# Original Article Effects of dexmedetomidine as a local anesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis

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**Abstract:** Background: Brachial plexus blocks (BPBs) improve postoperative analgesia, and reduce rescue analgesic consumption for upper limb surgeries. However, their benefits may be short lived. This meta-analysis was performed to examine whether perineural dexmedetomidine (DEX) combined with local anesthetics (LAs) for BPB can prolong the duration of analgesia compared with LA alone. Methods: All randomized controlled trials (RCTs) testing the impact of adding DEX to LAs for single-injection BPBs in adults undergoing upper limb surgery without general anesthesia were searched. The primary outcome was duration of analgesia, sensory block duration, motor block duration, and side effects; the secondary outcomes were block onset times, analgesic consumption, and hemodynamic parameters. Results: Thirteen trials (818 patients, 369 received DEX) were included. Dexmedetomidine prolonged the duration of analgesia by 285.02 min [95% confidence interval (CI): 181.55, 388.49, P<0.00001]. Motor block duration was prolonged by 250.63 min [95% CI: 148.10, 353.17, P<0.00001]. Sensory block duration was prolonged by 266.45 min [95% CI: 148.29, 384.61, P<0.00001]. DEX increased the risk of bradycardia [odds ratio 15.75; 95% CI: 4.02, 61.78, P<0.0001]. Conclusions: Perineural DEX combined with LAs prolong the duration of analgesia, however, the risk of bradycardia was increased at the same time.

Keywords: Dexmedetomidine, brachial plexus block

## Introduction

Brachial plexus blocks (BPBs) provide satisfied analgesia for upper limb surgery with decreased post-anesthesia care unit use, reduced side effects [1] and reduced rescue analgesic consumption [2, 3] compared with general anesthesia. However, these advantages were limited, especially in postoperative pain management period, due to the pharmacological duration of currently available local anesthetics (LAs) [4-6]. The duration of analgesia can be prolonged by increase the dose of LA [7] but the risk of LA systemic toxicity also increased [8]. And increase the dose of LA may not effective according to recent studies [9, 10]. Continuous catheter-based peripheral nerve blocks prolong the postoperative duration of analgesia [11, 12], but this technique needs additional cost. Another method to prolong the duration of analgesia is adding perineural adjuvants to LAs. Several perineural adjuvants, including opioids [13, 14], clonidine [15, 16], ketamine [17], dexamethasone [18, 19], magnesium [20] and midazolam [21] have been utilized to prolong the duration of analgesia of BPBs. Dexmedetomidine (DEX), a highly selective  $\alpha$ 2-adrenergic receptors ( $\alpha$ 2AR) agonist, was first used to prolong the duration of sensory and motor block in intravenous regional anesthesia by Memis and colleague [22]. Recent years, a series of clinical trials have assessed the effect of perineural dexmedetomidine on brachial plexus blocks. However, the results were no consistent. As a result, we systemically searched the available literature and performed this meta-analysis to determine whether perineural DEX combined with LAs for BPB can prolong the duration of analgesia.

#### Methods

We performed and reported this systematic review and meta-analysis according to the PRISMA recommendations [23].



# Eligibility criteria

All available randomized controlled trials (RCTs) that compared the effects of LA combined with perineural DEX with LA alone on single-injection brachial plexus nerve blocks in adults undergoing upper limb surgery without general anesthesia, and that reported at least one of the outcomes including duration of analgesia, motor block duration, sensory block duration, block onset times, side effects (bradycardia and hypotension), and postoperative rescue analgesic consumption, postoperative pain, hemodynamic parameters were included. RCTs that without a placebo control group, blocks performed for postoperative analgesia, and DEX administrated via intravenous were excluded. Editorials, review articles, meeting abstract and animal experimental studies were also excluded.

