

# Evaluation of ropivacaine combined with dexmedetomidine versus ropivacaine alone for epidural anesthesia

## A meta-analysis

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### Abstract

**Background:** Ropivacaine is considered the most commonly used for epidural anesthesia. We compared the efficiency and safety of ropivacaine alone (R group) and ropivacaine combined with dexmedetomidine (RD group).

**Method:** PubMed, the Cochrane Library, Google Scholar, Ovid Medline, the Web of Science, Scopus, Embase, and ScienceDirect were searched. We considered sensory and motor block, duration of anesthesia, time to rescue, hemodynamics, and adverse effects as the primary endpoints.

**Results:** Eleven randomized controlled trials were included with 337 patients in the R group and 336 patients in the RD group. The RD group had a shorter time to onset of sensory (mean difference [MD]: 3.97 [1.90–6.04] minutes;  $P = .0002$ ) and motor (MD: 2.43 [0.70–4.16] minutes;  $P = .006$ ) block and a longer duration of anesthesia (MD: -164.17 [-294.43 to -33.91];  $P = .01$ ) than the R group. Comparison of the time to rescue between the groups showed no significant difference (MD: -119.01 [-254.47–16.46] minutes;  $P = 0.09$ ). The R group showed more stable hemodynamics than the RD group in heart rate and arterial pressure at 10 minutes. The R group had a lower incidence of bradycardia and a higher incidence of shivering than the RD group.

**Conclusion:** RD may be a more suitable choice for epidural anesthesia with better anesthetic outcomes than R alone. However, the safety of the combination must be carefully assessed.

**Abbreviations:** AEs = adverse effects, BP = blood pressure, C = comparison, CI = confidence intervals, D = dexmedetomidine, DBP = diastolic blood pressure, EA = epidural anesthesia, HR = heart rate, I = Intervention, L = lumbar, MD = mean difference, O = outcomes, P = patients, R = ropivacaine group, RCT = random controlled trial, RD group = ropivacaine combined with dexmedetomidine, RR = risk ratios, SBP = systolic blood pressure.

**Keywords:** dexmedetomidine, epidural anesthesia, meta-analysis, ropivacaine

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## 1. Introduction

Epidural anesthesia (EA) is the most common technique for intraoperative surgical anesthesia and postoperative analgesia for many surgeries, such as lung surgeries, orthopedic surgery, and labor.<sup>[1]</sup> The alpha-2 adrenoreceptor agonist ropivacaine is the most common medicine used for epidural anesthesia.<sup>[2,3]</sup> However, when used alone, it has many disadvantages, including hypotension, oversedation, bradycardia, and prolongation of the second stage of labor.<sup>[4]</sup>

Dexmedetomidine is combined with local anesthetics to enhance the effect of anesthesia, reduce the dose of local anesthetics and decrease the incidence of adverse effects (AEs).<sup>[5,6]</sup> Many studies have also shown that dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist and a very effective adjuvant, with stable hemodynamics and sympathoadrenal function.<sup>[7,8]</sup> Used of the combination of ropivacaine and dexmedetomidine (RD) for EA is a current trend, but some scholars reported that the efficiency and safety of RD are not clear.<sup>[9,10]</sup> Attri et al reported that epidural dexmedetomidine as an adjuvant to ropivacaine prolonged the time of sensory and motor block and postoperative analgesia, reduced demand for rescue analgesics, and maintained hemodynamic stability.<sup>[11]</sup> However, Zhao et al suggested that epidural ropivacaine

(0.125%) combined with dexmedetomidine (0.5 mg/kg) alleviated pain sensations but showed no significant difference in prolonging the time of motor blockage.<sup>[12]</sup> Soni et al also reported that a ropivacaine (R group) had a lower incidence of AEs than an RD group.<sup>[13]</sup>

We performed a meta-analysis to answer this dispute by comparing the efficiency and safety of R and RD for EA.

## 2. Materials and methods

This meta-analysis and systemic review were performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Registration information: PROSPERO CRD42020177850).

### 2.1. Search strategy

The search date was 17 March 2020. Related articles were searched in PubMed, Scopus, Google Scholar, Web of Science, Ovid Medline, Embase, ScienceDirect, and the Cochrane Library to retrieve articles published before 17 March 2020. The following medical subject heading (MeSH) terms were used: “epidural anesthesia,” “ropivacaine,” and “dexmedetomidine.” Table 1 shows the search strategy. No language restrictions were used in the identification of eligible articles.

### 2.2. Selection criteria

The following inclusion criteria were used:

- (1) P (patients): patients who underwent EA;
- (2) I (intervention) and C (comparison): R group vs RD group;
- (3) O (outcomes): duration of anesthesia; time to rescue; sensory and motor block (time to onset of sensory block and time to onset of motor block); hemodynamics (heart rate [HR]; blood pressure [BP]: mean arterial pressure, systolic blood pressure [SBP], and diastolic blood pressure [DBP]); and AEs.
- (4) S (studies): randomized controlled trials (RCTs)

The exclusion criteria included

- (1) articles lacking original data,
- (2) meta-articles, animal experiments or meeting articles,
- (3) articles with abstracts only or duplicated data, and
- (4) articles comparing dexmedetomidine combined with other drugs or in which dexmedetomidine was used for purposes other than EA.

### 2.3. Data extraction

The extracted data included the article name, first author, publication year, type of study, nation, participant number, characteristics of participants (age, sex, weight, height, type of surgery and American Society of Anesthesiologists physical status), duration of anesthesia, time to rescue, time to onset of sensory and motor block, HR, BP (MAP, SBP, and DBP) at 10 and 45 minutes and AEs. Two investigators extracted the data. The HR and BP (MAP, SBP, and DBP) at 10 and 45 minutes were used to indicate the onset and peak times of the anesthesia, respectively, which are the most critical moments during surgery. A third investigator assessed the outcomes when disagreement arose between the 2 investigators.

### 2.4. Quality assessment

Two investigators used the Cochrane Collaboration’s “Risk of Bias” tool, which includes randomization (allocation conceal-

ment and sequence generation), selection of outcomes reported, blinding (personnel, participants, and outcome assessors), and completeness of outcome data, to assess the quality of the RCTs.<sup>[14]</sup> We used the five-point Jadad scale to assess the quality of the RCTs. The randomization, masking, and accountability of all patients were the 3 items of the scale, with scores  $\geq 3$  points indicating high-quality studies.<sup>[15]</sup> We used the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the level of evidence, which includes five evaluation items: inconsistency, risk of bias, imprecision, indirectness, and publication bias. High, moderate, low, and very low were the 4 types of evidence.<sup>[16]</sup>

### 2.5. Statistical analysis

We used STATA 12.0 (Stata Corp, TX) and Review Manager 5.3 (Nordic Cochrane Center, Oxford, UK) to evaluate the pooled data. We used the mean difference (MD) to analyze the duration of anesthesia, time to rescue, sensory and motor block, HR, MAP, SBP, and DBP. An MD  $> 0$  (with 95% confidence intervals [CIs]) indicated that the results favored the R group in the analysis of the duration of anesthesia, time to rescue, HR, MAP, SBP, and DBP at 10 and 45 minutes and favored the RD group in the times to onset of sensory and motor block and the decreases in the HR, MAP, SBP, and DBP amplitudes at 10 and 45 minutes. Otherwise, the results supported the RD or R group. Risk ratios (RRs) were used to analyze the dichotomous variables (AEs). An RR  $> 1$  (with 95% CI) indicated that the results favored the RD group in the analysis of AEs. To determine whether nationality, age, type of surgery, or dose of dexmedetomidine changed the results, we performed subgroup analysis of the duration of anesthesia, time to rescue, and HR at 10 minutes. We used the  $I^2$  statistic and  $\chi^2$  test to evaluate heterogeneity. When  $I^2 < 50\%$  or  $P > 0.1$ , we used the fixed-effects model to reflect the lack of significant heterogeneity. Otherwise, we used the random effects model. Publication bias and sensitivity analysis were performed using STATA. We used Egger linear regression tests<sup>[17]</sup> and Begg rank correlation<sup>[18]</sup> to evaluate the publication bias. Statistical significance was assumed when  $P < .05$ .

