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META-ANALYSIS

Pharmacological interventions for preventing rocuronium-induced pain responses and rocuronium-induced withdrawal responses: a systematic review and network meta-analysis

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Abstract

Study objective: Rocuronium is widely used during the induction of general anesthesia. However, it is associated with rocuronium-induced pain response, which can appear as a rocuronium-induced withdrawal response. The purpose of this study was to compare the effectiveness of pharmacological interventions in preventing rocuronium-induced pain response and rocuronium-induced withdrawal response using a network meta-analysis. **Design**: Systematic review and network meta-analysis (NMA) of RCTs. **Setting**: Pharmacological interventions to prevent rocuronium-induced pain response and rocuronium-induced pain response and rocuronium-induced withdrawal. **Data sources**: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar were systematically searched from its inception until Mar 2020. **Methods**: We searched multiple databases and extracted randomized controlled trials that compared two or more pharmacological interventions to prevent rocuronium-induced pain response and rocuronium-induced withdrawal response in adult patients who received rocuronium injections for general anesthesia. We conducted network meta-analysis and used surface under the cumulative ranking curve values and rankograms to present the hierarchy of the pharmacological interventions evaluated. **Results**: In total, 43 studies (5,291 patients) were included in this network meta-analysis and 31 pharmacological interventions were evaluated. The rankogram and cumulative ranking plot showed that oxycodone followed by a combination of lidocaine and sodium bicarbonate ($NaHCO_3$), esmolol, alfentanil, and rocuronium mixed with $NaHCO_3$ had the lowest frequency of rocuronium-induced withdrawal response. In terms of rocuronium-induced pain response, $NaHCO_3$ mixed with rocuronium showed the lowest frequency, followed by a combination of lidocaine and $NaHCO_3$, a combination of lidocaine and nitrous oxide, rocuronium mixed with lidocaine, and lidocaine. **Conclusions**: Lidocaine administration has been shown to reduce the incidence of rocuronium-induced pain response regardless of the method of injection or drug combination. The combination of lidocaine and $NaHCO_3$ or mixing $NaHCO_3$with rocuronium was effective at reducing rocuronium-induced withdrawal response. In particular, oxycodone was shown to be more effective than the other opioids evaluated and esmolol was also found to be effective at reducing rocuronium-induced withdrawal response.

Keywords

Network meta-analysis; Pain; Rocuronium; Withdrawal response

1. Introduction

Rocuronium bromide, an aminosteroidal non-depolarizing neuromuscular agent with a rapid onset of action and an intermediate duration, is widely used in rapid sequence intubation and the induction of general anesthesia [1–3]. However, it is often associated with injection pain, with an incidence of up to 80% [4, 5], and is reported to cause severe burning pain when injected intravenously prior to the loss of consciousness after the induction of anesthesia [6].

Although most patients do not complain of pain or recall any pain after recovery, rocuronium injection-induced pain at the injection site may cause a phenomenon called rocuronium-induced withdrawal response (RIWR) in the upper limbs of

TABLE 1. Characteristics of includes studies.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Abu-Halaweh SA	2013	N/S 5 mL	50	40.92 ± 13.20	27.48 ± 4.88 (BMI)	*P*	4 point scale (0-3)
		lidocaine 40 mg	50	40.6 ± 14.65	27.03 ± 4.33 (BMI)		
		remifentanil 1 mcg/kg	50	41.8 ± 16.55	26.92 ± 5.21 (BMI)		
		fentanyl 1 mcg/kg	50	46.4 ± 14.31	26.88 ± 5.48 (BMI)		
Ahmad N	2005	N/S 2 mL	30	41.7 ± 13.3	60.4 ± 13.3	W	4 point scale (1-4)
		lidocaine 40 mg	30	41.8 ± 11.3	61.3 ± 12.1		
		fentanyl 100 mcg	30	43.6 ± 11.7	58.0 ± 11.7		
Akcaboy ZN	2012	N/S 5 mL	40	40.5 ± 13.4	69.1 ± 14.7	*P*	4 point scale (0-3)
		lidocaine 0.5 mg/kg	40	42.2 ± 12.0	70.8 ± 14.3		
		ephedrine 70 mcg/kg	40	41.6 ± 8.8	73.2 ± 11.8		
An X	2017	N/S 5 mL	60	52 ± 10	63 ± 11	W	4 point scale (0-3)
		oxycodone (0.05 mg/kg)	60	53 ± 9	62 ± 10		
Aydin GB	2014	placebo PO	65	54.8 ± 14.1	74.7 ± 9.7	W	4 point scale (0-3)
		25 ng deketoprofen PO	73	51.1 ± 14.7	76.2 ± 8.9		
Ayoglu H	2007	N/S 3 mL	30	40.0 ± 13.2	72.3 ± 11.9	W	4 point scale (0-3)
		lidocaine 0.5 mg/kg	30	42.9 ± 13.5	69.4 ± 11.8		
		dexmedetomidine 0.25 mcg/kg	30	42.1 ± 12.4	71.1 ± 12.5		
		dexmedetomidine 0.25 mcg/kg + lido 0.25 mg/kg	30	37.1 ± 11.9	72.3 ± 11.8		
		dexmedetomidine 0.25 mcg/kg + lido 0.5 mg/kg	30	43.2 ± 12.9	71.2 ± 13.8		
Cakirgoz M	2018	placebo PO	50	30.8 ± 7.9	24.5 ± 2.4 (BMI)	W	4 point scale (0-3)
		gabapentin 1500 mg po	50	34.5 ± 10.7	25.9 ± 4.4 (BMI)		
Cheong KF	2000	N/S	30	34.9 (20-58)	66.8 ± 12.5	*P*	4 point sacle (0-3)
		lidocaine 10 mg	30	36.9 (18-62)	63.2 ± 15.2		
		lidocaine 30 mg	30	37.7 (20-55)	64.8 ± 10.5		
Han DW	2007	rocuronium 50 mg bolus	20	38.1 ± 10.7	52.3 ± 7.2	*P*	4 point scale (0-3)
		rocuronium 50 mg + N/S 3 mL	20	36.9 ± 7.4	56.6 ± 7.4		
		rocuronium 50mg + $NaHCO_3$	20	43.0 ± 8.3	56.3 ± 6.8		

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Joo J	2014	N/S	28	38.7 ± 12.5	63.6 ± 9.2	W	4 point scale (0-3)
		lidocaine 40 mg	28	37.6 ± 13.3	61.3 ± 13		
		dexmedetomidine 0.25 mcg/kg	27	40.6 ± 16.2	61.4 ± 11		
		dexmedetomidine 0.5 mcg/kg	27	42.5 ± 11.4	65.3 ± 11		
		dexmedetomidine 1 mcg/kg	27	41.7 ± 10.4	59.6 ± 14.4		
Kim E	2013	N/S + 100% O_2	50	38.32 ± 15.73	62.8 ± 11.1	W	4 point scale (0-3)
		lidocaine 0.5 mg/kg	50	35.52 ± 15.57	61.3 ± 13.3		
		67% N_2O/O_2	50	41.86 ± 15.67	63.9 ± 12.6		
		lidocaine 0.5 mg/kg + 67%N_2O/O_2	50	47.26 ± 13.97	63.2 ± 13.97	W	4 point scale (1-4)
Kim JH	2009	N/S	38	48.7 ± 16.2	64.4 ± 16.1		
		alfentanil 10 mcg/kg	36	45.0 ± 12.7	66.9 ± 12.7		
		remifentanil 1 mcg/kg	41	42.9 ± 14.2	64.3 ± 12.8		
Kim KS	2006	N/S	50	39.2 (20-60)	60.7 ± 15.1	W	4 point scale (0-3)
		N/S + intravenous occlusion	50	41.9 (21-63)	63.3 ± 16.5		
		lidocaine 1 mg/kg	50	36.7 (19-62)	67.6 ± 18.3		
		lidocaine 1 mg/kg + intravenous occlusion	50	34.9 (19-60)	62.4 ± 17.5		
Kim YH	2010	5% DW 1.5 mL	45	43.5 ± 10.6	63.0 ± 8.4	W	4 point scale (1-4)
		5% DW + 1.5 mg nafamostat mesilate (1.5 ml)	45	40.3 ± 11.4	65.7 ± 6.1		
Lee HJ	2009	N/S 2 mL	58	40.7 ± 13.0	62.0 ± 10.7	W	4 point scale (1-4)
		peniramine 2 mL	62	42.5 ± 11.9	63.5 ± 13.7		
Lee YC	2009	N/S 0.1 ml/kg	50	41.0 ± 13.3	61.2 ± 9.9	W	4 point scale (0-3)
		lidocaine 0.1 mg/kg	50	41.7 ± 11.3	63.7 ± 10.7		
		N/S + rocuronium for 1 sec	50	43.4 ± 12.0	59.8 ± 9.6		
Memis D	2002	N/S 3 mL	50	37.3 ± 15.1	77.1 ± 13.1	*P*	4 point scale (0-3)
		ondansetron 4 mg	50	40.5 ± 15.4	75.9 ± 10.3		
		lidocaine 30 mg	50	38.6 ± 17.3	76.1 ± 9.1		
		tramadol 50 mg	50	42.2 ± 14.1	79.1 ± 10.1		
		fentanyl 100 mcg	50	41.6 ± 8.82	75.2 ± 8.8		
Park JT	2005	N/S 2 mL	45	41 ± 15	61.2 ± 9.4	W	4 point scale (0-3)
		thiopental 50 mg	45	43 ± 15	61.3 ± 9.1		

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Park KB	2017	N/S	40	46.08 ± 13.30	63.92 ± 11.91	W	4 point scale (0-3)
		lidocaine 20 mg	40	45.72 ± 14.08	61.8 ± 10.48		
		palnonosetron 0.075 mg	40	46.33 ± 10.96	61.45 ± 11.9		
Singh M	2007	N/S 5 mL	20	40.7 ± 14.2	55.5 ± 10.9	*P*	5 point scale (0-4)
		lidocaine 1 mg/kg	20	38.4 ± 11.4	61.3 ± 11.9		
		fentanyl 1 mcg/kg	20	40.7 ± 11.4	60.0 ± 11.1		
		sufentanil 0.5 mcg/kg	20	34.4 ± 14.6	52.4 ± 13.7		
Sivakumar S	1999	100% O_2+ lidocaine 40 mg	40	36.78 ± 12.972	54.70 ± 9.196	W, *P*	4 point scale (0-3)
		50% N_2O + lidocaine 40 mg	40	35.12 ± 11.371	51.72 ± 7.432		
Tuncaki B	2004	rocuronium 0.06 mg/kg (10 mg/ml)	50	46.7 ± 18.3	25.3 ± 3.6 (BMI)	*P*	5 point scale (0-4)
		rocuronium 0.06 mg/kg + N/S	100				
Turan A	2003	N/S 3 mL	50	39.4 ± 13.2	80 ± 10.1	*P*	4 point scale (0-3)
		$MgSO_4$	50	42.2 ± 15.2	76.4 ± 12.1		
		lidocaine 30 mg	50	40.3 ± 14.5	74.1 ± 13.2		
		$NaHCO_3$ 2 mL	50	43.4 ± 10.1	75.5 ± 9.5		
		alfentanil 1000 mcg	50	38.3 ± 11.6	77.6 ± 10.7		
Uzun S	2014	N/S 5 mL	50	41.7 ± 13.3	71 ± 12.2	*P*	4 point scale (0-3)
		lidocaine 40 mg	50	41.8 ± 13.9	73.3 ± 14.5		
		paracetamol 50 mg	50	42.7 ± 11.9	68.7 ± 14.9		
Yavascaoglu B	2007	N/S 5 mL	40	42.9 ± 19.2	69.4 ± 12.3	W, *P*	W: 4 point scale (1-4)
		lidocaine 0.5 mg/kg	40	45.9 ± 11.7	71.1 ± 15.2		*P*: 4 point scale (0-3)
		esmolol 0.5 mg/kg	40	43.6 ± 15.5	69.3 ± 14.6		
26. Zhang Y	2012	N/S	40	45.18 ± 12.44	67.80 ± 8.46	*P*	4 point scale (0-3)
		lidocaine 40 mg	40	41.28 ± 14.12	68.38 ± 4.29		
		parecoxib 20 mg	40	45.24 ± 14.36	70.78 ± 4.12		
		parecoxib 40 mg	40	43.54 ± 15.01	69.07 ± 5.0		
Reddy MS	2001	N/S 5 mL	20	33.5 ± 13.5	63.5 ± 13.0	*P*	4 point scale (0-3)
		lidocaine 50 mg	20	41.4 ± 18.3	62.3 ± 10.2		
		ondansetron 4 mg	20	39.8 ± 14.2	64.0 ± 13.2		