## Search strategy

Electronic databases including Embase, Pub-Med, and the Cochrane Library were searched systematically without restriction to regions and languages. The following search strategy: ("brachial plexus block" [MeSH Terms] OR ("brachial" [All Fields] AND "plexus" [All Fields] AND "block" [All Fields]) OR "brachial plexus block" [All Fields] OR ("brachial" [All Fields] AND "plexus" [All Fields] AND "blocks" [All Fields]) OR "brachial plexus blocks" [All Fields]) AND ("dexmedetomidine" [MeSH Terms] OR "dexmedetomidine" [All Fields]) was used. The reference lists of included trials, published meta-analyses, and review articles were also searched manually to supplement the computer search. The final search was run on 23 August 2016.

#### Data extraction

Two reviewers (HX and YZ) extracted the data from included trials independently. The basic information of

included trials such as first author, year of publication, sample size, type of BPB, techniques used to locate the nerve (nerve stimulator or ultrasound), dose of perineural dexmedetomidine and LA, type of LA (long-acting or intermediate-acting) were extracted. Outcomes like duration of analgesia, motor block duration, sensory block duration, block onset times, side effects, and hemodynamic parameters, postoperative rescue analgesic consumption, postoperative pain score were also extracted.

## Outcomes to be assessed

We selected the duration of analgesia, motor block duration, sensory block duration, primary side effects such as bradycardia and hypotension as primary outcomes. Block onset times, postoperative rescue analgesic consumption, postoperative pain score, and hemodynamic parameters were analyzed as secondary outcomes.

#### Assessment for risk of bias

The risk of bias of included trails were assessed using The Cochrane Risk of Bias tool for

First Author	Voar	Jadad	Locate	BPB	Comparison		Outcome paramet				net	ers
T IISt Autiloi	Tear	score	technique	type	companson		1	2	3	4	5	6
Agarwal S [32]	2015	5	NST	SC	1. Bup 97.5 mg + NS 2. Bup 97.5 mg + DEX 100 μg	25 25	*	*	*	*	*	*
Ammar AS [33]	2012	4	US	IC	1. Bup 100 mg 2. Bup 100 mg + DEX 0.75 μg/kg	30 30	*	*	*	*	*	
Biswas S [35]	2014	5	NST	SC	1. Levo 175 mg + NS 2. Levo 175 mg + DEX 100 μg	30 30	*	*	*			
Das A [27]	2014	4	NST	SC	1. Rop 150 mg + NS 2. Rop 150 mg + DEX 100 µg	40 40	*	*	*	*	*	*
Das B [28]	2014	4	NST	SC	1. Rop 150 mg + placebo 2. Rop 150 mg + DEX 1 µg/kg	40 40	*	*	*	*	*	
Esmaoglu A [36]	2010	3	NST	AX	1. Levo 200 mg + NS 2. Levo 200 mg + DEX 100 μg	30 30	*	*	*	*	*	*
Gandhi R [34]	2012	4	NM	SC	1. Bup 95 mg + NS 2. Bup 95 mg + DEX 30 μg	35 35	*	*	*	*	*	*
Kathuria S [29]	2015	4	US	SC	1. Rop 150 mg 2. Rop 150 mg + DEX 30 μg 3. Rop 150 mg + DEX 30 μg (IV)	20 20 20	*	*	*	*	*	*
Kaygusuz K [37]	2012	4	NST	AX	1. Levo 195 mg + NS 2. Levo 195 mg + DEX 1 μg/kg	30 30	*	*	*	*	*	
Kwon Y [30]	2015	3	US	SC	1. Rop 200 mg + NS 2. Rop 200 mg + DEX 1 µg/kg	30 30		*		*	*	*
Mirkheshti A [39]	2014	4	US	IC	1. Lid 375 mg + NS 2. Lid 375 mg + DEX 100 μg 3. Lid 375 mg + Ketorolac 50 mg	34 34 35	*	*	*	*	*	
Song JH [38]	2014	5	NST	IC	1. Mep 400 mg 2. Mep 400 mg + DEX 1 μg/kg 3. Mep 400 mg + EP 200 μg	10 10 10	*	*	*			
Zhang Y [31]	2014	5	NST	AX	1. Rop 132 mg + NS 2. Rop 132 mg + DEX 50 μg 3. Rop 132 mg + DEX 100 μg	15 15 15		*	*	*	*	*