## 3. Results

### 3.1. RCT selection

We retrieved 845 related articles after the first search, and 651 articles after were removed due to duplicate data. After titles and abstracts were read, 79 reports were included for full-text review. Sixty-eight articles were excluded because they were noncomparative studies, did not compare the RD and R groups, were meeting articles, or included different patient types in the 2 groups. Eleven studies, with 337 patients in the R group and 336 patients in the RD group, were ultimately included<sup>[11–13,19–26]</sup> (Fig. 1).

### 3.2. Study characteristics

Across the included studies, all of the trials were published between 2014 and 2020, and the average age of the enrolled patients varied from 3.93 to 48.13 years. Patients had undergone thoracotomy, labor, cesarean section, lumbosacral spine surgery, infra-umbilical surgery, lower abdominal surgery, or lower limb surgery. Table 2 lists the baseline characteristics of the studies, and the quality of the articles is listed in Figure 2 and Table 3. The level of evidence of the results is presented in Table 4.

**Table 1****Search strategy.****PubMed**

The database was searched on March 17, 2020, n=36.

Search Strategy:

(Epidural analgesia [Title/Abstract] and (Ropivacaine [Title/Abstract] OR 1-Propyl-2',6'-pipecoloxylidide [Title/Abstract] OR 1 Propyl 2',6' pipecoloxylidide [Title/Abstract] OR Naropin [Title/Abstract] OR Ropivacaine Monohydrochloride [Title/Abstract] OR Ropivacaine Hydrochloride [Title/Abstract] OR AL 381 [Title/Abstract] OR AL-381 [Title/Abstract] OR AL381 [Title/Abstract] OR Naropeine [Title/Abstract] OR LEA 103 [Title/Abstract] OR LEA-103 [Title/Abstract] OR LEA103 [Title/Abstract]) and (Dexmedetomidine [Title/Abstract] OR MPV-1440 [Title/Abstract] OR MPV 1440 [Title/Abstract] OR MPV1440 [Title/Abstract] OR Precedex [Title/Abstract] OR Dexmedetomidine Hydrochloride [Title/Abstract] OR Hydrochloride, Dexmedetomidine [Title/Abstract])

**Web of Science**

The database was searched on March 17, 2020, n=137.

Search Strategy:

- 1.TOPIC: ("Epidural analgesia") (136432)
- 2.TOPIC: ("Ropivacaine" OR "1-Propyl-2',6'-pipecoloxylidide" OR "1 Propyl 2',6' pipecoloxylidide" OR "Naropin" OR "Ropivacaine Monohydrochloride" OR "Ropivacaine Hydrochloride" OR "AL 381" OR "AL-381"OR "AL381" OR "Naropeine" OR "LEA 103" OR "LEA-103" OR "LEA103") (6798)
- 3.TOPIC: ("Dexmedetomidine" OR "MPV-1440" OR "MPV 1440" OR "MPV1440" OR "Precedex" OR "Dexmedetomidine Hydrochloride" OR "Hydrochloride, Dexmedetomidine") (6179)
- 4.#1 AND #2 AND #3 (137)

**EMBASE**

The database was searched on March 17, 2020, n=193.

Search Strategy:

('Epidural analgesia':ti,ab,kw) AND ('Ropivacaine':ti,ab,kw OR '1-Propyl-2',6'-pipecoloxylidide':ti,ab,kw OR '1 Propyl 2',6' pipecoloxylidide':ti,ab,kw OR 'Naropin':ti,ab,kw OR 'Ropivacaine Monohydrochloride':ti,ab,kw OR 'Ropivacaine Hydrochloride':ti,ab,kw OR 'AL 381':ti,ab,kw OR 'AL-381':ti,ab,kw OR 'AL381':ti,ab,kw OR 'Naropeine':ti,ab,kw OR 'LEA 103':ti,ab,kw OR 'LEA-103':ti,ab,kw OR 'LEA103':ti,ab,kw) AND ('Dexmedetomidine':ti,ab,kw OR 'MPV-1440':ti,ab,kw OR 'MPV 1440':ti,ab,kw OR 'MPV1440':ti,ab,kw OR 'Precedex':ti,ab,kw OR 'Dexmedetomidine Hydrochloride':ti,ab,kw OR 'Hydrochloride, Dexmedetomidine':ti,ab,kw)

**Cochrane Library**

The database was searched on March 17, 2020, n=60.

Search Strategy:

("Epidural analgesia"): ti,ab,kw AND ("Ropivacaine" OR "1-Propyl-2',6'-pipecoloxylidide" OR "1 Propyl 2',6' pipecoloxylidide" OR "Naropin" OR "Ropivacaine Monohydrochloride" OR "Ropivacaine Hydrochloride" OR "AL 381" OR "AL-381"OR "AL381" OR "Naropeine" OR "LEA 103" OR "LEA-103" OR "LEA103"): ti,ab,kw AND ("Dexmedetomidine" OR "MPV-1440" OR "MPV 1440" OR "MPV1440" OR "Precedex" OR "Dexmedetomidine Hydrochloride" OR "Hydrochloride, Dexmedetomidine"): ti,ab,kw - (Word variations have been searched)

**Ovid MEDLINE**

The database was searched on March 17, 2020, n=184.

Search Strategy:

1. Epidural analgesia.ab. (6784)
  2. or/1 [Epidural analgesia] (6784)
  3. Ropivacaine.ab. (16489)
  4. 1-Propyl-2',6'-pipecoloxylidide.ab. (2430)
  5. 1 Propyl 2',6' pipecoloxylidide.ab.(2234)
  6. Naropin.ab. (1345)
  7. Ropivacaine Monohydrochloride.ab. (321)
  8. LEA 103.ab. (124)
  9. LEA-103.ab.(145)
  10. LEA103.ab. (311)
  11. or/3-10 [Ropivacaine] (9784)
  12. Dexmedetomidine.ab. (9657)
  13. MPV-1440.ab. (145)
  14. MPV 1440.ab. (112)
  15. MPV1440.ab. (113)
  16. Precedex.ab. (231)
  17. Dexmedetomidine Hydrochloride.ab. (451)
  18. Hydrochloride, Dexmedetomidine.ab. (531)
  19. or/12-18 [Dexmedetomidine] (6371)
  20. 2 and 11 and 19 (245)
- limit 20 to humans (184)

**ScienceDirect**

The database was searched on March 17, 2020, n=101.

Search Strategy:

Title, abstract, keywords

("Epidural analgesia") and ("Ropivacaine" OR "1-Propyl-2',6'-pipecoloxylidide" OR "1 Propyl 2',6' pipecoloxylidide" OR "Naropin" OR "Ropivacaine Monohydrochloride" OR "Ropivacaine Hydrochloride" OR "AL 381" OR "AL-381"OR "AL381" OR "Naropeine" OR "LEA 103" OR "LEA-103" OR "LEA103") and ("Dexmedetomidine" OR "MPV-1440" OR "MPV 1440" OR "MPV1440" OR "Precedex" OR "Dexmedetomidine Hydrochloride" OR "Hydrochloride, Dexmedetomidine"))

(continued)

**Table 1**

(continued).

