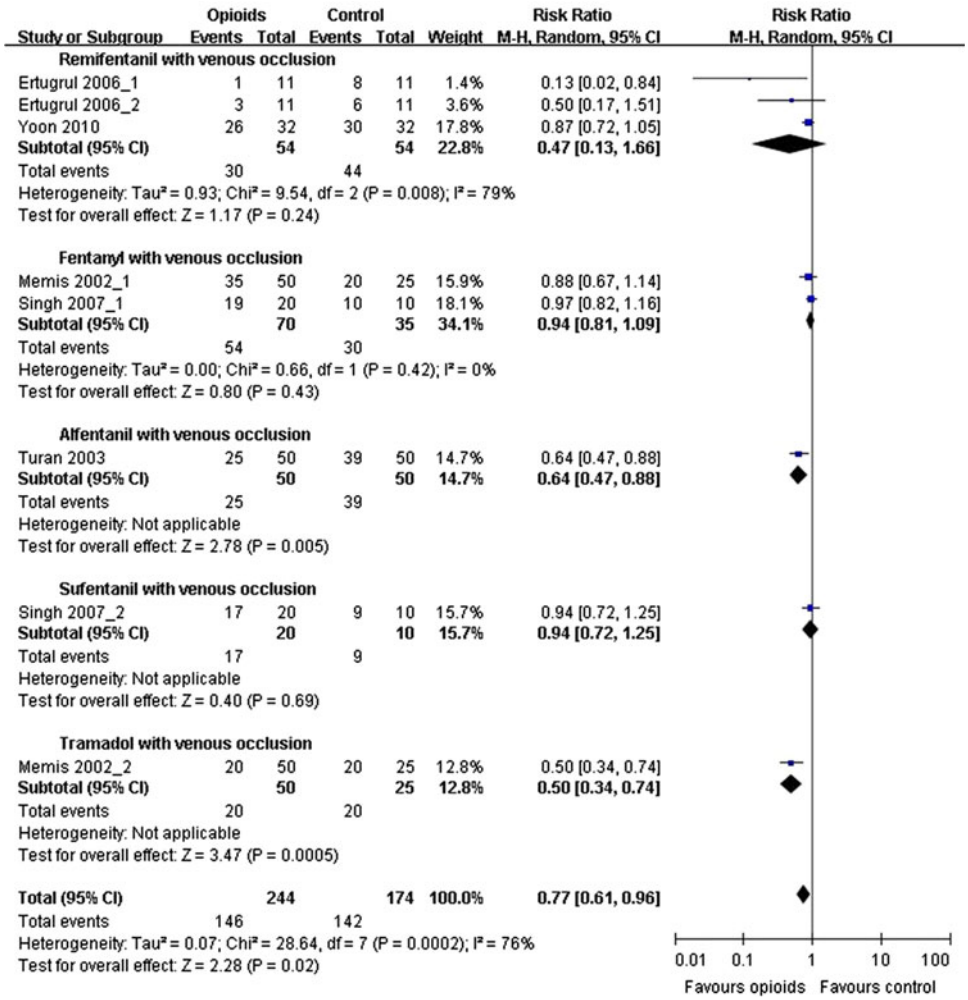

Fig. 5 Effect of opioids with venous occlusion for rocuronium-induced injection pain or withdrawal

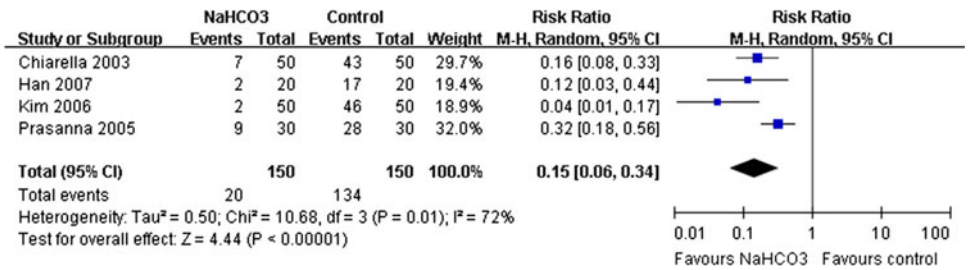

Fig. 6 Effect of sodium bicarbonate ($NaHCO_3$) admixture for rocuronium-induced injection pain or withdrawal

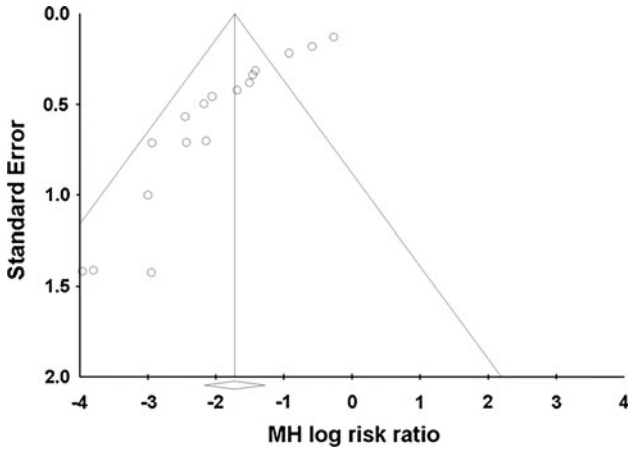

Fig. 7 Studies included in meta-analysis of pretreatment with opioids

admixture was lower compared with those of pretreatment with ketamine or lidocaine, and lidocaine or opioids with venous occlusion). Pretreatment of opioids also reduced IPWM better than the other four interventions. Indirect RRs ranged from 0.28 (opioids with venous occlusion) to 0.56 (lidocaine with venous occlusion). Pretreatment with opioids had a similar efficacy as $NaHCO_3$ admixture. RR reduction in IPWM had similar efficacy between three interventions (lidocaine with venous occlusion, pretreatment with ketamine, and lidocaine). Direct RRs varied between 0.41 and 0.50. Indirect RRs of five interventions ($NaHCO_3$ admixture; pretreatments with opioids, ketamine, and lidocaine; lidocaine with venous occlusion) were lower than those with opioids with venous occlusion.