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Shin YH	2011	N/S 5 ml	50	41.7 ± 11.5	65.0 ± 13.3	W	4 point scale (0-3)
		$MgSO_4$ 5 mg/kg	50	41.8 ± 12.4	64.9 ± 13.3		
		$MgSO_4$ 10 mg/kg	50	39.8 ± 13.4	65.9 ± 12.1		
		$MgSO_4$ 20 mg/kg	50	40.9 ± 14.9	63.4 ± 10.4		
Sharma S	2010	100% O_2	40	33.8 ± 11.0	57.6 ± 12.2	W, *P*	W: 2 point scale (Yes, No)
		50% N_2O	40	33.9 ± 10.4	57.8 ± 10.7		*P*: 4 point scale (0-3)
Akkaya T	2008	N/S 2 ml	40	38.5 ± 9.5	72.9 ± 11.1	W, *P*	W: 4 point scale (0-3)
		lidocaine 30 mg	40	37.7 ± 10.0	72.5 ± 10.8		*P*: 5 point scale (0-4)
		ketamine 0.5 mg/kg	40	37.0 ± 12.1	76.7 ± 11.2		
Han DW	2003	rocuronium	20	38.1 ± 10.7	52.3 ± 7.2	*P*	4 point scale (0-3)
		Rocuronium + N/S 3 ml	20	36.9 ± 7.4	56.6 ± 7.4		
		Rocuronium + $NaHCO_3$ 3 ml	20	43.0 ± 8.3	56.3 ± 6.8		
Chang HW	2005	N/S 3 ml	20	37.8 ± 11.3	64.0 ± 12.2	*P*	4 point scale (0-3)
		ketamine 0.1 mg/kg	20	35.6 ± 12.2	61.9 ± 12.9		
		ketamine 0.2 mg/kg	20	37.2 ± 12.7	59.8 ± 9.2		
		ketamine 0.3 mg/kg	20	37.7 ± 11.4	59.7 ± 9.7		
Jung SM	2005	N/S 5 ml + rocuronium	30	39.4 ± 12.8	61.6 ± 10.7	W, *P*	W: 4 point scale (0-3)
		2% lidocaine 5 ml + rocuronium	30	38.2 ± 14.2	63.7 ± 11.0		*P*: 5 point scale (0-4)
		$NaHCO_3$ 5 ml + rocuronium	30	37.9 ± 13.8	63.9 ± 12.8		
		lidocaine 2.5 ml + $NaHCO_3$ 2.5 ml+ rocuronium	30	33.4 ± 13.4	67.5 ± 9.3		
Choi YJ	2012	N/S	31	39.4 ± 12.4	63.6 ± 11.8	W	4 point scale (0-3)
		remifentanil 1 mcg/kg	31	42.7 ± 9.8	61.9 ± 12.0		
		lidocaine 1.5 mg/kg	32	43.9 ± 9.2	62.2 ± 9.3		
Borgeat A	1997	N/S	60	39 ± 15	73 ± 17	W	4 point scale (0-3)
		fentanyl 2 mcg/kg	62	42 ± 17	72 ± 18		
Cho KR	2014	N/S 1.5 ml	40	49.0 ± 14.1	60.0 ± 9.1	W	4 point scale (0-3)
		palnonosetron 0.075 mg	40	49.4 ± 15.2	61.7 ± 11.5		
Yoon JS	2011	placebo po	40	58.9 ± 8.3	64.9 ± 9.9	W	4 point scale (0-3)
		ganapentin 600 mg	42	60.0 ± 5.2	63.8 ± 8.2		

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Choi JH	2005	N/S 2 ml	20	40.3 ± 12.3	59.4 ± 9.1	P	3 point scale (0-2)
		ketamine 0.2 mg/kg	20	41.2 ± 9.8	55.8 ± 8.5		
		ketamine 0.5 mg/kg	20	39.0 ± 11.4	56.7 ± 10.2		
Byun JH	2005	N/S 2 ml	30	29.9 ± 9.5	57.0 ± 8.8	*P*	4 point scale (0-3)
		lidocaine 40 mg	30	34.9 ± 9.3	55.9 ± 9.3		
		0.5% metoclopramide 2 ml	30	31.4 ± 12.4	56.9 ± 9.9		
Choi HG	2006	rocuronium	50	40.3 ± 10.8	64.2 ± 9.1	W	4 point scale (0-3)
		rocuronium + SOBI 1 ml	50	44.9 ± 8.8	58.8 ± 8.0		
		rocuronium + SOBI 2.5 ml	50	46.2 ± 10.7	61.4 ± 10.1		
		rocuronium + SOBI 5 ml	50	43.2 ± 10.4	61.3 ± 9.2		
		rocuronium + SOBI 7 ml	50	42.9 ± 10.6	63.1 ± 11.6		
Jeon YH	2013	N/S	35	46.8 ± 11.5	62.3 ± 9.3	W	4 point scale (1-4)
		lidocaine 20 mg	35	48.5 ± 13.1	59.7 ± 8.3		
		ketorolac 10 mg	35	46.2 ± 16.3	61.9 ± 9.4		
		lidocaine 20 mg + ketorolac 10 mg	35	47.2 ± 13.8	62.1 ± 10.6		
Wee SY	2004	N/S 3 ml	30	34.8 ± 13.5	60.0 ± 10.0	*P*	4 point scale (0-3)
		lidocaine 20 mg	30	33.1 ± 11.4	58.7 ± 11.3		
		lidocaine 40 mg	30	38.1 ± 10.9	60.1 ± 7.5		
		lidocaine 60 mg	30	38.1 ± 10.9	61.4 ± 9.8		
Jung KT	2014	N/S	30	43 ± 12	63 ± 12	W	4 point scale (0-3)
		lidocaine 40 g	30	41 ± 14	63 ± 12		
		ketamine 0.5 g/kg	30	42 ± 10	65 ± 10		
		remifentanil 1 cg/kg	30	46 ± 14	60 ± 13		
Lee SK	2004	N/S 3 l	30	36.6 ± 9.5	62.6 ± 11.5	*P*	4 point scale (0-3)
		lidocaine 30 g	30	37.3 ± 8.9	61.4 ± 10.5		
		lidocaine 50 g	30	39.2 ± 12.0	64.2 ± 14.0		
		fentanyl 100 mcg	30	41.5 ± 11.5	66.6 ± 12.1		
		ondansetron 4 mg	30	39.3 ± 9.7	63.7 ± 9.8		

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Ki HS	2005	N/S 4 ml	20	41.6 ± 9.7	57.3 ± 8.8	W, *P*	W: 4 point scale (1-4)
		ondansetron 4 mg	20	41.5 ± 9.8	57.5 ± 7.5		*P*: 4 point scale (0-3)
		ondansetron 6 mg	20	41.2 ± 6.7	56.9 ± 8.3		
		ondansetron 8 mg	20	40.6 ± 7.8	57.0 ± 8.2		
Ikram M	2008	N/S 3 ml	60	□□.	□□.	W	4 point scale (0-3)
		lidocaine 30 mg	60				
Hwang SH	2003	N/S 2 ml	50	45.6 ± 13.9	59.9 ± 11.2	*P*	4 point scale (0-3)
		lidocaine 10 mg	50	46.1 ± 12.7	61.1 ± 9.7		
		lidocaine 20 mg	50	47.3 ± 11.7	61.8 ± 9.1		
		lidocaine 30 mg	50	44.1 ± 12.8	62.1 ± 9.4		
		lidocaine 40 mg	50	47.8 ± 13.3	61.9 ± 10.9		
Park SE	2008	N/S 5 ml	60	37.5 ± 10.3	60.5 ± 8.8	W	4 point scale (0-3)
		lidocaine 1 mg/kg	60	41.4 ± 9.3	60.5 ± 8.5		
		alfentanil 10 mcg/kg	60	40.7 ± 9.6	63.9 ± 9.6		
Cho HY	2007	N/S 0.1 ml/kg	20	37.8 ± 11.0	64.1 ± 8.2	W	4 point scale (0-3)
		1% lidocaine 0.5 mg/kg	20	39.1 ± 9.8	64.4 ± 10.5		
		1% lidocaine 1 mg/kg	20	40.3 ± 11.0	64.0 ± 7.6		
		fentanyl 1 mcg/kg	20	39.1 ± 9.5	63.8 ± 8.4		
Ates G	2014	N/S 5 ml	60	35.58 ± 11.92	74.95 ± 14.99	*P*	4 point scale (0-3)
		lidocaine 40 mg	60	39.27 ± 11.81	76.46 ± 14.72		
		paracetamol 50 mg	60	36.45 ± 12.94	70.93 ± 15.82		
Binarani M	2017	N/S 5 ml	45	38.49 ± 13.47	53.47 ± 8.17	W, *P*	W: 4 point scale (1-4)
		lidocaine 40 mg	45	35.98 ± 12.26	55.64 ± 11.02		*P*: 4 point scale (0-3)
		paracetamol 50 mg	45	38.07 ± 13.19	56.38 ± 10.29		
Pandey Amitesh	2019	100% O_2	40	39.00 ± 13.55	53.800 ± 1.02	W, *P*	W: 2 point scale (Yes, No)
		50% N_2O	40	35.85 ± 13.82	51.55 ± 9.083		*P*: 4 point scale (0-3)

TABLE 1. Continued.

First Author	Year	Study drugs	Number of patiens	Age	Weight	RIPS or RIWS	Grading system
Eun SS	2005	N/S 4 ml	30	34.8 ± 13.5	60.0 ± 10.0	*P*	4 point scale (1-4)
		lidocaine 60 mg	30	38.1 ± 10.9	60.1 ± 7.5		
		ondansetron 8 mg	30	33.1 ± 11.4	58.7 ± 11.3		
		tramadol 50 mg	30	38.1 ± 10.9	61.4 ± 9.8		
Honca M	2013	lidocaine 30 mg	50	40.1 ± 11.4	161.3 ± 5.7	*P*	4 point scale (0-3)
		tramadol 50 mg	50	42.3 ± 11.5	160.7 ± 4.9		
		sufentanil 10 mcg	50	40.1 ± 11.8	161.1 ± 5.6		
		meperidine 40 mg	50	38 ± 11.4	160.2 ± 6.6		
Goo EK	2009	N/S + rocuronium (5 : 1)	70	43.0 ± 15.6	63.3 ± 11.1	*P*	3 point scale (0-2)
		$NaHCO_3$ + rocuronium (5 : 1)	70	44.5 ± 16.5	62.3 ± 11.1		
Boota M	2017	lidocaine 20 mg	45	33.48 ± 6.75		W	
		lidocaine 20 mg + ketorolac 10 mg	45	34.55 ± 6.17			
Jung KT	2018	N/S 102 ml 100 ml/h	38	42.6 ± 13.3	66.6 ± 12.9	W	4 point scale (0-3)
		N/S nefopam 2 mg 100 ml/h	38	41.5 ± 12.1	62.9 ± 10.7		
Jeon YH	2010	N/S 5 ml	39	45.4 ± 11.1	61.9 ± 9.7	W	4 point scale (1-4)
		lidocaine 40 mg	39	45.9 ± 14.2	61.2 ± 8.8		
		paracetamol 50 mg	40	50.1 ± 10.6	62.0 ± 8.3		
Lee JI	2009	N/S	50	47.0 ± 13.3	64.4 ± 11.1	W	4 point scale (1-4)
		lidocaine 1 mg/kg	51	43.5 ± 13.3	65.0 ± 11.9		
		rocuronium 0.06 mg/kg 2 minutes before second large dose of rocuronium	50	46.5 ± 12.1	63.4 ± 11.7		
Kim YH	2007	rocuronium bolus	21	47.2 ± 12.0	59.1 ± 7.3	W	4 point scale (1-4)
		rocuronium 5 mg/ml	21	49.0 ± 14.0	57.6 ± 7.4		
		rocuronium 3.3 mg/ml	21	41.5 ± 14.6	59.7 ± 6.8		
Kim YS	2007	rocuronium bolus	40	39.4 ± 14.4	57.6 ± 7.4	W	4 point scale (0-3)
		rocuronium 2 mg/ml	40	43.7 ± 13.9	59.7 ± 6.8		

BMI; body mass index, D/W; distilled water, N/S; normal saline, P; rocuronium –induced pain response, PO; per OS, W; rocuroium-inducec withdrawal response.