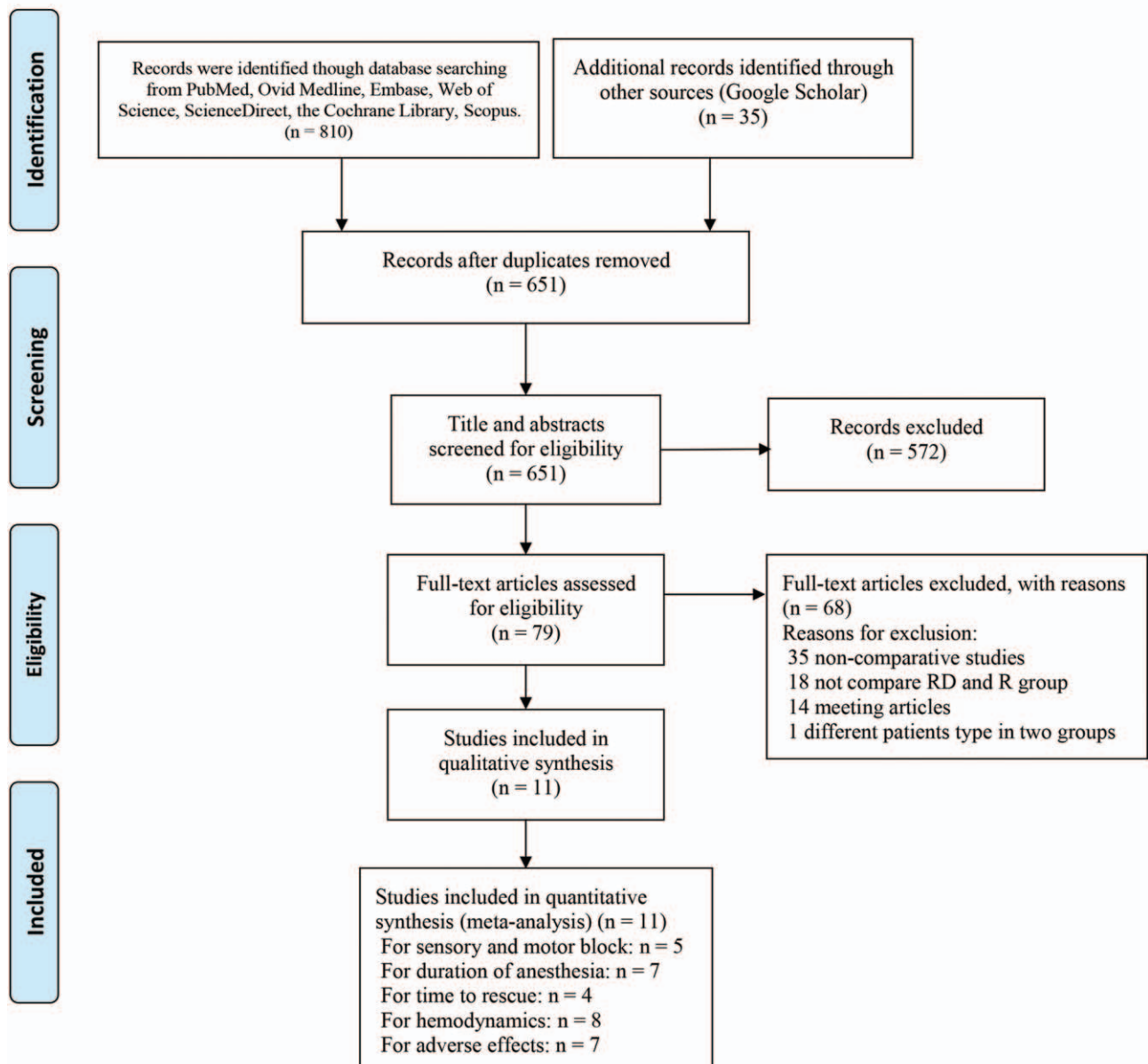
**Scopus**

The database was searched on March 17, 2020, n=99.

Search Strategy:

TITLE-ABS-KEY (("Epidural analgesia") and ("Ropivacaine" OR "1-Propyl-2',6'-pipecoloxylidide" OR "1 Propyl 2',6' pipecoloxylidide" OR "Naropin" OR "Ropivacaine Monohydrochloride" OR "Ropivacaine Hydrochloride" OR "AL 381" OR "AL-381"OR "AL381" OR "Naropeine" OR "LEA 103" OR "LEA-103" OR "LEA103") and ("Dexmedetomidine" OR "MPV-1440" OR "MPV 1440" OR "MPV1440" OR "Precedex" OR "Dexmedetomidine Hydrochloride" OR "Hydrochloride, Dexmedetomidine"))

The combined text and medical subject heading (MeSH) terms used were: "Epidural analgesia," "Ropivacaine," and "Dexmedetomidine."

**PRISMA 2009 Flow Diagram****Figure 1.** Flow chart of the study selection.

### 3.3. Efficiency of anesthesia

Five articles were included to assess the time to onset of sensory and motor block. The results showed that the RD group had a shorter time to onset of sensory block (MD: 3.97 minutes; 95% CI: 1.90–6.04;  $P=.0002$ ) and motor block (MD: 2.43 minutes; 95% CI: 0.70–4.16;  $P=.006$ ) (Fig. 3) than the R group.

Seven articles that included 212 patients in the R group and 211 in the RD group to assess the duration of the anesthesia between the groups. The RD group had a longer duration of anesthesia than the R group (MD: -164.17 minutes; 95% CI: -294.43 to -33.91;  $P=.01$ ) (Fig. 4A).

Four articles that included 260 patients were used to compare the time to rescue between the groups. The comparison between the groups showed no significant difference (MD: -119.01 minutes; 95% CI: -254.47 to 16.46;  $P=.09$ ) (Fig. 4B).

### 3.4. Hemodynamics

Three articles were used to evaluate whether the administration of dexmedetomidine was associated with a lower HR. The results showed that the R group had a higher HR than the RD group at 10 minutes (MD: 8.73 beats/min; 95% CI: 2.37–15.08;  $P=.007$ ) and 45 minutes (MD: 4.72 beats/min; 95% CI: 2.65–6.79;  $P<.00001$ ) (Table 5). We also used the decrease in the HR amplitude at 10 and 45 minutes to compare the efficiency between the groups. The results showed that the R group had a smaller decrease in the HR amplitude than the RD group at 10 minutes (MD: -6.03 beats/min; 95% CI: -10.97 to -1.09;  $P=.02$ ) and 45 minutes (MD: -4.46 beats/min; 95% CI: -8.52 to -0.40;  $P=.03$ ) (Table 6).

Two articles that included 110 patients were included to compare the MAP between the groups. The R group had a higher

**Table 2**

**Characteristics of the included studies.**

Study	Nation	Groups	Patients (n)	Male/female	Median age (yr)	Weight (kg)	Height (cm)	ASA	Surgery	Anesthesia position	Method	Outcomes
2014 Sarvesh <sup>[19]</sup>	India	R	30	28/2	6.67	22.6	—	I-II	Infra-umbilical surgery	dorsal sacrococcygeal	0.25%R 1ml/kg	②④
		RD	30	29/1	6.5	22	—				0.25%R 1ml/kg+ 1ug/kg D	
2014 Attri <sup>[11]</sup>	India	R	50	28/22	39.96	64.26	—	I-II	Lower limb orthopedic surgery	L3–4	0.75% R 20ml	①②③④
		RD	50	30/20	40.16	64.82	—				0.75% R 20ml+ 1ug/kg D	
2016 Kalappa <sup>[20]</sup>	India	R	30	14/16	44.13	60.13	158.31	—	Lumbosacral spine surgery	—	0.2% R	②③④
		RD	30	18/12	43.67	55.90	158.32				0.2% R+ 1ug/kg D	
2016 Zhao <sup>[12]</sup>	China	R	40	—/40	26.2	79.33	162.98	—	Labor	—	0.125% R	⑤
		RD	40	—/40	25.93	80.70	163.18				0.125% R+ 0.5mg/kg D	
2016 Soni <sup>[13]</sup>	India	R	20	7/13	45.7	—	—	I-II	Lower abdominal and lower limbs surgery	—	0.75% R 19ml	②④⑤
		RD	20	14/6	44	—	—				0.75% R 19ml + 1.5 μg/kg D 1ml	
2016 Kamal <sup>[21]</sup>	India	R	30	28/2	3.93	14.1	—	—	Lower abdominal surgery	—	0.25% R 1ml/kg	②④⑤
		RD	30	28/2	4.23	14.23	—				0.25% R 1ml/kg + 2ug/kg D	
2016 Kar <sup>[22]</sup>	India	R	27	17/10	36.8	54.3	161.3	—	Thoracotomy	T3–T4/T4–T5	0.5% R 7ml	②④⑤
		RD	26	19/7	36.1	55.3	163.9				0.5% R 7ml + 1ug/kg D	
2016 Joy <sup>[23]</sup>	India	R	30	13/17	48.13	63.37	159.07	I-II	Lower extremity and abdominal surgery	L1–L2, L2–L3 or L3–L4	0.5% R 15ml	①
		RD	30	13/17	46.57	62.2	157.53				0.5% R 15ml + 1ug/kg D	
2018 Kiran <sup>[24]</sup>	India	R	25	—	—	—	—	I-II	Infra-umbilical surgery	L2–L3	0.5% R 18ml	①③④⑤
		RD	25	—	—	—	—				0.5% R 18ml + 10 ug D	
2019 Ashem <sup>[25]</sup>	India	R	25	22/3	34.32	60.16	161.2	I-II	lower limbs surgery	L3–L4	0.75% R 20ml	①②③④⑤
		RD	25	19/6	39.72	57.96	161.9				0.75% R 20ml + 1ug/kg D	
2020 Tan <sup>[26]</sup>	China	R	30	—/30	32	68	160	II	cesarean section	L1–L2	1% R	①⑤
		RD	30	—/30	32	68	160				1% R + 5ug D	

ASA=American Society of Anesthesiology, D=dexmedetomidine, L=lumbar, R=ropivacaine, RD=ropivacaine combined with dexmedetomidine, T=thoracic. Outcomes: ① time to onset of sensory and motor block; ② duration of anesthesia; ③ time to rescue; ④ hemodynamics; ⑤ adverse effects.