Table 1. Main character of included studies

BPB = brachial plexus block, AX = axillary, SC = supraclavicular, IC = infraclavicular, Bup = bupivacaine, Levo = levobupivacaine, Rop = ropivacaine, Lid = lidocaine, Mep = mepivacaine, Ep = epinephrine, NS = normal saline, DEX = dexmedetomidine, N = number of patients, NST = nerve stimulator, US = ultrasound, NM = not mentioned. Outcome parameters: 1. Duration of analgesia; 2. Duration of motor block; 3. Duration of sensory block; 4. Motor block onset; 5. Sensory block onset; 6. Side effects. \* = Reported in the trial.

randomized controlled trials [24]. Two review authors (HHX and YZ) judged the bias of each included trails independently. Any disagreement was resolved by involving a third review author (ZMS). The scale evaluates the study for the following items: 1. Random sequence generation (checking for possible selection bias); 2. Allocation concealment (checking for possible selection bias); 3. Blinding of participants and personnel (checking for possible performance bias); 4. Blinding of outcome assessment (checking for possible detection bias); 5. Incomplete outcome data (checking for possible attrition bias); 6. Selective reporting (checking for possible reporting bias); 7. Other bias.

# Quality assessment

The Jadad scale was used to assess the methodological quality of RCTs [25].

## Statistical analysis

The meta-analyses were performed using Review Manager Version 5.3 (RevMan5.3, The Cochrane Library, Oxford, UK). Continuous and dichotomous variables were compared use weighted mean difference (WMD) and odds ratio (OR), respectively. All results were reported with 95% confidence intervals (CIs). Differences were considered statistically significant when P<0.05 and the 95% CI excluded 0 for



**Figure 2.** The risk of bias of each included trail judged by the review author using The Cochrane Risk of Bias tool. Green circle, low risk of bias; yellow circle, unclear risk of bias; red circle, high risk of bias.

the WMD or 1 for the OR. The  $\chi^2$  test was used for the heterogeneity test. The I<sup>2</sup> statistic was used to assess the heterogeneity of each individual outcome. When I<sup>2</sup><50%, the heterogeneity of pooled studies was considered low and a fixed effects model was used. When I<sup>2</sup>>50%, a significant heterogeneity was considered and the data were pooled with a random effects model [26]. Subgroup analysis was performed to identify the significant heterogeneity.

# Results

# Search result

The literature search yielded 86 records from electronic database and one record from other sources. Nineteen records were potentially relevant and six of those were excluded for various reasons: two records did not have a placebo control group; three records were performed with general anesthesia; one record was meeting abstract. Thirteen trials (818 patients, 369 received DEX) finally met our inclusion criteria. The study flow chart was presented in Figure 1. All included trails were designed as prospective, randomized, double-blinded and placebo controlled trials. Eleven trials used long-acting LA including ropivacaine [27-31], bupivacaine [32-34], and levobupivacaine [35-37]. Two trials used intermediate-acting LA including mepivacaine [38] and lidocaine [39]. Five different DEX doses, including 100 µg [27, 31, 32, 35, 36, 39] (46% of all trials), 50 µg [31], 30 µg [29, 34], 1 µg/kg [28, 30, 37, 38] (30% of all trials) and 0.75 µg/kg [33] were tested. One trial [31] had two DEX groups, received 100 µg and 50 µg respectively. The 100 µg group was analyzed in our meta-analysis. Ultrasound-guided was used to locate the brachial plexus (BP) in four trials [29, 30, 33, 39] and nerve stimulator was used in 8 trials [27, 28, 31, 32, 35-38]. The method to locate the brachial plexus was not mentioned in one trial [34]. Patients in seven trials [27-29, 31, 33, 34, 39] were given a variety of premedication, and were not given in the other six trials [30, 32, 35-38]. BPBs were performed via supraclavicular [27-30, 32, 34, 36], infraclavicular [33, 38, 39] and axillary [31, 36, 37]. Two trials had a Jadad score of 3. seven trials had a score of 4 and four studies had a score of 5. Table 1. presented the main character of included trials. The risk of bias of included trails was showed in Figure 2.