TABLE 2. Risk of bias assessment.

First Author	Year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Abu-Halaweh SA	2013	Low	Low	Low	Low	Low	Low
Ahmad N	2005	Low	Low	Low	Some concern	Low	Some concern
Akcaboy ZN	2012	Low	Low	Low	Low	Low	Low
An X	2017	Some concern	Low	Low	Low	Low	Some concern
Aydin GB	2014	Some concern	Low	Low	Low	Low	Some concern
Ayoglu H	2007	Some concern	Low	Low	Low	Low	Some concern
Cakirgoz M	2018	Some concern	Low	Low	Low	Low	Some concern
Cheong KF	2000	Low	Some concern	Low	Low	Low	Some concern
Han DW	2007	Some concern	Low	Low	Some concern	Low	High
Joo J	2014	Some concern	Low	Low	Low	Low	Some concern
Kim E	2013	Some concern	Low	Low	Low	Low	Some concern
Kim JH	2009	Some concern	Low	Low	Low	Low	Some concern
Kim KS	2006	Low	Low	Low	Low	Low	Low
Kim YH	2010	Some concern	Low	Low	Low	Low	Some concern
Lee HJ	2009	Low	Some concern	Low	Some concern	Low	High
Lee YC	2009	Low	Low	Low	Low	Low	Low
Memis D	2002	Some concern	Low	Low	Some concern	Low	High
Park JT	2005	Some concern	Some concern	Low	Some concern	Low	High
Park KB	2017	Low	Low	Low	Low	Low	Low
Singh M	2007	High	Low	Low	Low	Low	High
Sivakumar S	1999	Low	Low	Low	Low	Low	Low
Tuncaki B	2004	Low	Low	Low	Low	Low	Low
Turan A	2003	Some concern	Some concern	Low	Some concern	Low	High
Uzun S	2014	Low	Low	Low	Low	Low	Low
Yavascaoglu B	2007	Some concern	Low	Low	Low	Low	Some concern
Zhang Y	2012	Some concern	Low	Low	Low	Low	Some concern
Reddy MS	2001	Low	Low	Low	Low	Low	Low
Shin YH	2011	Low	Some concern	Low	Low	Low	Some concern
Sharma S	2010	Low	Low	Low	Low	Low	Low
Akkaya T	2008	Some concern	Low	Low	Low	Low	Some concern

TABLE 2. Continued

First Author	Year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Han DW	2003	Some concern	Some concern	Low	Some concern	Low	High
Chang HW	2005	Low	Low	Low	Low	Low	Low
Jung SM	2005	Low	Low	Low	Some concern	Low	Some concern
Choi YJ	2012	Low	Low	Low	Low	Low	Low
Borgeat A	1997	Low	Low	Low	Low	Low	Low
Cho KR	2014	Low	Low	Low	Low	Low	
Yoon JS	2011	Some concern	Some concern	Low	Some concern	Low	High
Choi JH	2005	Some concern	Some concern	Low	Some concern	Low	High
Byun JH	2005	Some concern	Some concern	Low	Some concern	Low	High
Choi HG	2006	Some concern	Some concern	Low	Some concern	Low	High
Jeon YH	2013	Low	Low	Low	Low	Low	Low
Wee SY	2004	Some concern	Some concern	Low	Low	Low	High
Jung KT	2014	Low	Low	Low	Low	Low	Low
Lee SK	2004	Some concern	Some concern	Low	Some concern	Low	High
Ki HS	2005	Low	Low	Low	Low	Low	Low
Ikram M	2008	Some concern	Low	Low	Low	Low	Some concern
Hwang SH	2003	Low	Low	Low	Low	Low	Low
Park SE	2008	Some concern	Some concern	Low	Low	Low	High
Cho HY	2007	Low	Low	Low	Low	Low	Low
Ates G	2014	Low	Low	Low	Low	Low	Low
Binarani M	2017	Low	Low	Low	Low	Low	Low
Pandey Amitesh	2019	Low	Low	Low	Low	Low	Low
Eun SS	2005	Some concern	Some concern	Low	Some concern	Low	High
Honca M	2013	Low	Low	Low	Low	Low	Low
Goo EK	2009	Low	Low	Low	Low	Low	Low
Boota M	2017	Low	Low	Low	Low	Low	Low
Jung KT	2018	Low	Low	Low	Low	Low	Low
Jeon YH	2010	Low	Low	Low	Low	Low	Low
Lee JI	2009	Low	Low	Low	Low	Low	Low
Kim YH	2007	Low	Low	Low	Low	Low	Low
Kim YS	2007	Low	Low	Low	Low	Low	Low

TABLE 3. The GRADE evidence quality for each outcome.

Outcomes	Number of studies	Quality assessment					Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
RIWR	**39**	serious	not serious	not serious	not serious	not serious	⊕⊕⊕◯ Moderate
RIPR	**30**	serious	not serious	not serious	not serious	not serious	⊕⊕⊕◯ Moderate

RIWR; Rocuronium Induced Withdrawal Response, RIPR; Rocuronium Induced Pain.

patients during the induction of general anesthesia [7]. This may increase the risk of venous catheter displacement, difficulties with intravenous drug injection, pulmonary aspiration, reflux of gastric contents, and the patient falling out of bed [8]. Additionally, pain and emotional distress during the induction of anesthesia may lead to bronchospasm, asthma, and myocardial ischemia attacks [9].

Therefore, various strategies to prevent the rocuronium-induced pain response (RIPR) and RIWR such as the use of lidocaine [4, 10–22], opioids [4, 14, 23], β-blockers [17], antihistamines [24], nitrous oxide (N_2O) [12, 25], magnesium sulfate ($MgSO_4$) [26], ketamine [20], and sodium bicarbonate ($NaHCO_3$) [27], as well as the dilution of rocuronium with normal saline [5] have been attempted and suggested by anesthesiologists.

Although many studies have intensively investigated and compared the effectiveness and efficacy of various strategies at preventing RIPR and RIWR, their findings were diverse. There have been several meta-analyses [3, 28, 29] that integrated the results from various studies. However, each study was limited to pair-wise meta-analysis and examined only two or three pharmacological interventions. No previous network meta-analysis (NMA) has yet compared the effectiveness and efficacy of all available pharmacological interventions. Further, these meta-analyses included old studies conducted prior to 2014. Recently, newer pharmacological interventions and methodologies to prevent RIPR and RIWR have been developed and proposed and large-scale and high-quality studies have been published.

NMA complements traditional pair-wise meta-analysis by combining direct and indirect comparisons of treatments. It also provides an objective ranking of various treatments based on the corresponding surface under the cumulative ranking curve (SUCRA) [30]. Therefore, we reviewed all articles that investigated the effects of pharmacological interventions employed to prevent RIPR and RIWR and performed an NMA to compare and quantify the rank order of effectiveness for pharmacological interventions in preventing RIPR and RIWR during general anesthesia.

2. Methods

2.1 Protocol and registration

We developed the protocol for this systematic review and NMA according to the preferred reporting requirements for systematic review and meta-analysis protocol (PRISMA-P) statement [31]. We registered the protocol in the PROSPERO network (registration number: CRD42019145893; www.crd.york.ac.uk/prospero) on November 6, 2019.

This systematic review and NMA of pharmacological interventions for preventing RIPR and RIWR was performed in accordance with the protocol recommended by the Cochrane Collaboration [32] and was reported according to the PRISMA extension for NMA guidelines [33].

2.2 Eligibility criteria

2.2.1 Inclusion criteria

We only included randomized controlled trials (RCTs) that compared two or more pharmacological interventions employed to prevent RIPR and RIWR.

The PICO-SD information was as follows:

1. Patients (P): all patients that received rocuronium injection under general anesthesia.

2. Intervention (I): pharmacological interventions to prevent RIPR and RIWR, which may be applied in various ways (intravenous bolus, intravenous continuous infusion, a mixture with other pharmacological agents, or inhalational).

3. Comparison (C): other pharmacological interventions, placebo, or no treatment.

4. Outcome measurements (O): the outcomes are the incidence of RIPR and RIWR.

5. Study Design (SD): RCTs.

2.2.2 Exclusion criteria

1. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other irrelevant studies.

2. Studies that failed to report the outcomes of interest.

There were neither language limitations nor date restrictions in our study.

2.3 Information sources and search strategy

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar

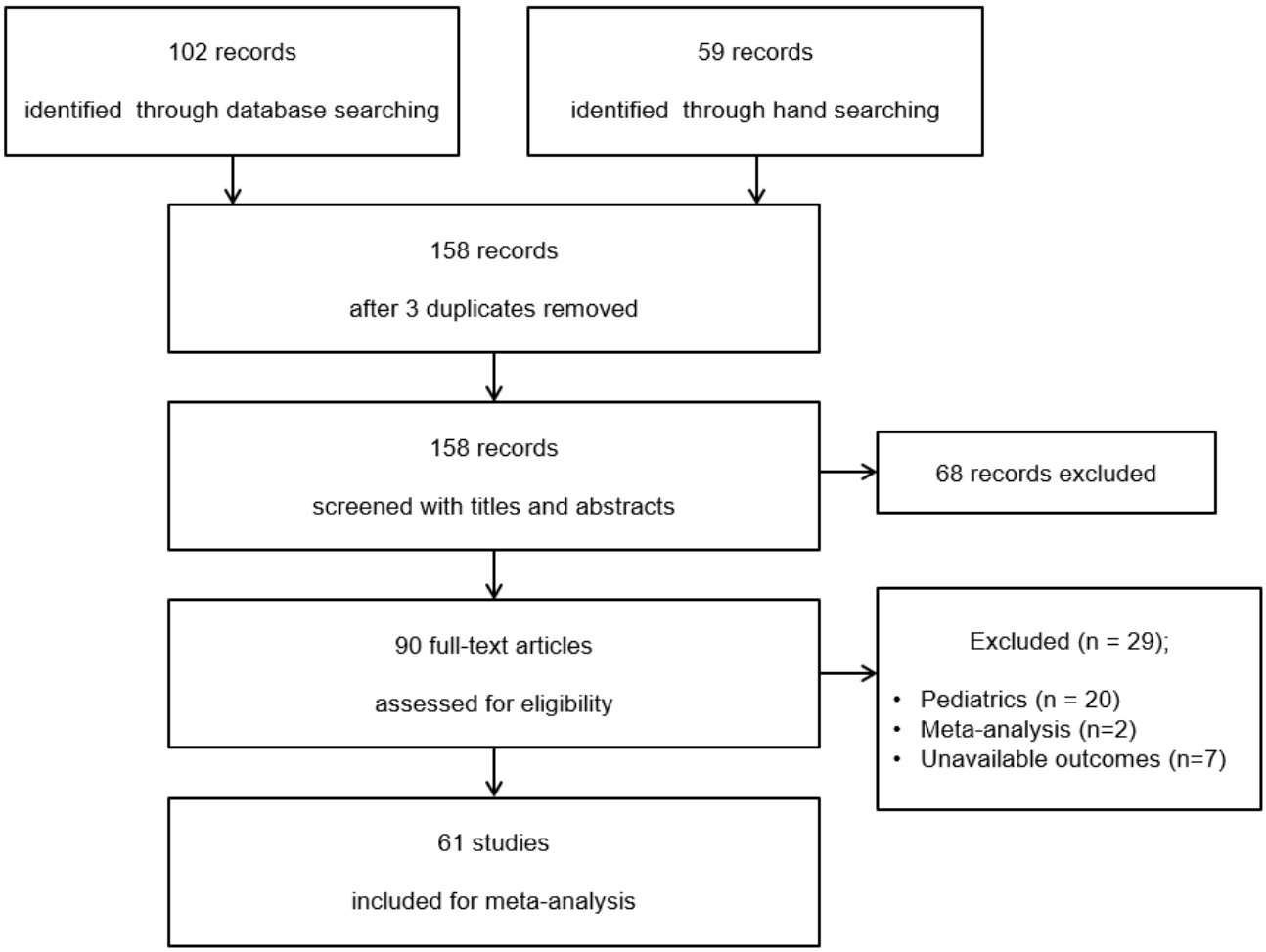

FIGURE 1. PRISMA flowchart of included and excluded trials.

using search terms related to pharmacological interventions for the prevention of RIPR and RIWR from inception to Mar 2020.