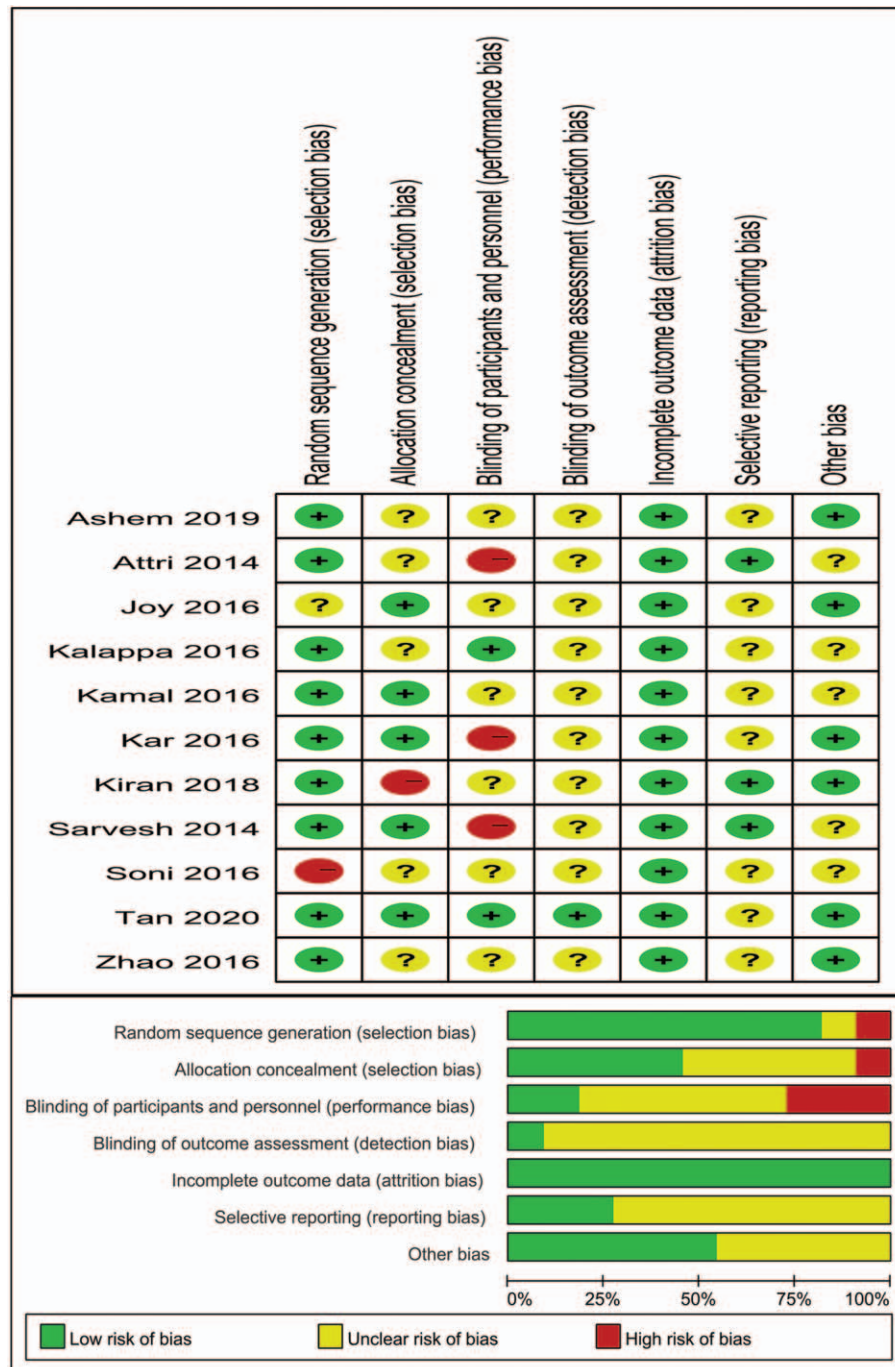


Figure 2. Risk of bias assessments for studies in a Cochrane review.

MAP than the RD group at 10 minutes (MD: 7.77 mm Hg; 95% CI: 5.13–10.41;  $P < .00001$ ) and 45 minutes (MD: 3.45 mm Hg; 95% CI: 0.83–6.06;  $P = .01$ ) (Table 5). The results also showed that the R group had a smaller decrease in the MAP amplitude than the RD group at 10 minutes (MD: -7.01 mm Hg; 95% CI: -9.99 to -4.03;  $P < .00001$ ). However, no significant difference was found at 45 minutes (MD: -2.28 mm Hg; 95% CI: -5.18 to 0.61;  $P = .12$ ) (Table 6).

Two articles that included 140 patients were used to compare the SBP and DBP between the groups. The R group had a higher

SBP and DBP than the RD group at 10 minutes (SBP: MD: 7.21 mm Hg; 95% CI: 3.17–11.24;  $P = .0005$ ), (DBP: MD: 3.26 mm Hg; 95% CI: 0.44–6.09;  $P = .02$ ) and 45 minutes (SBP: MD: 5.38 mm Hg; 95% CI: 2.03–8.74;  $P = .002$ ), (DBP: MD: 4.20 mm Hg; 95% CI: 1.55–6.85;  $P = .002$ ) (Table 5). The decrease in the SBP amplitude in the R group at 10 and 45 minutes was smaller than that in the RD group (10 minutes: MD: -7.50 mm Hg; 95% CI: -14.56 to -0.43;  $P = .04$ ), (45 minutes: MD: -7.39 mm Hg; 95% CI: -11.61 to -3.18;  $P = .0006$ ). The decrease in the DBP amplitude at 10 and 45 minutes in the R group was smaller than

**Table 3**  
Quality assessment of all included studies.

Study	Randomization	Masking	Accountability of all patients	Quality (scores)
2014	Sarvesh <sup>[19]</sup>	**	**	*
2014	Attri <sup>[11]</sup>	**	*	*
2016	Kalappa <sup>[20]</sup>	**	**	*
2016	Zhao <sup>[12]</sup>	**	*	*
2016	Soni <sup>[13]</sup>	*	*	*
2016	Kamal <sup>[21]</sup>	**	*	*
2016	Kar <sup>[22]</sup>	**	**	*
2016	Joy <sup>[23]</sup>	*	**	*
2018	Kiran <sup>[24]</sup>	**	**	*
2019	Ashem <sup>[25]</sup>	*	**	*
2020	Tan <sup>[26]</sup>	**	**	*