# Duration of analgesia

Data regarding duration of analgesia were available in 11 trials included and presented in **Figure 3**. However, the definition of the duration of analgesia were not consistent and reported as Visual Analog Scale (VAS) $\geq$ 3 [27, 32], VAS>3 [39], VAS $\geq$ 4 [29], VAS>4 [35-37]; time to first analgesic request [28, 33]; time to

# Dexmedetomidine on brachial plexus block

	DEX+LA LA alone							Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV. Random, 95% CI [min]	IV, Random, 95% CI [min]
1.1.1 Intermediate-ac	ting LA								
Mirkheshti A [39]	217	81	34	180	95	34	9.4%	37.00 [-4.96, 78.96]	-
Song JH [38]	358.9	36.2	10	295.7	52.1	10	9.4%	63.20 [23.88, 102.52]	
Subtotal (95% CI)			44			44	18.8%	50.95 [22.26, 79.64]	•
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.80, df = 1 (P = 0.37); l <sup>2</sup> = 0%									
Test for overall effect: Z = 3.48 (P = 0.0005)									
112 one nating IA									
1.1.2 Long-acting LA	770 4	400.0	05	044.4	54.0	05	0.00/	FOF 00 1470 04 FOO 001	-
Agarwal S [32]	//6.4	130.8	25	241.4	51.2	25	9.3%	535.00 [479.94, 590.06]	
Ammar AS [33]	403	33.2	30	233	30.4	30	9.5%	170.00 [153.89, 186.11]	
Biswas S [35]	997	154.23	30	801.13	200.08	30	8.9%	195.87 [105.47, 286.27]	
Das A [27]	846.67	102.09	40	544.07	55.4	40	9.4%	302.60 [266.60, 338.60]	-
Das B [28]	413.73	89.92	40	197.35	28.67	40	9.4%	216.38 [187.13, 245.63]	
Esmaoglu A [36]	1,008.69	164.04	30	887.14	260.82	30	8.6%	121.55 [11.29, 231.81]	
Gandhi R [34]	732.4	95.1	35	194.8	60.4	35	9.4%	537.60 [500.28, 574.92]	-
Kathuria S [29]	967.55	310.5	20	536.75	251.19	20	7.5%	430.80 [255.77, 605.83]	
Kaygusuz K [37]	1,279.54	138.42	30	736.8	45.31	30	9.3%	542.74 [490.62, 594.86]	
Subtotal (95% CI)			280			280	81.2%	339.26 [225.75, 452.77]	•
Heterogeneity: Tau <sup>2</sup> =	28604.10; Chi	<sup>2</sup> = 566.75,	df = 8 (	P < 0.00001);	<sup>2</sup> = 99%				
Test for overall effect:	Z = 5.86 (P < 0	0.00001)							
Total (05% CI)			224			224	100.0%	295 02 1494 55 299 401	
10121 (85% CI)			324			324	100.0%	203.02 [101.35, 388.49]	
Heterogeneity: Tau <sup>2</sup> =	29285.73; Chr	= 746.37,	ar = 10	(P < 0.00001	); 1* = 99%				-500 -250 0 250 500
Test for overall effect:	Z = 5.40 (P < 0	0.00001)							LA alone DEX+LA
Test for subgroup differences: Chi <sup>2</sup> = 23,29, df = 1 (P < 0.00001), l <sup>2</sup> = 95,7%									

**Figure 3.** Forest plot showing duration of analgesia. The sample size, mean, standard deviations (SD), and the pooled estimates of the mean difference were shown. The 95% confidence interval (CI) is shown as lines for individual studies and as diamonds for pooled estimates. DEX = dexmedetomidine, LA = local anesthetic.