The search terms used in MEDLINE and EMBASE are presented in the Supplementary material. Reference lists were imported into Endnote software 8.1 (Thompson Reuters, CA, USA) and duplicate articles were removed. Additional but relevant articles were identified by scanning the reference lists of articles obtained from the original search.

2.4 Study selection

The titles and abstracts identified through the search strategy described above were reviewed independently by two investigators (SKP and GJC). To minimize data duplication due to multiple reporting, papers from the same authors, organization, or country were compared. Articles that met the inclusion criteria were assessed separately by two investigators (SKP and GJC) and any disagreements were resolved through discussion. In cases where agreement could not be reached, disputes were resolved with the help of a third investigator (HK).

2.5 Data extraction

Using a standardized extraction form, the following data were extracted independently by two investigators (SKP and YJC): 1) title, 2) name of first author, 3) name of journal, 4) year of publication, 5) study design, 6) type of pharmacological intervention, 7) dose of pharmacological agents, 8) country, 9) risk of bias, 10) inclusion criteria, 11) exclusion criteria, 12) age, 13) number of subjects, 14) incidence of RIPR, and 15) incidence of RIWR.

If the provided information was inadequate or missing, attempts were made to contact the study authors and additional information was requested. If unsuccessful, missing information was calculated from the available data if possible or extracted from figures using the open source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net).

2.6 Risk of bias assessment

The quality of the studies was independently assessed by two of the study's authors (SKP and HK) using the Revised Cochrane risk of bias tool for randomized tria (RoB 2.0). Risk of bias was assessed in the following domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of the reported results. Based on the results of the risk of bias assessment, a formal overall risk of bias rating was assigned to each study as

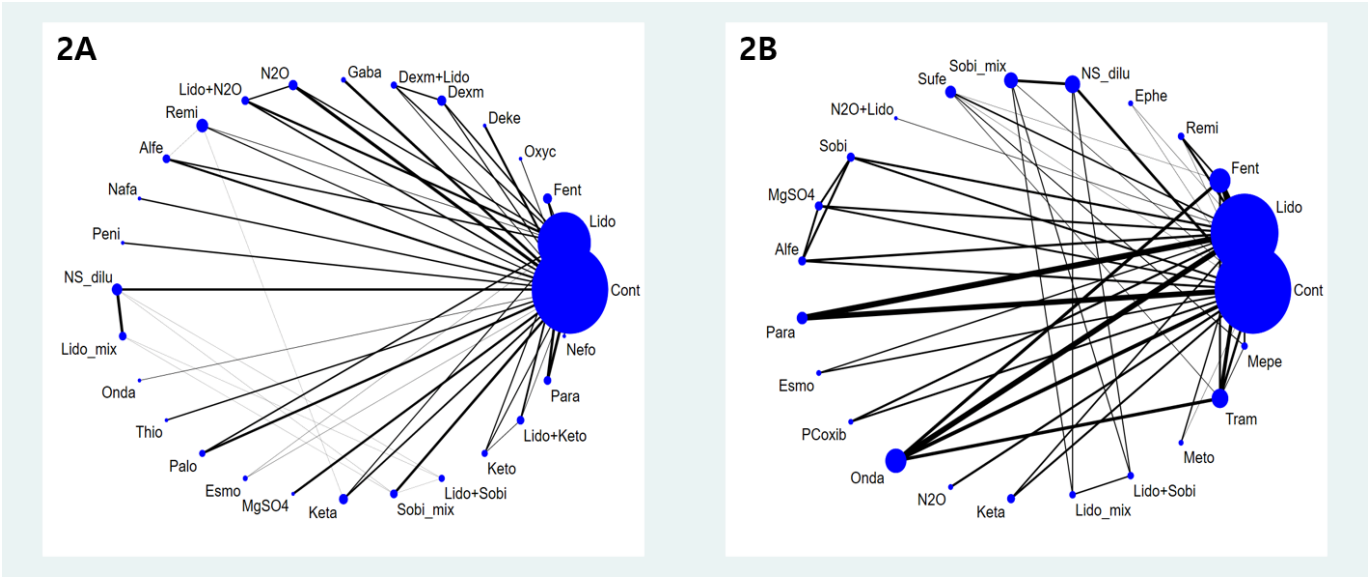

FIGURE 2. Network plot of included studies comparing different pharmacological strategies. The nodes show a comparison of pharmacological regimens to prevent rocuronium induced pain responses and rocuronium induced withdrawal responses, and the edges show the available direct comparisons among the pharmacological regimens. The nodes and edges are weighed on the basis of the number of included patients and inverse of standard error of effect. A) rocuronium induced withdrawal response, B) rocuronium induced pain response.

Alfe; alfentanil, Deke; deketoprofen, Dexm; dexmedetomidine, Dexm+Lido; combination of dexmedetomidine and lidocaine, Ephe; ephedrine Esmo; esmolol, Fent; fentanyl, Gaba; gabapentin, Keta ; ketamine, Keto; ketorolac, Lido; lidocaine, Lido_mix; mixed with lidocaine, Lido+Keto; combination of lidocaine and ketorolac, Lido+Sobi ; combination of lidocaine and $NaHCO_3$, Mepe; meperidine, Meto; metoclopramide, Nafa; nafamostat mesilate, N_2O+Lido; combination of N_2O and lidocaine, NS_dilu; normal saline dilution, Onda; ondansetron, Oxyc; oxycodone, Palo; palonosetron, Para; paracetamol, PCoxib; parecoxib, Peni; peniramine, Remi; remifentani, Sobi; $NaHCO_3$, Sufe; sufentanil, Sobi_mix; mixed with $NaHCO_3$, Tram; tramadol, Thio; thiopental.

follows: “low risk of bias”, “some concern”, or “high risk of bias” [34].

2.7 Statistical analysis

Ad hoc tables were created to summarize data from the included studies by listing their key characteristics and any important questions related to the review objectives. After extracting the data, the investigators determined the feasibility of a meta-analysis.

A multiple-treatment comparison NMA is a meta-analysis generalization method that includes both direct and indirect comparisons of treatments. A random-effects NMA based on a frequentist framework was performed with STATA software (version 15; StataCorp LP, College Station, TX) using the *mvmeta* command and NMA graphical tools developed by Chaimani *et al*. [35]. STATA command used for this network meta-analysis was presented in the supplementary file.

Before conducting the NMA, we evaluated the transitivity assumption by examining the comparability of the risk of bias (all vs. removing studies with a high risk of bias arising from the randomization process, bias in the measurement of outcomes, and the overall risk of bias), demographics, and types of pharmacological interventions as potential treatment-effect modifiers across comparisons.

A network plot linking the pharmacological agents used to prevent RIPR or RIWR and their combination with other pharmacological agents was created to depict the types of pharmacological interventions employed, the number of patients treated with different pharmacological agents, and the level of pair-wise comparisons. The nodes showed the pharmacological interventions being compared and the edges showed the available direct comparisons among the pharmacological interventions. The nodes and edges were weighed based on the number of patients and the inverse of the standard error of effect.

We evaluated the consistency assumption for the entire network using the design-by-treatment interaction model. In addition, we evaluated each closed loop in the network to evaluate local inconsistencies between the direct and indirect effect estimates for the same comparison. For each loop, we estimated the inconsistency factor (IF) as the absolute difference between the direct and indirect estimates for each paired comparison in the loop [36].

The mean summary effects with the confidence interval (CI) were presented together with their predictive intervals (PrIs) to facilitate the interpretation of the results, taking into consideration the magnitude of heterogeneity. PrIs provide an interval that is expected to encompass the estimated period a future study will be conducted.

A rankogram and cumulative ranking curve were drawn for each pharmacological agent. Rankogram plots indicate the probability that a treatment will assume a specific rank

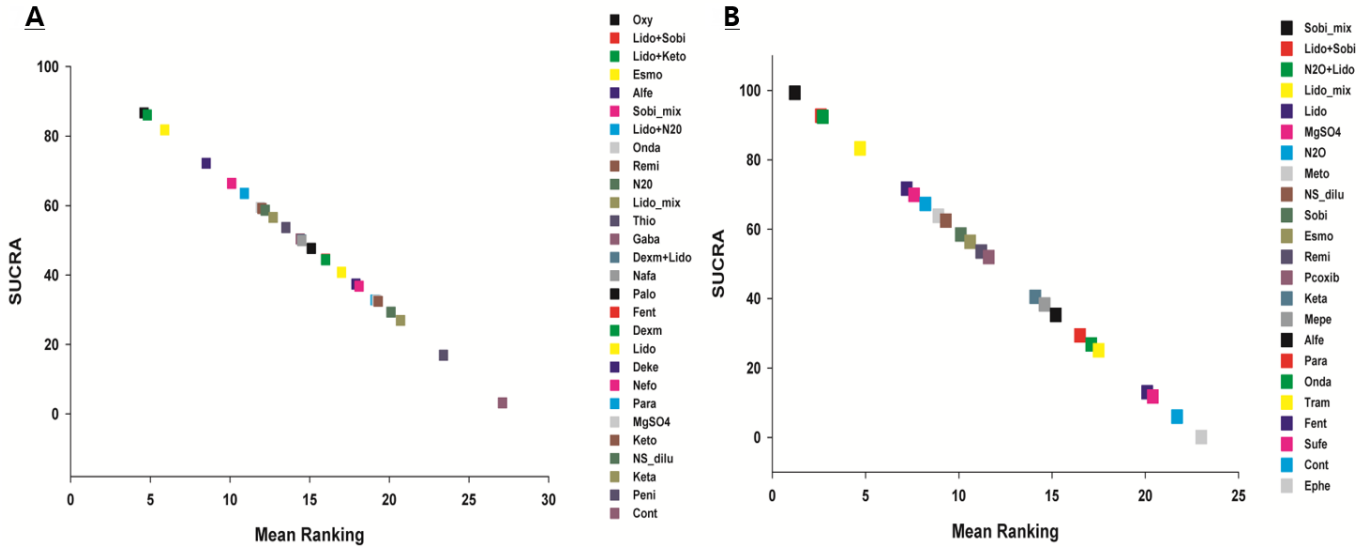

FIGURE 3. Expected mean ranking and SUCRA values. X-axis corresponds to expected mean ranking based on SUCRA (surface of under cumulative ranking curve) value, and Y-axis corresponds to SUCRA value. A) rocuronium induced withdrawal response, B) rocuronium induced pain response.