Discussion

This meta-analysis demonstrated that $NaHCO_3$–rocuronium admixture and pretreatment with opioids has similar efficacy in terms of preventing rocuronium-induced IPWM. These pharmacological treatments were superior to the other four efficacious interventions of ketamine pretreatment, lidocaine pretreatment, lidocaine with venous occlusion, and opioid pretreatment with venous occlusion. Pretreatment with opioids was one of the most effective pharmacological treatments (RR = 0.16). Opioid injection without venous occlusion is more effective when proper onset time of each opioid is allowed for the drug to reach the effect site. Thus, fentanyl needs more time to be fully effective in reducing IPWM than remifentanil and alfentanil [22]. Pretreatment with opioids with venous occlusion before rocuronium injection could also reduce the risk of IPWM (RR = 0.77). However, this was the least-effective pharmacological intervention compared with the other five efficacious interventions (pretreatments with opioids, ketamine, and lidocaine; venous occlusion along with pretreatment with lidocaine and opioids). Regarding opioid interventions, pretreatment without venous occlusion is an effective and simple intervention. A $NaHCO_3$–rocuronium admixture is one of the most effective methods for rocuronium-induced IPWM (RR = 0.15). Pretreatment with lidocaine with or without venous occlusion is also effective (RR = 0.40 and 0.47, respectively).

When there are several interventions with similar efficacy, other considerations are necessary, such as simplicity, cost, and personal choice. Considering that opioids are

Table 2 Indirect comparisons between effective pharmacologic interventions

	Interventions vs. control by R (metaphor)	Sodium bicarbonate admixture	Opioid pretreatment	Lidocaine with venous occlusion	Ketamine pretreatment	Lidocaine pretreatment
Sodium bicarbonate admixture	0.15 (0.07, 0.33)*	1.00				
Opioid pretreatment	0.18 (0.11, 0.28)*	0.82 (0.31, 2.14)	1.00			
Lidocaine with venous occlusion	0.41 (0.34, 0.49)*	0.48 (0.30, 0.78)*	0.56 (0.32, 1.00)*	1.00		
Ketamine pretreatment	0.42 (0.25, 0.70)*	0.37 (0.15, 0.92)*	0.45 (0.21, 0.98)*	0.84 (0.53, 1.34)	1.00	
Lidocaine pretreatment	0.50 (0.39, 0.64)*	0.37 (0.20, 0.69)*	0.45 (0.24, 0.84)*	0.76 (0.57, 1.01)	0.94 (0.55, 1.63)	1.00
Opioids with venous occlusion	0.79 (0.66, 0.94)*	0.24 (0.14, 0.40)*	0.28 (0.16, 0.50)*	0.50 (0.39, 0.65)*	0.59 (0.37, 0.95)*	0.65 (0.48, 0.87)*

Values are relative risk (RR) (95 % confidence interval). Indirect comparison was performed by R package metafor using restricted maximum likelihood. Each intervention's RR against control was slightly different compared with direct comparisons

* $P < 0.05$

commonly used for balanced anesthesia and therefore in terms of simplicity of application, unless contraindicated, their routine use during induction seems logical, with a RR for reducing rocuronium-induced IPWM of about 84 %. Meanwhile, $NaHCO_3$ admixture might be impractical, because it adds additional procedural steps during anesthetic induction and makes pretreatment time consuming due to removal of air bubbles [29]. In addition, the admixture alters rocuronium pharmacology, which increases potency, speeds up onset time, and prolongs recovery compared with rocuronium alone [48].

This study has several limitations. One is that we excluded non-English articles. However, as language-limited articles are not reported to cause bias for estimating the effectiveness of different interventions [49], it is unlikely that the exclusion would alter our results. Concerning bias analysis, funnel plots and Begg–Mazumdar testing for pretreatment with opioids showed significant asymmetry. In general, positive results of the studies analyzed may be easier to report than negative ones, which means there is the risk of unpublished negative results. Therefore, pretreatment with opioids was efficacious in this meta-analysis, but their effects may be overestimated. In addition, some interventions that reached statistical significance (e.g., antiemetics, antihistamines, $MgSO_4$, etc.) cannot readily be deemed efficacious, as only a few trials investigated them. Further research is needed to elucidate the efficacy of these interventions and their underlying mechanisms.

In conclusion, this meta-analysis suggests that opioids, lidocaine, ketamine, and $NaHCO_3$ effectively alleviate rocuronium-induced IPWM. Considering efficacy and convenience, pretreatment with opioids without venous occlusion is recommended for preventing rocuronium-induced IPWM during anesthesia induction. Future studies should elucidate IPWM intensity score and nonpharmacological preventive methods.

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