**Table 4**  
Evidence assessment with the GRADE system.

Primary outcomes	No. of Studies	No. of participants		Differences* (95%CI)	Risk of Bias†	Quality assessment				Quality
		R	RD			Inconsistency	Indirectness	Imprecision	PublicationBias‡	
Sensory and motor block										
Time to onset of sensory block	4	130	130	3.97 [1.90, 6.04]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Time to onset of motor block	5	160	160	3.12 [1.85, 4.40]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Duration of anesthesia	7	212	211	-164.17 [-294.43, -33.91]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low
Time to rescue	4	130	130	-119.01 [-254.47, 16.46]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low
HR										
At 10 min	3	95	95	5.45 [0.01, 10.89]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low
At 45 min	3	95	95	4.72 [2.65, 6.79]	Low	Serious (-1)	No indirectness	No imprecision	Unlikely	Medium
Decreasing amplitude at 10 min	3	95	95	7.44 [4.85, 10.03]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Decreasing amplitude at 45 min	3	95	95	5.34 [3.07, 7.62]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
BP										
MAP										
At 10 min	2	55	55	7.77 [5.13, 10.41]	Low	Very serious (-2)	No indirectness	Serious (-1)	Unlikely	Very low
At 45 min	2	55	55	3.45 [0.83, 6.06]	Low	No inconsistency	No indirectness	Serious (-1)	Unlikely	Medium
Decreasing amplitude at 10 min	2	55	55	7.01 [4.03, 9.99]	Low	Very serious (-2)	No indirectness	Serious (-1)	Unlikely	Very low
Decreasing amplitude at 45 min	2	55	55	2.28 [-0.61, 5.18]	Low	No inconsistency	No indirectness	Serious (-1)	Unlikely	Medium
SBP										
At 10 min	2	70	70	7.21 [3.17, 11.24]	Low	Serious (-1)	No indirectness	No imprecision	Unlikely	Medium
At 45 min	2	70	70	5.38 [2.03, 8.74]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Decreasing amplitude at 10 min	2	70	70	8.05 [-0.4, 16.49]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low
Decreasing amplitude at 45 min	2	70	70	7.39 [3.18, 11.61]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
DBP										
At 10 min	2	70	70	3.26 [0.44, 6.09]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
At 45 min	2	70	70	4.20 [1.55, 6.85]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
	2	70	70	5.90 [2.83, 8.96]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High

(continued)

**Table 4**  
(continued).

Primary outcomes	No. of Studies	No. of participants		Differences* (95%CI)	Risk of Bias†	Quality assessment					Quality
		R	RD			Inconsistency	Indirectness	Imprecision	PublicationBias‡		
Decreasing amplitude at 10 min											
Decreasing amplitude at 45 min	2	70	70	6.75 [3.75,9.74]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low	
<b>Adverse effects</b>											
Hypotension	5	130	130	0.36 [0.12,1.10]	Low	Very serious (-2)	No indirectness	No imprecision	Unlikely	Low	
Nausea or vomiting	5	145	145	1.17 [0.65,2.09]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	
Shivering	3	80	80	2.82 [1.13,7.01]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	
Pruritus	1	30	30	1.33 [0.33,5.45]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	
Bradycardia	5	127	127	0.29 [0.13,0.65]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	
Dry mouth	2	45	45	0.33 [0.07,1.56]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	
Oversedation	1	30	30	1.50 [0.27,8.34]	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High	

DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, R = ropivacaine, RD = ropivacaine combined with dexmedetomidine, SBP = systolic blood pressure.

\* Differences: Mean difference (MD) for sensory and motor block, duration of anesthesia, time to rescue, HR, MAP, SBP, DBP; risk ratios (RR) for adverse effects.

† Risk of bias assessed using the Jada for randomized studies.

‡ Publication bias was assessed by Egger and Begg tests.

that in the RD group (10 minutes: MD: -3.29 mm Hg; 95% CI: -6.36 to -0.23;  $P = .04$ ) (45 minutes: MD: -5.25 mm Hg; 95% CI: -8.24 to -2.25;  $P = .0006$ ) (Table 6). The curves of the MDs in HR (A), MAP (B), SBP (C), and DBP (D) between the R and RD group are presented in Figure 5.

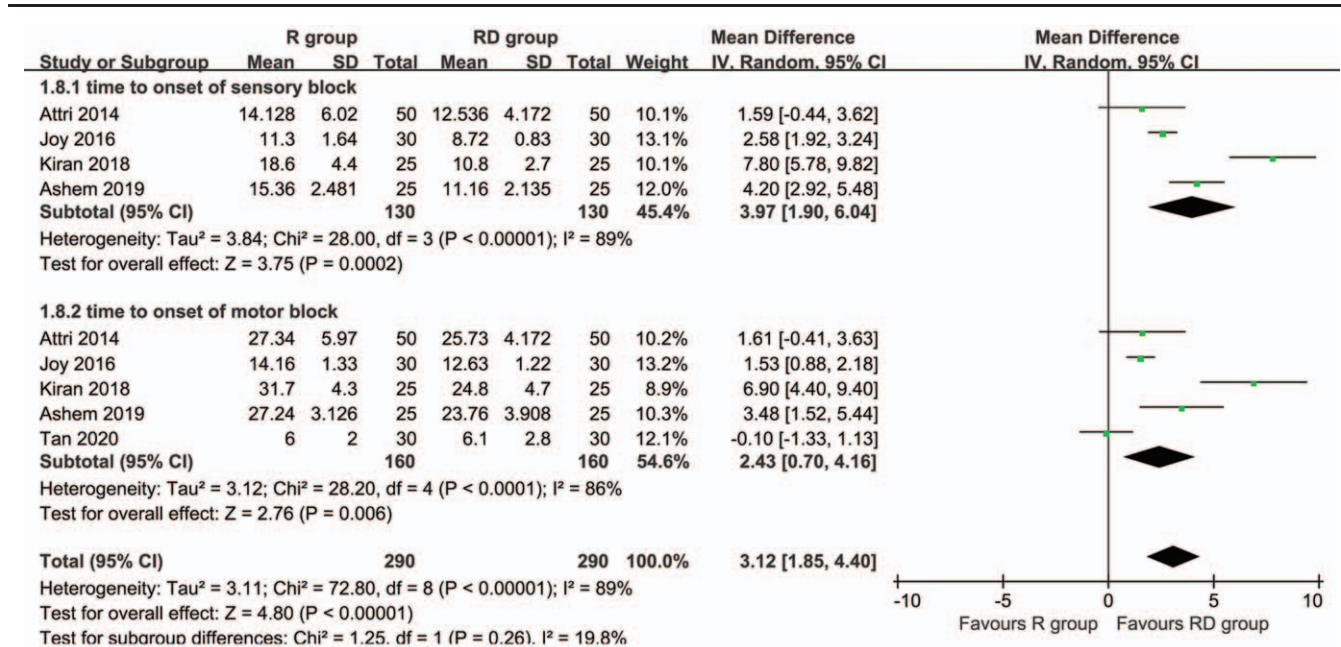
**3.5. Adverse effects**

No significant difference in the total AEs was found between the R and RD groups (RR: 0.67; 95% CI: 0.22–2.05;  $P = .48$ ) (Table 7). The following main AEs were reported: hypotension,

nausea or vomiting, shivering, pruritus, bradycardia, dry mouth, and oversedation. The results showed that the R group had a higher incidence of shivering (RR: 2.82; 95% CI: 1.13–7.01;  $P = .03$ ), and lower incidence of bradycardia (RR: 0.29; 95% CI: 0.13–0.65;  $P = .003$ ) than the RD group. No significant differences in other AEs were found (Table 7).