Alfe; alfentanil, Deke; deketoprofen, Dexm; dexmedetomidine, Dexm+Lido; combination of dexmedetomidine and lidocaine, Ephe; ephedrine Esmo; esmolol, Fent; fentanyl, Gaba; gabapentin, Keta ; ketamine, Keto; ketorolac, Lido; lidocaine, Lido_mix; mixed with lidocaine, Lido+Keto; combination of lidocaine and ketorolac, Lido+Sobi ; combination of lidocaine and $NaHCO_3$, Mepe; meperidine, Meto; metoclopramide, Nafa; nafamostat mesilate, N_2O+Lido; combination of N_2O and lidocaine, NS_dilu; normal saline dilution, Onda; ondansetron, Oxyc; oxycodone, Palo; palonosetron, Para; paracetamol, PCoxib; parecoxib, Peni; peniramine, Remi; remifentani, Sobi; $NaHCO_3$, Sufe; sufentanil, Sobi_mix; mixed with $NaHCO_3$, Tram; tramadol, Thio; thiopental.

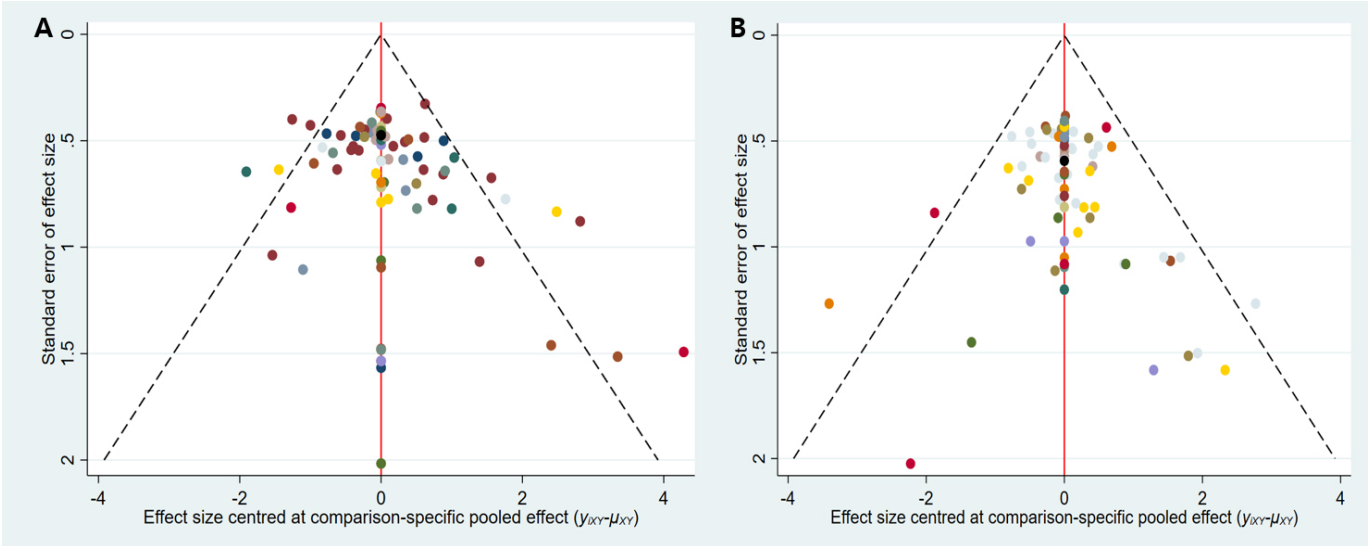

FIGURE 4. Comparison-adjusted funnel plot. (A) rocuronium induced withdrawal response, (B) rocuronium induced pain response.

according to a specific outcome. We used the SUCRA values to represent the hierarchy of the pharmacological agents with regard to the incidence of RIPR or RIWR. SUCRA is a relative ranking measure that accounts for uncertainty in the treatment order, i.e. both the location and variance of all relative treatment effects. A higher SUCRA value is regarded as a more positive result for an individual intervention [37].

A comparison-adjusted funnel plot was used to assess the existence of small-study effects [38].

2.8 Quality of the evidence

The evidence grade was determined using the guidelines for the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which sequentially assesses the evidence quality followed by assessing the risk–benefit balance and subsequently judging the strength of the recommendations [39].

3. Results

3.1 Study selection

From MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar, 102 studies were initially identified and a subsequent manual search revealed 59 additional studies. After adjusting for duplicates, 158 studies remained. Of these, 68 studies were discarded after reviewing their titles and abstracts.

The remaining 90 studies were reviewed in detail, after which 29 studies were excluded for the following reasons: pediatric study [7, 40–58], meta-analysis [3, 59], and did not report the outcomes of interest [60–66]. Thus, 61 studies met the inclusion criteria and were included in this systematic review and meta-analysis (Fig. 1). The kappa value for the selected articles between the two reviewers was 0.826.

3.2 Study characteristics

Table **??** summarizes the characteristics of the 61 studies that met the inclusion criteria. The pharmacological strategies used to prevent RIPR or RIWR consisted of lidocaine (Lido) [4, 10–22, 27, 67–82, 82, 84–91], fentanyl (Fent) [4, 14, 23, 67, 75, 82, 88], oxycodone (Oxyc) [92], deketoprofen [93], dexmedetomidine (Dexm) [10, 11], a combination of dexmedetomidine and lidocaine (Dexm + Lido) [10], gabapentin (Gaba) [9, 94], N_2O [12, 25, 95], a combination of lidocaine and N_2O (Lido + N_2O) [12, 16], remifentanil (Remi) [70, 72, 96], alfentanil (Alfe) [27, 74, 96], nafamostat mesilate [97], peniramine (Peni) [24], normal saline dilution (NS_dilu) [5, 98–104], rocuronium mixed with lidocaine (Lido_mix) [5, 54], ondansetron (Onda) [14, 85, 88, 91, 105], tramadol (Tram) [14, 21, 91], thiopental (Thio) [106], palonosetron (Palo) [15, 107], esmolol (Esmo) [17], $MgSO_4$ [26, 27], ketamine (Keta) [20, 69, 108, 109], ketorolac (Keto) [19], a combination of lidocaine and ketorolac (Lido + Keto) [19, 77], sufentanil (Sufe) [21, 82], meperidine (Mepe) [21], metoclopramide (Meto) [86], $NaHCO_3$(Sobi) [27], rocuronium mixed with $NaHCO_3$ (Sobi_mix) [54, 98, 101, 103, 104, 110], a combination of lidocaine and $NaHCO_3$ (Lido + Sobi) [98], parecoxib (PCoxib) [84], paracetamol (Para) [76, 78, 90, 111], and ephedrine (Ephe) [80].

3.3 Study quality assessment

Table 2 presents the risk of bias assessment for the included studies performed using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0).

3.4 Synthesis of results

For all outcomes for each specific datum, we generated the network plot (Fig. 2), inconsistency plot (Fig. S1), predictive interval plot compared with placebo (Fig. S2), rankogram (Fig. S3), cumulative ranking curve (Fig. S4), expected mean ranking and SUCRA values for each pharmacological agent with the outcomes (Fig. 3), and the comparison-adjusted funnel plot (Fig. 4). Figs. 2-4 and supplementary Figs. 1-4 present a summary of the results (A and B in each Figure correspond to RIWR and RIPR, respectively).

3.5 Rocuronium-induced withdrawal response

In total, 39 studies (4,631 patients) measured the withdrawal response in adults. Fig. 2A depicts the network plot of all eligible comparisons for this endpoint. After examining the comparability of the risk of bias, demographics, and types of pharmacological interventions as potential treatment-effect modifiers, we concluded the transitivity assumption was not violated.

Although all 28 management modalities (nodes) were connected to the network, two comparisons [control (Cont) and Lido] were more directly comparable than the other 26 nodes.

The evaluation of network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency [χ^2 (24) = 28.10, P = 0.2560].

Twenty-eight loops were closed in the network generated from the comparison of the withdrawal response in adults, but six loops (Cont-Keto-Lido + Keto [71], NS_dilu-Sobi_mix-Lido + Sobi [98], and Lido_mix-Sobi_mix-Lido + Sobi [98]) consisted of only multi-arm trials. Although most loops showed no significance in the local inconsistency between the direct and indirect point estimates, two loops (Lido-Remi-Alfe and Lido-Dexm-Dexm + Lido) showed significant inconsistency (Fig. S1A).

Oxyc, Esmo, Lido + Keto, and Alfe administration resulted in a lower frequency of RIWR than the control in terms of the 95% CI and PrIs. Lido + Sobi, Sobi_mix, Lido + N_2O, Remi, Lido_mix, N_2O, Thio, Gaba, Dexm + Lido, Palo, Fent, Dexm, Lido, and Para administration resulted in a lower frequency of RIWR than the control only in terms of the 95% CI (Appendix 1, Fig. S2A). The lack of significance in the 95% PrIs suggests that future RCTs may change the significance of the efficacy of these comparisons. The rankogram showed that Lido + Sobi and Esmo had the lowest frequency of RIWR in adults (Fig. S3A). The cumulative ranking plot was created and the SUCRA probabilities of the different pharmacological interventions to prevent RIWR were calculated (Fig. S4A).

The expected mean rankings and SUCRA values for each pharmacological intervention employed to prevent RIWR are presented in Fig. 3A.

According to the SUCRA values, the frequency of RIWR was lowest with the administration of Oxyc (86.7%), Lido + Sobi (86.1%), Lido + Keto (86.1%), Esmo (81.8%), Alfe (72.2%) and Sobi_mix (66.4%).

The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a lower likelihood of publication bias (Fig. 4A).

3.6 Rocuronium-induced pain response

In total, 30 studies (3,835 patients) measured the pain response in adults. Fig. 2B presents the network plot of all eligible comparisons for this endpoint. After examining the comparability of the risk of bias, demographics, and types of pharmacological interventions as potential treatment-effect modifiers, we concluded the transitivity assumption was not violated.

Although all 23 management modalities (nodes) were connected to the network, two comparisons (Cont and Lido) were

more directly comparable than the other 21 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency [χ^2 (27) = 37.12, P = 0.0928].

There were 43 closed loops in the network generated from the comparisons of the pain response in adults, but 10 loops (Cont-Sobi-$MgSO_4$[27], Cont-Sobi-Alfe [27], Cont-$MgSO_4$-Alfe [27], Lido-Sobi-$MgSO_4$ [27], Lido-$MgSO_4$-Alfe [27], Lido-Sobi-Alfe [27], Sobi- $MgSO_4$-Alfe [27], NS_dilu-Lido_mix-Lido + Sobi_mix [98], Sobi_mix-Lido_mix-Lido + Sobi [98], and Sufe-Tram-Mepe [21]) consisted of only multi-arm trials. All loops showed no significance in the local inconsistency between the direct and indirect point estimates (Fig. S1B).

Sobi_mix, N_2O + Lido, Lido + Sobi, Lido_mix, $MgSO_4$, Lido, N_2O, Meto, NS_dilu, Sobi, Esmo, Remi, PCoxib, Keta, Mepe, Alfe, Para, Onda, and Tram administration resulted in a lower pain response frequency than the control in terms of the 95% CI and PrI (Appendix 2, Fig. S2B).

The rankogram and cumulative ranking plot showed that Sobi_mix induced the lowest frequency of RIPR (Fig. S3B, 4B).

The expected mean rankings and SUCRA values for each pharmacological agent showed that Sobi_mix (99.3%) was followed by Lido + Sobi (92.7%), N_2O + Lido (92.4%), Lido_mix (83.3%), and Lido (71.7) (Fig. 3B).

The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a lower likelihood of publication bias (Fig. 4B).

3.7 Quality of the evidence

Three outcomes were evaluated using the GRADE system. The quality of evidence for RIWR and RIPR was moderate (Table 3).