	DE	X+LA		LA alone				Mean Difference	Mean D	Mean Difference		
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min	IV. Random	95% CI [min]		
1.2.1 Intermediate-act	ting LA											
Mirkheshti A [39]	170	67	34	117	90	34	7.8%	53.00 [15.29, 90.71]		*		
Song JH [38]	349.9	28.2	10	283.7	43.7	10	7.9%	66.20 [33.97, 98.43]		*		
Subtotal (95% CI)			44			44	15.7%	60.63 [36.12, 85.13]		•		
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi² = 0.:	27, df = 1 (	P = 0.6	0); l <sup>2</sup> = 0%								
Test for overall effect: Z = 4.85 (P < 0.00001)												
1.2.2 Long-acting LA												
Agarwal S [32]	702	111.6	25	208	22.7	25	7.8%	494.00 [449.36, 538.64]		-		
Ammar AS [33]	155.5	15.8	30	105.7	16.2	30	7.9%	49.80 [41.70, 57.90]		•		
Biswas S [35]	840	50.23	30	512	60.13	30	7.9%	328.00 [299.96, 356.04]		· · · ·		
Das A [27]	624.2	200.9	40	516.8	155.85	40	7.6%	107.40 [28.60, 186.20]		-		
Das B [28]	312	49.91	40	184.7	36.76	40	7.9%	127.30 [108.09, 146.51]				
Esmaoglu A [36]	773	67.62	30	575	65	30	7.9%	198.00 [164.44, 231.56]		*		
Gandhi R [34]	660.2	60.4	35	100.7	48.3	35	7.9%	559.50 [533.88, 585.12]		•		
Kathuria S [29]	754.6	180.5	20	387.85	129.31	20	7.4%	366.75 [269.44, 464.06]				
Kaygusuz K [37]	804.27	71.33	30	540.14	54.25	30	7.9%	264.13 [232.06, 296.20]				
Kwon Y [30]	768.7	151.8	30	606.3	153.7	30	7.6%	162.40 [85.10, 239.70]				
Zhang Y [31]	1,033.8	273.76	15	511.86	135.51	15	6.7%	521.94 [367.36, 676.52]				
Subtotal (95% CI)			325			325	84.3%	286.52 [166.65, 406.39]		•		
Heterogeneity: Tau <sup>2</sup> = 39990.83; Chi <sup>2</sup> = 2033.37, df = 10 (P < 0.00001); l <sup>2</sup> = 100%												
Test for overall effect:	Z = 4.68 (P < 0	0.00001)										
Total (95% CI)			369			369	100.0%	250.63 [148.10, 353.17]		•		
Heterogeneity: Tau <sup>2</sup> =	34564.56; Chi	<sup>2</sup> = 2065.74	, df = 1	2 (P < 0.0000	1);   <sup>2</sup> = 99%							
Test for overall effect:	Z = 4.79 (P < 0	0.00001)	• Track 25						-1000 -600	0 500 1000		
Test for subaroup differences: Chi <sup>2</sup> = 13.10. df = 1 (P = 0.0003).   <sup>2</sup> = 92.4%												

**Figure 4.** Forest plot showing duration of motor block. The sample size, mean, standard deviations, and the pooled estimates of the mean difference are shown. The 95% confidence interval is shown as lines for individual studies and as diamonds for pooled estimates. DEX = dexmedetomidine, LA = local anesthetic.