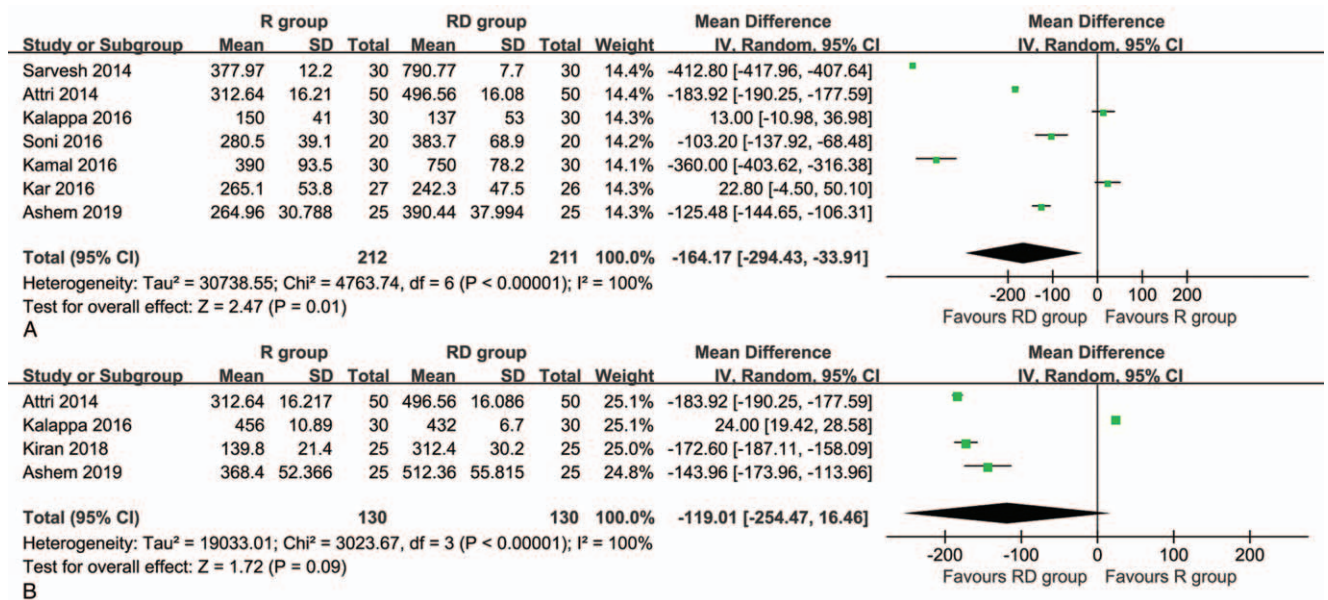
**3.6. Subgroup analysis**

We performed subgroup analysis to evaluate whether the efficiency of the R and RD groups was consistent across



**Figure 3.** Forest plot of the time to onset of sensory and motor block associated with the ropivacaine group and ropivacaine combined with dexmedetomidine.





**Figure 4.** Forest plot of the duration of anesthesia (A) and time to rescue (B) associated with the ropivacaine group and ropivacaine combined with dexmedetomidine.

**Table 5**

**Comparison of the HR and BP at 10 and 45minutes in the R and RD groups.**

Hemodynamics	R group (n)	RD group (n)	MD (95% CI)	P value	Heterogeneity	
					I <sup>2</sup> (%)	P value
At 10 min						
HR <sup>[12,20,24]</sup>	95	95	8.73 [2.37, 15.08]	.007	81	.005
MAP <sup>[12,20]</sup>	55	55	7.77 [5.13,10.41]	<.00001	0	.4
SBP <sup>[12,20]</sup>	70	70	7.21 [3.17,11.24]	.0005	38	.2
DBP <sup>[12,20]</sup>	70	70	3.26 [0.44,6.09]	.02	34	.22
At 45 min						
HR <sup>[12,20,24]</sup>	95	95	4.72 [2.65,6.79]	<.00001	47	.15
MAP <sup>[12,20]</sup>	55	55	3.45 [0.83,6.06]	.01	0	.7
SBP <sup>[12,20]</sup>	70	70	5.38 [2.03,8.74]	.002	0	.99
DBP <sup>[12,20]</sup>	70	70	4.20 [1.55,6.85]	.002	0	.55

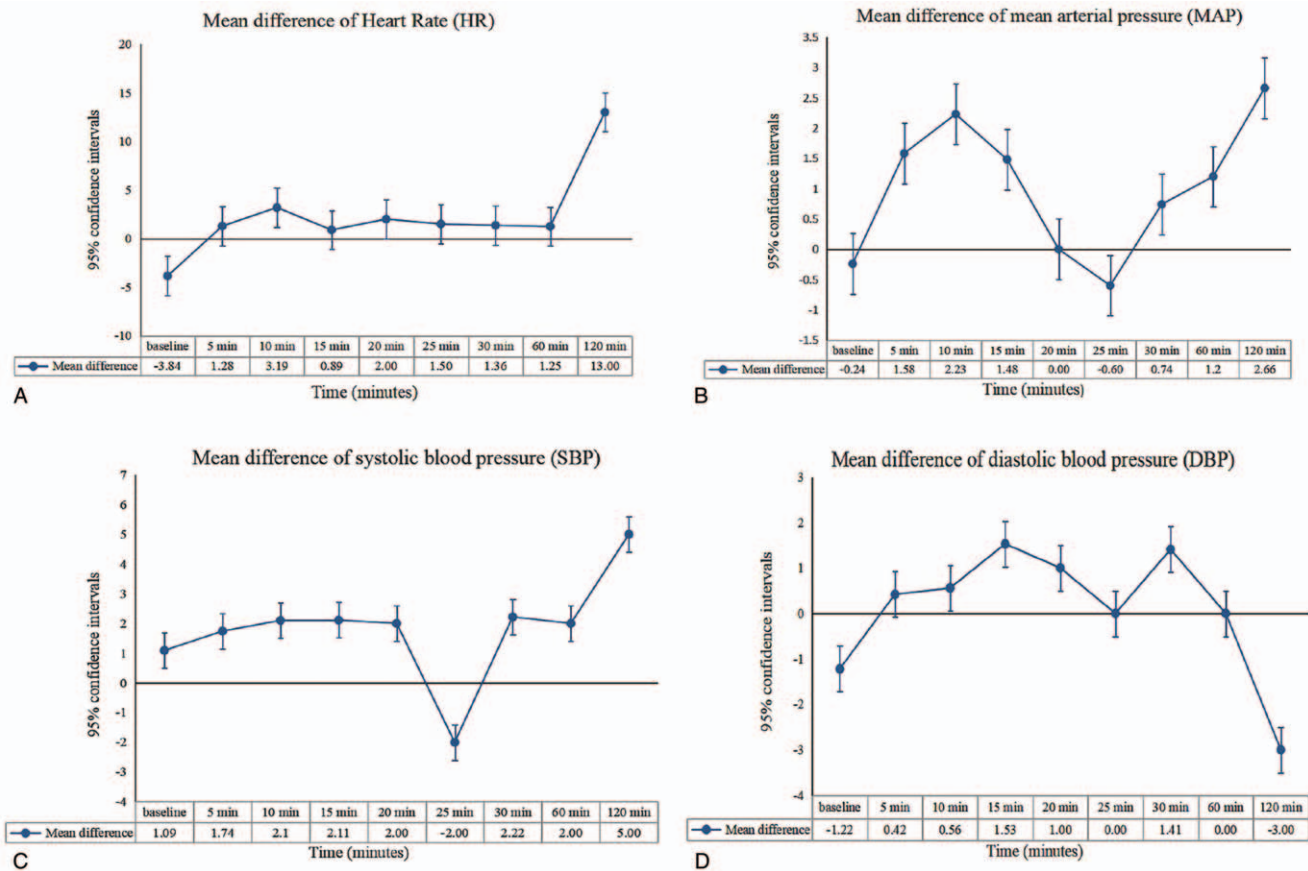
DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, MD = mean difference, R group = ropivacaine alone, RD group = ropivacaine combined with dexmedetomidine, SBP = systolic blood pressure.

**Table 6**

**Comparison of the decreasing amplitudes of HR and BP at 10 and 45minutes in the R and RD groups.**

Hemodynamics	R group (n)	RD group (n)	MD (95% CI)	P value	Heterogeneity	
					I <sup>2</sup> (%)	P value
The decreasing amplitude at 10 min						
HR <sup>[12,20,24]</sup>	95	95	-6.03 [-10.97, -1.09]	.02	68	.04
MAP <sup>[12,20]</sup>	55	55	-7.01 [-9.99, -4.03]	<.00001	31	.23
SBP <sup>[12,20]</sup>	70	70	-7.50 [-14.56, -0.43]	.04	54	.14
DBP <sup>[12,20]</sup>	70	70	-3.29 [-6.36, -0.23]	.04	100	0
The decreasing amplitude at 45 min						
HR <sup>[12,20,24]</sup>	95	95	-4.46 [-8.52, -0.40]	.03	62	.07
MAP <sup>[12,20]</sup>	55	55	-2.28 [-5.18, 0.61]	.12	0	.98
SBP <sup>[12,20]</sup>	70	70	-7.39 [-11.61, -3.18]	.0006	0	.54
DBP <sup>[12,20]</sup>	70	70	-5.25 [-8.24, -2.25]	.0006	100	0

DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, MD = mean difference, R = ropivacaine, RD = ropivacaine combined with dexmedetomidine, SBP = systolic blood pressure.