4. Discussion

Our study showed a decreasing incidence of RIWR in the order of Oxyc, Lido + Sobi, Lido + Keto, Esmo, Alfe, and Sobi_mix, and a decreasing incidence of RIPR in the order of Sobi_mix, Lido + Sobi, N_2O + Lido, Lido_mix, and Lido.

RIWR-or even generalized movements-may be associated with severe pain during rocuronium administration [23]. Although the mechanisms underlying RIPR and RIWR remain unclear, the low pH of rocuronium is considered a potential cause of the pain, as rocuronium is an acidic solution (pH 4.0) with sodium acetate, acetic acid, or sodium hydroxide [13]. Direct stimulation to free nerve endings in the vessel wall, thus activating C-nociceptors [112, 113], and indirect stimulation of chemonociceptors by the release of endogenous mediators such as histamine, bradykinin, kinin, and other substances [9] are suggested mechanisms.

This may explain the findings in the present NMA that the administration of Sobi_mix with rocuronium to neutralize the acidic solution was the most effective pharmacological strategy to reduce RIPR and the sixth most effective pharmacological strategy to reduce RIWR.

These results are in close agreement with a previous report by Kwak *et al*. [29] in which the incidence of RIWR was lower with an $NaHCO_3$ admixture compared to that with other pharmacological interventions (ketamine, lidocaine, and lidocaine or opioids with venous occlusion). Although the results of direct comparisons were not presented, $NaHCO_3$ showed an excellent prophylactic effect against RIWR in another meta-analysis (relative risk, 0.35; 95% CI, 0.20-0.60) [3].

Further, our NMA showed that Lido + Sobi was the second-most effective pharmacological strategy to prevent both RIWR and RIPR amd Lido + Sobi showed more effectiveness than Lido alone in terms of RIWR and RIPR. Although Lido + Sobi was expected to have a local anesthetic effect in addition to a neutralizing effect, some investigators insisted that the prophylactic effect of Lido + Sobi against RIWR is due to the neutralization and dilution effects rather than a local anesthetic effect or an inhibitory effect on the release of kinin [114].

The acidity of rocuronium also provides a rationale for the attenuation or avoidance of pain evocation from the injection by dilution with normal saline [115] and our NMA showed that NS_dilu was effective at reducing RIPR in terms of both the 95% CI and PrI. However, Kim and Yoon et al. reported that 0.9% normal saline mixed with rocuronium decreased injection pain without changing the pH or osmolarity [116].

In our NMA, lidocaine was shown to reduce both RIWR and RIPR regardless of the administration method such as bolus injection as pretreatment (Lido), admixtures with rocuronium (Lido_mix), or co-administration with another medication (Lido + Keto, Lido + Sobi, Dexm + Lido, or Lido + N_2O). Although lidocaine bolus injection and Lido_mix only decreased the RIWR in terms of the 95% CI, they decreased the RIPR in terms of both the 95% CI and PrI. Further, Lido + Keto was effective at reducing RIWR in terms of both the 95% CI and PrI while Lido + Sobi, Lido + N_2O, and Lido + Dexm decreased the frequency of RIWR in terms of the 95% CI. Lido + Sobi and Lido + N_2O decreased the frequency of RIPR in terms of both the 95% CI and PrI. The mechanism through which lidocaine reduces RIPR and RIWR is known to be a local anesthetic effect in the veins and the stabilization of the kinin cascade [117].

Opioids are some of the most commonly used interventions. Compared to the control, our study showed that RIWR was decreased with Oxyc and Alfe administration in terms of both the 95% CI and PrI, and with Remi and Fent administration in terms of the 95% CI. Remi, Mepe, and Alfe decreased RIPR in terms of both the 95% CI and PrI compared to the control. As drugs with a central analgesic effect need more time to reach the effect site [4] and opioids need time to show an effect in preventing RIPR and PIWR, opioids were believed to exert their effect through a central rather than peripheral mechanism in RIWR studies [96]. Stein et al. demonstrated that several selective opioid agonists (μ, δ, and κ) can modulate responses to noxious stimulation by algogenic substances such as rocuronium through a peripheral opioid receptor-specific site of action in inflammation and that κ receptor agonists may be effective as peripheral analgesics [118]. In addition, the mechanism of the local anesthetic effect of opioids was known to be receptor-mediated or a nonspecific membrane-conduction blocking effect [40]. In our study, oxycodone was the second-most effective opioid for preventing RIWR, which

may be explained by the high affinity of oxycodone for the κ receptor rather than the μ receptor [119]. Animal studies have also shown that the antinociceptive effect of oxycodone appears to be mediated by the κ receptor [120–122]. Reducing the excitability of nerve cells through interactions with the G-protein is another suggested mechanism for oxycodone [123].

Esmolol is also effective at reducing RIWR and RIPR. Esmolol is an ultra-short-acting β1 receptor antagonist. Chia *et al*. reported that intraoperative esmolol injection reduced the postoperative opioid requirement and attenuated the intraoperative nociceptive stimulation [17]. Hageluken *et al*. demonstrated that a β antagonist acts on G proteins in isolated cell membranes [124]. A G protein receptor agonist acts upon the pre-synaptic inhibition of neurotransmitter release and post-synaptic inhibition through the regulation of voltage-gated Ca^{2+}channels, which is known to resemble the antinociceptive mechanism of clonidine [125].

Lido + N_2O also showed efficacy in reducing RIWR and RIPR, potentially due to the synergistic effect of the central and partial antinociceptive effect of N_2O and the local anesthetic effect of lidocaine. This is because N_2O reportedly interacts with various receptors such as opioid (μ, δ, and κ), γ-aminobutyric acid (GABA), and N-methyl-d-aspartate (NMDA) receptors [43]. However, careful interpretation may be warranted for RIPR because the possibility of fewer pain complaints due to the sedative effect of N_2O cannot be ruled out.

The authors of this NMA acknowledge several limitations in this study. First, the methodological quality of some included studies was poor. The randomization method was not stated clearly in most trials and few trials reported the blinding of the outcome assessors. Blinding and allocation concealment were unreported in these RCTs, indicating a potential risk of bias. Second, as with all meta-analyses, there were clinical and methodological heterogeneities among the 65 studies. As our NMA was based on various small-scale single-center trials, there was a lack of evidence for some interventions and some study designs were under-represented. These studies may not provide sufficient power to clearly discriminate the effectiveness of the pharmacological interventions. Third, although all included studies compared the effects of two or more pharmacological interventions as modalities for preventing RIWR or RIPR, the dose spectrum of pharmacological interventions differed among the studies.

Despite the above limitations, our systematic review and NMA demonstrates the strengths of a rigorous methodology with a sensitive search strategy and is the first NMA to compare and quantify the rank order of effectiveness for pharmacological interventions employed to prevent RIWR and RIPR during general anesthesia.

In conclusion, lidocaine administration has been shown to reduce the incidence of RIPR regardless of the injection method or combination. A combination of lidocaine and $NaHCO_3$ or the mixture of $NaHCO_3$with rocuronium was effective at reducing RIWR. In particular, oxycodone was shown to be more effective than the other opioids evaluated and esmolol was also found to be effective at reducing RIWR.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1337289156412227584/attachment/SV2020100701-Supplementary.rar.

APPENDIX

Appendix 1: League table for rocuronium-induced withdrawal response.
Appendix 2: League table for rocuronium-pain response.
Appendix associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1337289156412227584/attachment/SV2020100701-Supplementary.rar.

REFERENCES

[1] Wright P, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. Anesthesiology. 1994; 81: 1110-1115.
[2] Mehta MP, Choi WW, Gergis SD, Sokoll MD, Adolphson A. Facilitation of rapid endotracheal intubations with divided doses of nondepolarizing neuromuscular blocking drugs. Anesthesiology. 1985; 62: 392-395.
[3] Choi GJ, Lee S, Lee JH, Park SG, Kang H. Pharmacological and non-pharmacological intervention for rocuronium-induced withdrawal movement in the Korean population: A meta-analysis of 41 studies including 4,742 subjects. Korean Journal of Anesthesiology. 2014; 66: 419-432.
[4] Ahmad N, Choy CY, Aris EA, Balan S. Preventing the withdrawal response associated with rocuronium injection: a comparison of fentanyl with lidocaine. Anesthesia & Analgesia. 2005; 100: 987-990.
[5] Lee YC, Jang YH, Kim JM, Lee SG. Rapid injection of rocuronium reduces withdrawal movement on injection. Journal of Clinical Anesthesia. 2009; 21: 427-430.
[6] Moorthy SS, Dierdorf SF. Pain on injection of rocuronium bromide. Anesthesia & Analgesia. 1995; 80: 1067.
[7] Oh AY, Seo KS, Goo EK, Park YO, Kim SJ, Kim JH. Prevention of withdrawal movement associated with injection of rocuronium in