sense first pain [38] and time to first complaint of pain [34]. Perineural dexmedetomidine combined with LAs may prolong the duration of analgesia by 285.02 min [95% (Cl): 181.55, 388.49, P<0.00001]. The heterogeneity among the pooled studies was significant [ $l^2 = 0.99$ ; P<0.00001]. Subgroup analyses were performed to identify the significant heterogeneity according to different type of LAs utilized (longacting and intermediate-acting). For long-acting LAs, DEX prolonged the DOA by 339.26 min [95% (Cl): 225.75, 452.77, P<0.00001]. However, the heterogeneity was still high [ $I^2 = 0.99$ ; P<0.00001]. For intermediate-acting LAs, DEX prolonged the DOA by 50.95 min [95% (Cl): 22.26, 79.64, P = 0.0005] with low heterogeneity ( $I^2 = 0$ , P = 0.37).

## Duration of motor block

Duration of motor block were reported in all 13 trials reviewed (738 patients, 369 receiving

	DE	X+LA		LA	alone			Mean Difference	Mean Difference		
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV. Random, 95% CI [min	IV. Random, 95% Cl [min]		
1.3.1 Intermediate-ac	ting LA										
Mirkheshti A [39]	180	74	34	137	92	34	7.9%	43.00 [3.31, 82.69]	-		
Song JH [38]	367.9	35.8	10	289.7	52.9	10	7.9%	78.20 [38.61, 117.79]	÷		
Subtotal (95% CI)			44			44	15.8%	60.63 [26.13, 95.12]	◆		
Heterogeneity: Tau <sup>2</sup> =	210.52; Chi <sup>2</sup> =	1.51, df =	1 (P = 0	).22);   <sup>2</sup> = 34%							
Test for overall effect: Z = 3.44 (P = 0.0006)											
1.3.2 Long-acting LA											
Agarwal S [32]	755.6	126.8	25	234.8	47.9	25	7.8%	520.80 [467.67, 573.93]	. T		
Ammar AS [33]	179.4	14.4	30	122.7	15.2	30	8.0%	56.70 [49.21, 64.19]	•		
Biswas S [35]	898	32.33	30	645	70.11	30	7.9%	253.00 [225.37, 280.63]			
Das A [27]	846.67	102.09	40	544.07	55.4	40	7.9%	302.60 [266.60, 338.60]			
Das B [28]	379.4	55.09	40	211.6	47.88	40	7.9%	167.80 [145.18, 190.42]			
Esmaoglu A [36]	887	66.23	30	673	73.77	30	7.9%	214.00 [178.52, 249.48]	· · · · ·		
Gandhi R [34]	732.4	48.9	35	146.5	36.4	35	7.9%	585.90 [565.70, 606.10]			
Kathuria S [29]	789.45	187.72	20	451.6	113.36	20	7.6%	337.85 [241.74, 433.96]			
Kaygusuz K [37]	924.15	78.27	30	664.62	61.7	30	7.9%	259.53 [223.87, 295.19]			
Kwon Y [30]	869.1	120.7	30	654.8	145.2	30	7.8%	214.30 [146.73, 281.87]			
Zhang Y [31]	1,190	456	15	689	269	15	5.6%	501.00 [233.08, 768.92]			
Subtotal (95% CI)			325			325	84.2%	305.40 [169.76, 441.04]	•		
Heterogeneity: Tau <sup>2</sup> =	50866.45; Chi	<sup>2</sup> = 2770.63	, df = 1	0 (P < 0.0000	1); l <sup>2</sup> = 100	%					
Test for overall effect:	Z = 4.41 (P < 0	0.0001)									
Total (95% CI)			369			369	100.0%	266.45 [148.29. 384.61]	•		
Heteroceneity: Tau <sup>2</sup> =	45683.08: Chi	<sup>2</sup> = 2809.46	df = 1	2 (P < 0.0000	1): I <sup>2</sup> = 100 <sup>4</sup>	%					
Test for overall effect:	7 = 4 42 (P < 1	00001)		- (	.,,				-1000 -500 0 500 1000		
Test for subgroup differences: ChP = 11 75, df = 1 (P = 0.0006)  P = 91.5%								LA alone DEX+LA			