**Figure 5.** Curves of the mean differences in heart rate (A), mean arterial pressure (B), systolic blood pressure (C), and diastolic blood pressure (D) between the ropivacaine group and ropivacaine combined with dexmedetomidine.

subgroups. Young age (<10 years) (MD: -391.02 minutes; 95% CI: -441.97 to -340.08;  $P < .00001$ ), 1.5  $\mu\text{g}/\text{kg}$  dexmedetomidine (MD: -103.20 minutes; 95% CI: -137.92 to -68.48;  $P < .00001$ ) and 2.0  $\mu\text{g}/\text{kg}$  dexmedetomidine (MD: -360 minutes; 95% CI: -403.62 to -316.38;  $P < .00001$ ) may prolonged the duration of anesthesia in the RD group (Table 8).

**3.7. Sensitivity analysis**

The results showed significant heterogeneity in the duration of anesthesia and time to rescue. Sensitivity analysis revealed that each study was stable and reliable (Fig. 6).

**3.8. Publication bias**

Publication bias analysis revealed the following publication biases: duration of anesthesia (Begg test  $P = 0.548$ ; Egger test  $P = 0.204$ ) (Fig. 7A); time to rescue (Begg test  $P = 1.000$ ; Egger test  $P = 0.536$ ) (Fig. 7B); HR at 10 minutes (Begg test  $P = 1.000$ ; Egger test  $P = .905$ ) (Fig. 7C).

**4. Discussion**

Epidural anesthesia is a common and unique anesthesia technique that is used for intraoperative surgical anesthesia

**Table 7**  
Adverse effects associated in the R and RD groups.

Adverse effects	R group (event/total)	RD group (event/total)	Total incidence rate (%)	RR (95% CI)	P value	Heterogeneity	
						$I^2$ (%)	P value
Total adverse effects <sup>[12,13,21,22,24,25,26]</sup>	60/197	93/196	38.9	0.67 [0.22,2.05]	.48	95	<.00001
Hypotension <sup>[13,21,24,25,26]</sup>	16/130	43/130	22.7	0.36 [0.12,1.10]	.07	64	.02
Nausea or vomiting <sup>[12,13,21,24,26]</sup>	21/145	18/145	13.4	1.17 [0.65,2.09]	.60	0	.61
Shivering <sup>[24,25,26]</sup>	15/80	5/80	12.5	2.82 [1.13,7.01]	.03	0	.69
Pruritus <sup>[26]</sup>	4/30	3/30	12.0	1.33 [0.33,5.45]	.69	-	-
Bradycardia <sup>[13,22,24,25,26]</sup>	6/127	23/126	11.5	0.29 [0.13,0.65]	.003	22	.28
Dry mouth <sup>[13,25]</sup>	2/45	6/45	8.9	0.33 [0.07,1.56]	.16	0	.53
Oversedation <sup>[26]</sup>	3/30	2/30	8.3	1.50 [0.27,8.34]	.64	-	-

R=ropivacaine, RD group=ropivacaine combined with dexmedetomidine group, RR=risk ratios.

**Table 8**  
**Subgroup analysis of the duration of anesthesia, time to rescue, and HR at 10 minutes.**

Group	Duration of anesthesia				Time to rescue				HR at 10 min			
	No. of studies	MD (95% CI)	P	I <sup>2</sup> (%)	No. of studies	MD (95% CI)	P	I <sup>2</sup> (%)	No. of studies	MD (95% CI)	P	I <sup>2</sup> (%)
Total	7	-164.17 [-294.43, -33.91]	.01	100	4	-119.01 [-254.47, 16.46]	.09	100	3	5.45 [0.01, 10.89]	.05	74
Nation												
China	-	-	-	-	-	-	-	-	1	8.28 [4.69, 11.87]	<.00001	-
India	7	-164.17 [-294.43, -33.91]	.01	100	4	-119.01 [-254.47, 16.46]	.09	100	2	3.66 [-5.24, 12.55]	.42	81
Age (yr)												
≤ 10	2	-391.02 [-441.97, -340.08]	<.00001	82	-	-	-	-	-	-	-	-
10-30	-	-	-	-	-	-	-	-	1	8.28 [4.69, 11.87]	<.00001	-
>30	5	-75.71 [-164.47, 13.05]	.09	99	3	-101.13 [-264.79, 62.52]	.23	100	1	-0.98 [-6.76, 4.80]	.74	-
NR	-	-	-	-	1	-172.60 [-187.11, -158.09]	<.00001	-	1	8.10 [2.94, 13.26]	.002	-
Surgery												
Thoracotomy	1	22.80 [-4.50, 50.10]	.1	-	-	-	-	-	-	-	-	-
Lower abdominal and lower limbs surgeries	4	-190.49 [-254.60, -126.38]	<.00001	97	2	-166.74 [-205.51, -127.97]	<.00001	-	-	-	-	-
Infraumbilical surgeries	1	-412.80 [-417.96, -407.64]	<.00001	-	1	-172.60 [-187.11, -158.09]	<.00001	-	1	8.10 [2.94, 13.26]	.002	-
Lumbosacral spine surgeries	1	13.00 [-10.98, 36.98]	.29	-	1	24.00 [19.42, 28.58]	<.00001	-	1	-0.98 [-6.76, 4.80]	.74	-
Labor	-	-	-	-	-	-	-	-	1	8.28 [4.69, 11.87]	<.00001	-
Does of dexmedetomidine												
0.5 µg/kg	-	-	-	-	-	-	-	-	1	8.28 [4.69, 11.87]	<.00001	-
1 µg/kg	5	-137.61 [-293.22, 17.99]	.08	100	3	-101.13 [-264.79, 62.52]	.23	100	1	-0.98 [-6.76, 4.80]	.74	-
1.5 µg/kg	1	-103.20 [-137.92, -68.48]	<.00001	-	-	-	-	-	-	-	-	-
2 µg/kg	1	-360.00 [-403.62, -316.38]	<.00001	-	-	-	-	-	-	-	-	-
NR	-	-	-	-	1	-172.60 [-187.11, -158.09]	<.00001	-	1	8.10 [2.94, 13.26]	.002	-

HR = heart rate, MD = mean difference, NR = not reported.

and postoperative analgesia for many surgeries. However, this technique has some disadvantages when used alone. Many studies reported that RD group was more efficient and associated with fewer AEs. However, comparisons of the efficiency and safety of R and RD for EA are lacking. The present study is the first meta-analysis to evaluate the efficiency and safety of R and RD. The RD group had a shorter time to onset of sensory and motor block and a longer duration of anesthesia than the R group. However, no significant difference in the time to rescue was found between the groups. The R group had more stable

hemodynamics than the RD group with stable HR and MAP at 10 min. The R group had a lower incidence of bradycardia and a higher incidence of shivering than the RD group. Subgroup analyses revealed that young age (<10 years) and administration of 1.5 or 2.0 µg/kg dexmedetomidine may prolonged the duration of anesthesia in the RD group.

Analysis of the efficiency of anesthesia revealed that the RD group had a shorter time to onset of sensory and motor block and a longer duration of anesthesia than the R group. Attri et al reported that an RD group had a longer duration of sensory and