children: comparison of remifentanil, alfentanil and fentanyl. Acta Anaesthesiologica Scandinavica. 2007; 51: 1190-1193.
[8] Lui JT, Huang SJ, Yang CY, Hsu JC, Lui PW. Rocuronium-induced generalized spontaneous movements cause pulmonary aspiration. Chang Gung Medical Journal. 2002; 25: 617-620.
[9] Cakirgoz MY, Demirel I, Duran E, Ozer AB, Turkmen UA, Ersoy A, *et al*. Gabapentin pretreatment for propofol and rocuronium injection pain: A randomized, double-blind, placebo-controlled study. Nigerian Journal of Clinical Practice. 2018; 21: 43-48.
[10] Ayoglu H, Altunkaya H, Ozer Y, Yapakci O, Cukdar G, Ozkocak I. Does dexmedetomidine reduce the injection pain due to propofol and rocuronium? European Journal of Anaesthesiology. 2007; 24: 541-545.
[11] Joo J, Baek J, Lee J. Dexmedetomidine reduces pain associated with rocuronium injection without causing a decrease in BIS values: a dose-response study. Journal of Clinical Anesthesia. 2014; 26: 475-479.
[12] Kim E, Kim CH, Kim HK, Kwon JY, Lee DW, Kim HY. Effect of nitrous oxide inhalation on pain after propofol and rocuronium injection. Journal of Anesthesia. 2013; 27: 868-873.
[13] Kim KS, Kim YS, Jeon WJ, Yeom JH. Prevention of withdrawal associated with the injection of rocuronium in adults and children. Journal of Clinical Anesthesia. 2006; 18: 334-338.
[14] Memis D, Turan A, Karamanlioglu B, Sut N, Pamukcu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. Anesthesia & Analgesia. 2002; 94: 1517-1520, table of contents.
[15] Park KB, Jeon Y, Yi J, Kim JH, Chung SY, Kwak KH. The effect of palonosetron on rocuronium-induced withdrawal movement. Revista Brasileira de Anestesiologia. 2017; 67: 337-341.
[16] Sivakumar S, Singh NR, Singh LD, Rajkumar G, Thokchom RS, Devi LE. A comparative study of lignocaine and nitrous oxide for rocuronium injection pain. Journal of Medical Society. 2015; 29: 64-68.
[17] Yavascaoglu B, Kaya FN, Ozcan B. Esmolol pretreatment reduces the frequency and severity of pain on injection of rocuronium. Journal of Clinical Anesthesia. 2007; 19: 413-417.
[18] Choi YJ, Park HS, Lee H, Yoon SZ. Single pretreatment of remifentanil may reduce pain after propofol and rocuronium injection in rapid sequence induction. Korean Journal of Anesthesiology. 2012; 63: 413-418.
[19] Jeon Y, Ha JH, Lee JE, Lee HC, Ryu T, Kwak KH. Rocuronium-induced withdrawal movement: influence of ketorolac or a combination of lidocaine and ketorolac pretreatment. Korean Journal of Anesthesiology. 2013; 64: 25-28.
[20] Jung KT, Kim HJ, Bae HS, Lee HY, Kim SH, So KY, *et al*. Effects of lidocaine, ketamine, and remifentanil on withdrawal response of rocuronium. Korean Journal of Anesthesiology. 2014; 67: 175-180.
[21] Honca M, Purtuloglu T, Honca T, Sizlan A, Deniz S, Kose A, *et al*. Effects of the menstrual cycle on injection pain due to rocuronium. Journal of Clinical Anesthesia. 2013; 25: 399-402.
[22] Lee JI, Lim SH, Lee SE, Kim YH, Lee JH, Lee KM, *et al*. Priming technique can alleviate the withdrawal responses associated with intravenous administration of rocuronium. Korean Journal of Anesthesiology. 2009; 56: 628-633.
[23] Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? British Journal of Anaesthesia. 1997; 79: 382-383.
[24] Lee HJ, Han SJ, Kim H, Lee IO, Kong MH, Kim NS, *et al*. Antihistamine pretreatment to reduce incidence of withdrawal movement after rocuronium injection. Journal of Korean Medical Science. 2009; 24: 879-882.
[25] Sharma S, Sharma D, Jain A, Jain A. Effect of nitrous oxide on pain due to rocuronium injection: A randomised, double-blind, controlled clinical trial. Indian Journal of Anaesthesia. 2010; 54: 142-146.
[26] Shin YH, Choi SJ, Jeong HY, Kim MH. Evaluation of dose effects of magnesium sulfate on rocuronium injection pain and hemodynamic changes by laryngoscopy and endotracheal intubation. Korean journal of anesthesiology. 2011; 60: 329-333.
[27] Turan A, Memis D, Karamanlioglu B, Sut N, Pamukcu Z. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. Anaesthesia & Intensive Care. 2003; 31: 277-281.
[28] Prabhakar H, Singh GP, Ali Z, Kalaivani M, Smith MA. Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults. Cochrane Database of Systematic Reviews. 2016; 2: CD009346.
[29] Kwak HJ, Kim JY, Kim YB, Min SK, Moon BK, Kim JY. Pharmacological prevention of rocuronium-induced injection pain or withdrawal movements: a meta-analysis. Journal of Anesthesia 2013; 27: 742-749.
[30] Cui Y, Li G, Cao R, Luan L, Kla KM. The effect of perioperative anesthetics for prevention of postoperative delirium on general anesthesia: A network meta-analysis. Journal of Clinical Anesthesia. 2020; 59: 89-98.
[31] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. British Medical Journal. 2015; 350: g7647.
[32] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, *et al*. Cochrane handbook for systematic reviews of intervention. The Cochrane Collaboration. 2019.
[33] Cornell JE. The PRISMA extension for network meta-analysis: bringing clarity and guidance to the reporting of systematic reviews incorporating network meta-analyses. Annals of Internal Medicine. 2015; 162: 797-798.
[34] Higgins J, Thomas J, Chandler J, Cumpston M, Li TJ, Page M, et al. Chapter 8: Assessing risk of bias in a randomized trial. 2019. In: Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. 2019.
[35] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013; 8: e76654.
[36] White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods. 2012; 3: 111-125.
[37] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of Clinical Epidemiology. 2011; 64: 163-171.
[38] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. British Medical Journal. 2011; 342: d549.
[39] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, *et al*. Grading quality of evidence and strength of recommendations. British Medical Journal. 2004; 328: 1490.
[40] Abu-Halaweh SA, Aloweidi AK, Qudaisat IY, Al-Hussami MO, Al Zaben KR, Abu-Halaweh AS. Pretreatment with remifentanil, fentanyl, or lidocaine to prevent withdrawal after rocuronium using venous occlusion technique in children and adolescents: a prospective randomized placebo-controlled double-blind study. Journal of Anesthesia. 2014; 28: 886-890.
[41] Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanil to prevent withdrawal after rocuronium in children. British Journal of Anaesthesia. 2007; 98: 120-123.
[42] Kim JY, Kwak HJ, Kim JY, Park KS, Song JS. Prevention of rocuronium-induced withdrawal movement in children: A comparison of remifentanil with alfentanil. Paediatric Anaesthesia. 2008; 18: 245-250.
[43] Kwak HJ, Chae YJ, Lee SY, Kim YJ, Kim JY. Combination of nitrous oxide and lidocaine to prevent withdrawal after rocuronium in children. Korean Journal of Anesthesiology. 2010; 58: 446-449.
[44] Liou JT, Hsu JC, Liu FC, Ching-Wah Sum D, Lui PW. Pretreatment with small-dose ketamine reduces withdrawal movements associated with injection of rocuronium in pediatric patients. Anesthesia & Analgesia. 2003; 97: 1294-1297.
[45] Park SH, Oh AY, Goo EK, Nahm FS, Min SW, Hwang JW, *et al*. A short period of inhalation induction with sevoflurane prevents rocuronium-induced withdrawal in children. Acta Anaesthesiologica Scandinavica. 2011; 55: 87-91.
[46] Shevchenko Y, Jocson JC, McRae VA, Stayer SA, Schwartz RE, Rehman M, *et al*. The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents. Anesthesia & Analgesia. 1999; 88: 746-748.
[47] Yoon JR, Jeon Y, Yoo Y, Shin HJ, Ahn JH, Lim CH. The analgesic effect of remifentanil on prevention of withdrawal response associated with the injection of rocuronium in children: no evidence for a peripheral action. Journal of International Medical Research. 2010; 38: 1795-1800.
[48] Shabana AM, Nasr ES. Prevention of rocuronium injection pain in

paediatrics: Ketamine versus midazolam? A prospective randomized double blind study. Egyptian Journal of Anaesthesia. 2011; 27: 141-144.

[49] Cheong SH, Kim SY, Lee KM, Choe YK, Kim YJ, Park JW, *et al*. The Effect of Pretreatment with Ketamine on Vascular Pain Due to an Intravenous Rocuronium Injection in Pediatric Patients. Korean Journal of Anesthesiology. 2003; 45: 447-450.

[50] Na YC, Lee HG, Lee SH, Jang EA, Yoon MH. The efficacy of sevolflurane inhalation alone or its combination with intravenous remifentanil against withdrawal movements on rocuronium injection in children. Korean Journal of Anesthesiology. 2014; 67: 373.

[51] Jung JD, An TH, Song HS. The dose-dependent effect of remifentanil for withdrawal responses on injection of recuronium in children. Anesthesia and Pain Medicine. 2009; 4: 170-173.

[52] Polat R, Akın M, Keskin G, Ünal D, Dönmez A. Prevention of withdrawal movement associated with the injection of rocuronium in children: Comparison of paracetamol and lidocaine. Turkish journal of anaesthesiology and reanimation. 2016; 44: 86-90.

[53] Lee JY, Lee KC, Kim HS, Bang MS, Chang YJ. The dose-dependent effect of alfentanil on the rocuronium induced withdrawal in children. Anesthesia and Pain Medicine. 2009; 4: 348-351.

[54] Jung SM, Kim SH, Lim YS, Kwon HU, Kang PS, Park CW. The effect of sodium bicarbonate or lidocaine mixed with rocuronium on withdrawal movement in pediatric patients. Korean Journal of Anesthesiology. 2005; 48: 514-519.

[55] Kwak HJ, Kim YB, Kim EJ, Kim JY. Prevention of rocuronium-induced withdrawal movement in children: a comparison of remifentanil with lidocaine. Korean Journal of Anesthesiology. 2008; 54: 437-440.

[56] Chang SH, Kim HY, Park JY, Lee HW, Lim HJ, Yoon SM. The preventive effect of lidocaine on the withdrawal associated with the injection of rocuronium in children. Korean Journal of Anesthesiology. 2004; 46: 665-669.

[57] Park SJ, Lee JY, Jee DL. The effect of rocuronium diluted with 0.9% nacl on withdrawal response during injection in pediatric patients. Korean Journal of Anesthesiology. 2006; 51: 157-161.

[58] Kim KS, Chae YJ, Park SY, Cho HB, Kim JS. The effect of pretreatment with lidocaine for the withdrawal movement associated with the injection of rocuronium in children. Korean Journal of Anesthesiology. 2002; 43: 572-574.

[59] He Q, Zhou C, Zhu Y. The effect of 5-hydroxytryptamine receptor antagonist in preventing pain/limb shrinkage reaction associated with rocuronium injection. BioMed Research International. 2018; 2018: 4128415.

[60] Lee SS, Yoon H. A comparison of the effect of lidocaine or sodium bicarbonate mixed with rocuronium on withdrawal movement, mean arterial pressure and heart rate during rocuronium injection. Journal of Korean Academy of Nursing. 2009; 39: 270-278.

[61] Sari M, Iyilikci L, Bayindir S, Ellidokuz H, Gunerli A. Comparison of the effectiveness of pretreatment by fentanyl and remifentanil on rocuronium induced injection pain. Saudi Medical Journal. 2008; 29: 374-378.

[62] Goyal R, Jindal P, Khurana G. A comparison of granisetron and nitroglycerine for attenuating rocuronium pain: A double-blinded randomized, placebo controlled trial. Saudi Journal of Anaesthesia. 2014; 8: 83-87.

[63] Lim CS, Shin YS. The effects of remifentanil pretreatment on rocuronium injection pain and cardiovascular response during anesthetic induction. Korean Journal of Anesthesiology. 2006; 50: 637-641.

[64] Ko H-M, Hong H-P, Yoon J-Y, Yoon J-U, Lee D-W, Kim C-H. Desflurane inhalation provide cardiovascular stability during intubation but prevention of rocuronium injection pain. Journal of the Korean Dental Society of Anesthesiology. 2013; 13: 117-120.

[65] Erbabacan E, Köksal GM, Tütüncü ÇA, Ekici B, Tunalı Y, Kaya G, *et al*. Comparison of the effects of different concentrations of rocuronium on injection pain and hemodynamics using isolated forearm technique. Turkish journal of anaesthesiology and reanimation. 2013; 41: 162-166.

[66] Mubarak KK, Ummer SU. Effect of pretreatment with intravenous thiopentone versus lignocaine on pain due to rocuronium bromide: a comparative study. Journal of Evidence Based Medicine and Healthcare. 2016; August : 3699-3703.

[67] Abu-Halaweh SA, Aloweidi AK, Qudaisat IY, Al-Hussami MO, Atyat BS, Al-Mustafa M, *et al*. Comparison of three methods of preventing rocuronium induced pain on injection using venous occlusion technique: a randomized prospective double blind controlled study. Middle East Journal of Anesthesiology. 2013; 22: 87-92.

[68] Kim KS, Kim YS, Jeon WJ, Yeom JH. Prevention of withdrawal associated with the injection of rocuronium in adults and children. Journal of Clinical Anesthesia. 2006; 18: 334-338.

[69] Akkaya T, Toygar P, Bedirli N, Yazicioğlu D, Gümüş H. Effects of pretreatment with lidocaine or ketamine on injection pain and withdrawal movements of rocuronium. Turkish Journal of Medical Sciences. 2008; 38: 577-582.

[70] Choi YJ, Park HS, Lee H, Yoon SZ. Single pretreatment of remifentanil may reduce pain after propofol and rocuronium injection in rapid sequence induction. Korean Journal of Anesthesiology. 2012; 63: 413-418.

[71] Jeon Y, Ha JH, Lee JE, Lee HC, Ryu T, Kwak KH. Rocuronium-induced withdrawal movement: influence of ketorolac or a combination of lidocaine and ketorolac pretreatment. Korean Journal of Anesthesiology. 2013; 64: 25-28.

[72] Jung KT, Kim HJ, Bae HS, Lee HY, Kim SH, So KY, *et al*. Effects of lidocaine, ketamine, and remifentanil on withdrawal response of rocuronium. Korean Journal of Anesthesiology. 2014; 67: 175-180.

[73] Ikram M, Ishaque M, Masood N, Abbas A. Effects of pre-treatment with lignocaine on pain of rocuronium injection and withdrawal movements of the arm. Annals of Punjab Medical College (APMC). 2008; 2: 113-116.