**Figure 5.** Forest plot showing duration of sensory block. The sample size, mean, standard deviations (SD), and the pooled estimates of the mean difference are shown. The 95% confidence interval (CI) is shown as lines for individual studies and as diamonds for pooled estimates. DEX = dexmedetomidine, LA = local anesthetic.

perineural dexmedetomidine) and presented in Figure 4. Adding DEX to LAs may prolong the duration of motor block by 250.63 min [95% (CI): 148.10, 353.79, P<0.00001]. The heterogeneity was significant [ $I^2 = 0.99$ ; P<0.00001]. Subgroup analyses were also conducted to identify the significant heterogeneity. For longacting LAs, DEX prolonged the duration of motor block by 286.52 min [95% (CI): 166.65, 406.39, P<0.00001]. The heterogeneity was still significant [I<sup>2</sup> = 1; P<0.00001]. For intermediate-acting LAs, DEX prolonged the duration of motor block by 60.63 min [95% (CI): 36.12, 85.13, P<0.00001]. The heterogeneity was low  $(I^2 = 0, P = 0.60)$ . Sensitivity analysis were also performed, and the results were not changed.

# Duration of sensory block

Duration of sensory block were evaluated in all 13 included trials (738 patients, 369 receiving perineural dexmedetomidine). The pooled analysis revealed a prolongation of sensory block by 266.45 min [95% (Cl): 148.29, 384.61 P<0.00001]. The I<sup>2</sup> value of 0.915 indicated significant heterogeneity. Further subgroup analysis investigating different types of LAs were performed. DEX increased the duration of sensory block by 305.40 min [95% (Cl): 169.76, 441.04, P<0.00001] with long-acting LAs and by 60.63 min [95% (Cl): 26.13, 95.12, P = 0.0006] with intermediate-acting LAs.

geneity was high in long-acting LAs group [ $I^2 = 1$ ; P<0.00001] and low in intermediate-acting LAs group [ $I^2 = 0.34$ ; P = 0.22]. Results were presented in **Figure 5**. Sensitivity analysis did not change the results.

# Bradycardia and hypotension

Hypotension was observed in three trials, defined as systolic blood pressure <80 millimeter of mercury [34] and >20% below baseline value [29, 31]. Patients received DEX had a higher risk of hypotension [odds ratio (OR) = 5.37, 95% (CI): 0.88, 32.63, P = 0.07], but not reach statistical significance. The heterogeneity was low  $[I^2 = 0, P = 0.91]$ . Bradycardia was reported in six trials and defined as HR<50 beats/min [29, 30, 32, 36] and <40 beats/min [34]. One trial did not mention the definition of bradycardia [27]. DEX increased the risk of bradycardia [OR = 15.75, 95% (CI): 4.02, 61.78, P<0.0001]. The I<sup>2</sup> value of 0.12 suggests a low heterogeneity. Figure 6 presented the results. A fixed model was used to analyze the trials.

# Sensory and motor block onset

Eleven trials reported the onset times of sensory and motor block. The sensory and motor block onset times were decreased by -3.74 min [95% (Cl): -5.69, -1.79, P = 0.0002] and -4.06 min [95% (Cl): -6.02, -2.10, P<0.0001] respec-