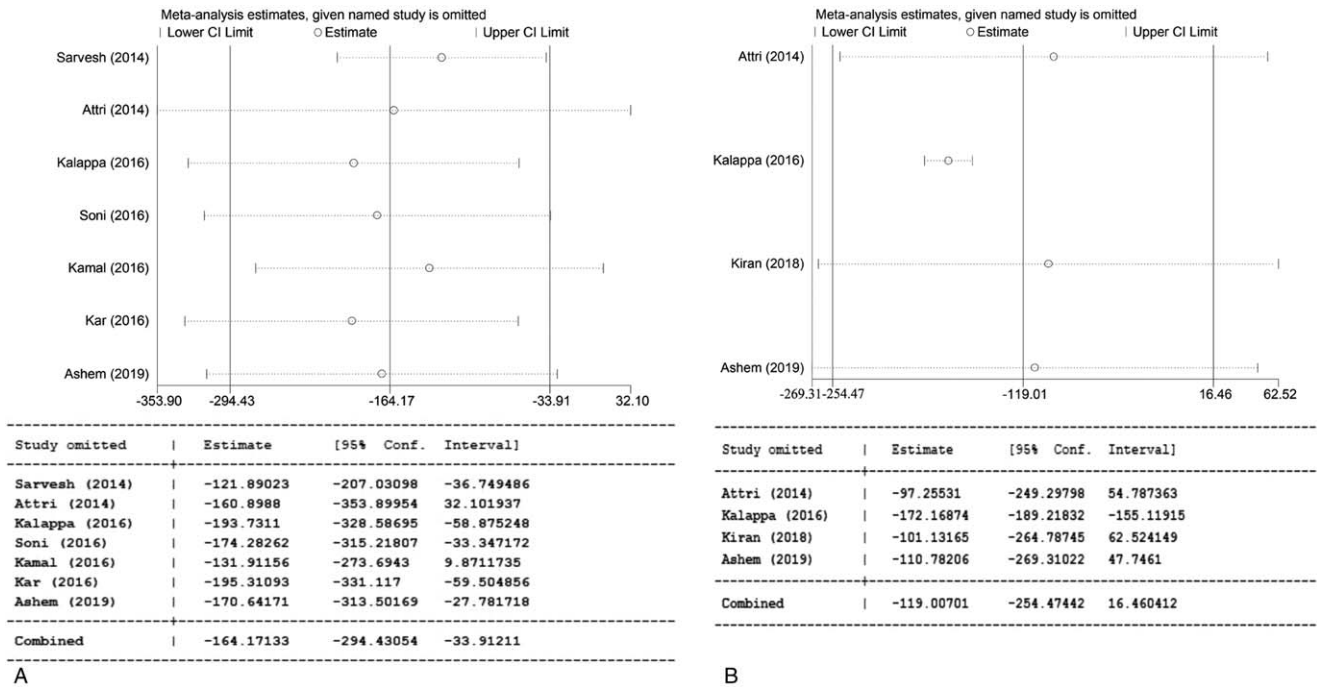


Figure 6. Sensitivity analysis of the duration of anesthesia (A) and time to rescue (B).

motor block than an R group (sensory block:  $375.20 \pm 15.97$  minutes in the R group;  $535.18 \pm 19.85$  minutes in the RD group [ $P < .001$ ]), (motor block:  $259.80 \pm 15.48$  minutes in the R group;  $385.92 \pm 17.71$  minutes in the RD group [ $P < .001$ ]).<sup>[11]</sup> Kiran et al also suggested that the RD group had a shorter time to onset of sensory block than the R group (RD:  $10.8 \pm 2.7$ ; R:  $18.6 \pm 4.4$ ).<sup>[24]</sup> As mentioned in previous studies, dexmedetomidine inhibits the release of C-fiber neurotransmitters and via the hyperpolarization of postsynaptic dorsal horn neurons.<sup>[27–29]</sup> The complementary action of local anesthetics and 2 adrenergic agonists explains the profound analgesic properties.<sup>[30]</sup> This synergistic effect may explain the shorter time to onset of sensory and motor block in the RD group. To determine whether nationality, age, type of surgery, or dose of dexmedetomidine changed the results, we performed subgroup analysis. The advantage of RD was primarily reflected in young patients and at

a dose of 1.5 or 2.0  $\mu\text{g}/\text{kg}$  dexmedetomidine. These data suggest that the RD group has a longer duration of anesthesia and shorter time to onset of sensory and motor block.

To fully assess the efficiency of the R and RD groups, we also evaluated the HR, MAP, SBP, DBP, and decreases in their amplitudes at 10 and 45 minutes in the 2 groups. Our article found that the R group had more stable hemodynamics than the RD group with higher HR, MAP, SBP, and DBP at 10 and 45 minutes, smaller decreases in the HR, MAP, SBP, and DBP amplitudes at 10 minutes, and smaller decreases in the HR, SBP, and DBP amplitudes at 45 minutes. These results are similar to those of Krian et al<sup>[24]</sup> who reported that HR and MAP in the RD group were lower than the R group. Some studies reported that the use of dexmedetomidine as an adjuvant to ropivacaine for EA decreased the HR and BP.<sup>[31,32]</sup> However, the results of Kalappa et al and Kamal et al suggested no clinically significant

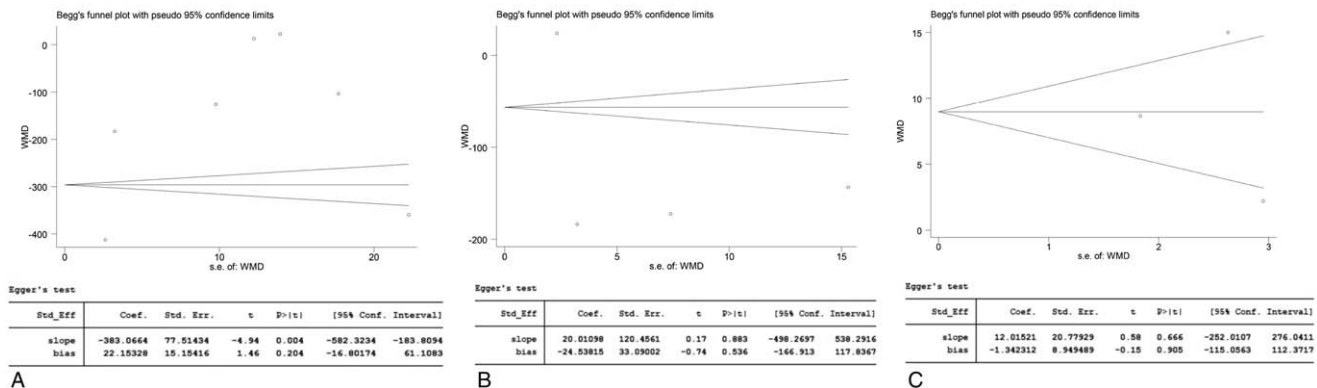


Figure 7. Publication bias of the duration of anesthesia (A), time to rescue (B), and heart rate at 10 minutes (C).



hemodynamic changes in either groups.<sup>[20,21]</sup> Although these results were statistically significant, whether these decreases are a major clinical concern is controversial, especially when they can be controlled with atropine administration.

Differences in major AEs between the R and RD groups remain controversial and were assessed in present article. Both techniques were safe with a similar incidence rate of the total AEs. The major AEs were hypotension (22.7%), nausea or vomiting (13.4%), and shivering (12.5%). Kiran et al showed that the R group had milder AEs than the RD group.<sup>[24]</sup> However, Zhao et al and Kamal et al reported that both therapies were safe.<sup>[12,21]</sup> Our article suggests that the R group had a lower incidence of bradycardia and a higher incidence of shivering than the RD group, similar to findings in previous studies.<sup>[33–35]</sup> Dexmedetomidine can be combined with alpha-2 adrenoreceptors in the dorsal horn of the spinal cord to suppress the spontaneous firing rate of neurons and sympathetic tone.<sup>[36]</sup> These characteristics may explain the lower incidence of bradycardia and a higher incidence of shivering in the R group.

Our article has several limitations that call for caution in the interpretation of the results. First, this meta-analysis only included 11 articles with 673 patients, which limits the reliability of the results. Second, the different clinical centers, different periods, different devices, and different postoperative pain assessments increased the heterogeneity of the results. Although we used the random effects model to analyze data with high heterogeneity, we should interpret the results conservatively. Third, some of the included articles lacked information about the method of randomization and allocation concealment, which may decrease the quality of the articles. Fourth, the sample size in the subgroup analysis was underpowered, and these results should be interpreted cautiously.

Our study is different from that of Qian<sup>[37]</sup> for the following reasons. First, the purposes of these 2 studies were different: our study solved the problem of the necessity of the addition of dexmedetomidine, and Qian's study compared the efficiency of dexmedetomidine + ropivacaine and fentanyl + ropivacaine. Second, the data were retrieved from different databases. Qian's study also included the Wanfang and China National Knowledge Infrastructure (CNKI) databases. Third, we performed subgroup analysis to evaluate whether the efficiency of the R and RD groups was consistent across the subgroups, while Qian did not.

## 5. Conclusion

RD may be a more suitable choice for EA with better anesthetic function than R. However, RD showed more obvious interference effects on hemodynamics than the R. A higher incidence of bradycardia and a lower incidence of shivering were found in the RD group. Subgroup analyses suggested that a younger age (<10 years old) and the use of 1.5 or 2.0 µg/kg dexmedetomidine prolonged the duration of anesthesia in the RD group. However, more high-quality studies are needed to evaluate the differences between R and RD.

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