[74] Park SE, Park SH, Cho YW, Son HW, Lee JH, Kim DY. Hemodynamic responses of pretreatments designed to reduce withdrawal movements following rocuronium injection: a comparison of alfentanil with lidocaine. Korean Journal of Anesthesiology. 2008; 54: 507-512.

[75] Cho HY, Kim DY, Chung RK. The effect of lidocaine or fentanyl on withdrawal movement during rocuronium injection. Korean Journal of Anesthesiology. 2007; 53: 174-179.

[76] Binarani M, Singh YA, Lairenlakpam DS, Singh SM, Eshori L, Sinam N. Efficacy of pretreatment with intravenous paracetamol and lidocaine on rocuronium injection pain: a randomized, double-blinded, placebo-controlled study. Journal of Medical Society. 2017; 31: 99-103.

[77] Boota M, Wasim MH, Ali L. Comparison of lidocaine and a combination of lidocaine and ketorolac pretreatment on withdrawal movement induced by rocuronium injection. Anaesthesia, Pain & Intensive Care. 2019; : 31-36.

[78] Jeon Y, Baek SU, Park SS, Kim SO, Baek WY, Yeo JS. Effect of pretreatment with acetaminophen on withdrawal movements associated with injection of rocuronium: a prospective, randomized, double-blind, placebo controlled study. Korean Journal of Anesthesiology. 2010; 59: 13-16.

[79] Lee JI, Lim SH, Lee SE, Kim YH, Lee JH, Lee KM, *et al*. Priming technique can alleviate the withdrawal responses associated with intravenous administration of rocuronium. Korean Journal of Anesthesiology. 2009; 56: 628-633.

[80] Akcaboy ZN, Akcaboy EY, Soyal OB, Turhan G, Gogus N. Can ephedrine pretreatment be effective in alleviating rocuronium injection pain? Medical Principles & Practice. 2012; 21: 323-327.

[81] Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. British Journal of Anaesthesia. 2000; 84: 106-107.

[82] Singh M, Chauhan H, Rath GP, Prabhakar H, Bithal PK, Dash HH. Effect of narcotic pretreatment on pain after rocuronium injection: a randomized, double-blind controlled comparison with lidocaine. Journal of Anesthesia. 2007; 21: 510-512.

[83] Uzun S, Erden IA, Canbay O, Aypar U. The effect of intravenous paracetamol for the prevention of rocuronium injection pain. Kaohsiung Journal of Medical Sciences. 2014; 30: 566-569.

[84] Zhang Y, Xiang Y, Liu J. Prevention of pain on injection of rocuronium: a comparison of lidocaine with different doses of parecoxib. Journal of Clinical Anesthesia. 2012; 24: 456-459.

[85] Reddy M, Chen FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection: a randomised, double-blind controlled comparison with lidocaine. Anaesthesia. 2001; 56: 902-905.

[86] Byun JH, Kim JS, Park SW, Kang WJ. The Effect of Metoclopramide or Lidocaine Pretreatment on Pain during Rocuronium Injection. Korean Journal of Anesthesiology. 2005; 49: 35-39.

[87] Wee SY, Lee HY, An TH, So GY, Lim KJ, Jung JD, *et al*. The dose-dependent analgesic effect of lidocaine for pain on injecting rocuronium. Korean Journal of Anesthesiology. 2004; 47: 327-330.
[88] Lee SK, Lee JM, Kim YM, Moon HS. Pain on injection of rocuronium: the effect of pretreatment of lidocaine, fentanyl, and ondansetron. Korean Journal of Anesthesiology. 2004; 46: 151-154.
[89] Hwang SH, Jeon YH, Baek WY. The prevention of rocuronium injection pain by lidocaine pretreatment. Korean Journal of Anesthesiology. 2003; 45: 451-455.
[90] Ates G, Kose EA, Oz G, Apan A. Effect of paracetamol pretreatment on rocuronium-induced injection pain: a randomized, double-blind, placebocontrolled comparison with lidocaine. Journal of Clinical and Analytical Medicine. 2014; 5: 508-510.
[91] Eun SS, An TH. The comparison of the effects of ondansetron, lidocaine, and tramadol for the prevention of pain on injection of rocuronium. Korean Journal of Anesthesiology. 2005; 48: 20-23.
[92] An X, Li C, Sahebally Z, Wen X, Zhao B, Fang X. Pretreatment with oxycodone simultaneously reduces etomidate-induced myoclonus and rocuronium-induced withdrawal movements during rapid-sequence induction. Medical Science Monitor. 2017; 23: 4989-4994.
[93] Aydin GB, Polat R, Ergil J, Sayin M, Caparlar CO. Comparison of randomized preemptive dexketoprofen trometamol or placebo tablets to prevent withdrawal movement caused by rocuronium injection. Journal of Anesthesia. 2014; 28: 471-474.
[94] Yoon JS, Jeon HJ, Cho SS, Lee JD, Kang KO, Ryu SW, *et al*. Effect of pretreatment with gabapentin on withdrawal movement associated with intravenous rocuronium injection. Korean Journal of Anesthesiology. 2011; 61: 367-371.
[95] Pandey A, Singh DL, Singh RN, Singh PL, Thokchom RS, Meitei J. Nitrous oxide for the prevention of rocuronium injection pain: A randomized, double-blind, controlled clinical trial. Journal of Medical Society. 2013; 27: 140-143.
[96] Kim JH, Kim JH, Han SH, Hwang JW, Oh AY. Alfentanil is comparable to remifentanil in preventing withdrawal movement following rocuronium injection. Journal of Clinical Anesthesia. 2009; 21: 9-12.
[97] Kim YH, Go YK, Lee JU, Chung WS, Shin YS, Han KC, *et al*. Pretreatment with nafamostat mesilate, a kallikrein inhibitor, to decrease withdrawal response associated with rocuronium. Journal of Anesthesia. 2010; 24: 549-552.
[98] Jung SM, Ko NY, Lim YS, Kang PS, Kwon HU. Comparison of Premixed NaHCO3 and lidocaine on rocuronium injection pain. Korean Journal of Anesthesiology. 2005; 48: 483-488.
[99] Kim YH, Yoon MJ. Dilution of rocuronium with 0.9% NaCl reduces withdrawal movement during anesthetic induction. Anesthesia and Pain Medicine. 2007; 2: 22-25.
[100] Kim YS, Lee JA. The effect of dilution with 0.9% normal saline on reducing withdrawal movement induced by rocuronium injection. Anesthesia and Pain Medicine. 2007; 2: 26-29.
[101] Han DW, Koo BN, Choi SH, Lee JS, Shin YS, Sharma M, *et al*. Neutralized rocuronium (pH 7.4) before administration prevents injection pain in awake patients: a randomized prospective trial. Journal of Clinical Anesthesia. 2007; 19: 418-423.
[102] Tuncali B, Karci A, Tuncali BE, Mavioglu O, Olguner CG, Ayhan S, *et al*. Dilution of rocuronium to 0.5 mg/mL with 0.9% NaCl eliminates the pain during intravenous injection in awake patients. Anesthesia & Analgesia. 2004; 99: 740-743, table of contents.
[103] Han DW, Koo BN, Hwang SI, Shin YS, Kim KJ. Rocuronium injection pain is attenuated by NaHCO3. Korean Journal of Anesthesiology. 2003; 45: 697-701.
[104] Goo EK, Hwang JW, Kim HJ, Na HS, Park HP, Jeon YT, *et al*. Effect of bicarbonate on injection pain and onset of rocuronium. Anesthesia and Pain Medicine. 2009; 4: 260-264.
[105] Ki HS, So KY, Chung CD. The dose-dependent analgesic effect of ondansetron for pain on injection of rocuronium in adult. Korean Journal of Anesthesiology. 2005; 48: 145-148.
[106] Park JT, Choi JC, Yoo YS, Lee YB, Kim SY, Lim HK. The effect of pretreatment with thiopental on reducing pain induced by rocuronium injection. Yonsei Medical Journal. 2005; 46: 765-768.
[107] Cho K, Lee SH, Lee W, Chu BK, Kim MH, Lim SH, *et al*. Effect of pretreatment with palonosetron on withdrawal movement associated with rocuronium injection. Korean Journal of Anesthesiology. 2014; 66: 23-27.
[108] Chang HW, Kim SR, Lee YK. The effect of ketamine for pain on rocuronium injection pain. Korean Journal of Anesthesiology. 2005; 48: 479-482.
[109] Choi JH, Hwang JH, Shin YS. Comparison of the quantitative effect of ketamine on the vascular pain associated with intravenous rocuronium administration. Korean Journal of Anesthesiology. 2005; 49: 30-34.
[110] Choi HG, Kim DS, Chang TH, Kim SH, Kim KH, Ryu SJ. Appropriate dosage of 8.4% sodium bicarbonate for preventing injection pain of rocuronium during anesthetic induction. Korean Journal of Anesthesiology. 2006; 51: 162-166.
[111] Uzun S, Erden İA, Canbay O, Aypar U. The effect of intravenous paracetamol for the prevention of rocuronium injection pain. The Kaohsiung Journal of Medical Sciences. 2014; 30: 566-569.
[112] Arndt J, Klement W. Pain evoked by polymodal stimulation of hand veins in humans. The Journal of Physiology. 1991; 440: 467-478.
[113] Kindgen-Milles D, Klement W, Arndt J. The nociceptive systems of skin, paravascular tissue and hand veins of humans and their sensitivity to bradykinin. Neuroscience letters. 1994; 181: 39-42.
[114] Jung SM, Kim SH, Lim YS, Kwon HU, Kang PS, Park CW. The effect of sodium bicarbonate or lidocaine mixed with rocuronium on withdrawal movement in pediatric patients. Korean Journal of Anesthesiology. 2005; 48: 514-519.
[115] Klement W, Arndt J. Pain on iv injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. British Journal of Anaesthesia. 1991; 66: 189-195.
[116] Kim YH, Yoon MJ. Dilution of rocuronium with 0.9% NaCl reduces withdrawal movement during anesthetic induction. Anesthesia and Pain Medicine. 2007; 2: 22-25.
[117] Scott R, Saunders D, Norman J. Propofol: clinical strategies for preventing the pain of injection. Anaesthesia. 1988; 43: 492-494.
[118] Stein C, Millan MJ, Shippenberg TS, Peter K, Herz A. Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors. Journal of Pharmacology and Experimental Therapeutics. 1989; 248: 1269-1275.
[119] Gallego AO, Baron MG, Arranz EE. Oxycodone: a pharmacological and clinical review. Clinical and Translational Oncology. 2007; 9: 298-307.
[120] Olesen AE, Staahl C, Arendt-Nielsen L, Drewes AM. Different effects of morphine and oxycodone in experimentally evoked hyperalgesia: a human translational study. British Journal of Clinical Pharmacology. 2010; 70: 189-200.
[121] Iadarola MJ, Douglass J, Civelli O, Naranjo JR. Differential activation of spinal cord dynorphin and enkephalin neurons during hyperalgesia: evidence using cDNA hybridization. Brain Research. 1988; 455: 205-212.
[122] Nielsen CK, Ross FB, Lotfipour S, Saini KS, Edwards SR, Smith MT. Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. Pain. 2007; 132: 289-300.
[123] Xiang X, Yuan X, Lian Y, Fang J, Wu Y. Effect of oxycodone hydrochloride combined with flurbiprofen axetil for intravenous patient-controlled analgesia in lower abdominal patients: a randomized trial. Medicine. 2018; 97: e9911.
[124] Hagelüken A, Grünbaum L, Nürnberg B, Harhammer R, ScHunack W, Seifert R. Lipophilic β-adrenoceptor antagonists and local anesthetics are effective direct activators of G-proteins. Biochemical Pharmacology. 1994; 47: 1789-1795.
[125] Chia Y, Chan M, Ko N, Liu K. Role of β-blockade in anaesthesia and postoperative pain management after hysterectomy. British Journal of Anaesthesia. 2004; 93: 799-805.

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