# Dexmedetomidine on brachial plexus block

	DEX+	LA	LA alo	ne	Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
1.6.1 Bradycardia							
Agarwal S [32]	1	25	0	25	15.6%	3.12 [0.12, 80.39]	
Das A [27]	4	40	0	40	18.4%	9.99 [0.52, 191.90]	
Esmaoglu A [36]	7	30	0	30	18.9%	19.47 [1.06, 358.38]	
Gandhi R [34]	2	35	0	35	17.2%	5.30 [0.25, 114.47]	•
Kwon Y [30]	7	30	0	30	18.9%	19.47 [1.06, 358.38]	
Zhang Y [31]	15	15	0	15	10.8%	961.00 [17.91, 51566.38]	
Subtotal (95% CI)		175		175	100.0%	15.75 [4.02, 61.78]	-
Total events	36		0				
Heterogeneity: Tau <sup>2</sup> = {	0.36; Chi <sup>2</sup>	= 5.70	, df = 5 (F	= 0.34	);   <sup>2</sup> = 129	6	
Test for overall effect: 2	2 = 3.95 (	P < 0.0	001)				
162 Hypotenelon							
Condhi D [24]	2	25	0	25	24 5%	5 30 10 25 114 471	
Kathuria S [20]	1	20	0	20	30.6%	3 15 10 12 82 161	
Zhang V [21]	2	15	0	15	34.0%	9 69 10 41 194 291	
Subtotal (95% CI)	3	70	U	70	100.0%	5 37 [0 88 32 63]	
Total events	6		0			0.01 [0.00] 01.00]	
Heterogeneity: Tau <sup>2</sup> = (	0.00: Chi2	= 0.20	df = 2 (F	= 0.91	): $ ^2 = 0\%$		
Test for overall effect: 2	2 = 1.83 (	P = 0.0	7)				
			.,				
							0.001 0.1 1 10 1000
							LA alone DEX+LA

**Figure 6.** Forest plot showing side effects. The sample size, events, and the pooled estimates of the odds ratio are shown. The 95% confidence interval (CI) is shown as lines for individual studies and as diamonds for pooled estimates. DEX = dexmedetomidine, LA = local anesthetic.

Table 2. The sensory and motor block onset

Outcomes	Studies included	DEX mean	Control mean	Weighed mean difference [95% confidence interval]	P-value for statistical significance	l <sup>2</sup> test for heterogeneity	<i>P</i> -value for heterogeneity
Sensory block onset (min)	27-34, 36, 37, 39	11.67	15.17	-3.74 [-5.69, -1.79]	0.0002	0.95	<0.00001
Motor block onset (min)	27-34, 36, 37, 39	13.99	18.29	-4.06 [-6.02, -2.10]	<0.0001	0.96	<0.00001
DEX = dexmedetomidine.							

tively. The heterogeneity was both high,  $l^2 = 0.95$  (P<0.00001) for sensory and  $l^2 = 0.96$  (P<0.00001) for motor. The results were

## Other outcomes

showed in Table 2.

Analgesic consumption was reported in four trials. One trial recorded the analgesic consumption of the first 12 hour [37] postoperative, two trials recorded the first 24 hour [27, 29] postoperative, and one trial recorded the first 48 hour [33] postoperative. Three trials used diclofenac sodium as a rescue analgesic [27, 29, 37] and one trial used morphine [33]. Due to the difference of analgesic used and duration of recorded postoperative, we presented this outcome qualitatively in **Table 3**. Postoperative pain was assessed in three trials. Two trials used visual analog scale [27, 37] and one trial used verbal rating scale [33]. The results were also presented in **Table 3**. Hemodynamic parameters like heart rate, systolic arterial blood pressure, diastolic arterial blood pressure, and mean arterial blood pressure were reported in a graph manner without any description of absolute value in 6 trials [32, 35-39] and only one trial reported the absolute value [30]. The results were showed in **Table 3** qualitatively.

# Discussion

This meta-analysis of 13 RCTs (818 patients, 369 received DEX) comparing the efficacy of perineural DEX combined with LA and LA alone in brachial plexus blocks showed that perineural DEX as adjuvants prolonged the duration of analgesia, motor block duration and sensory block duration, decreased onset of sensory and motor block. However, the risk of bradycardia was increased. Postoperative rescue analgesic consumption and pain score were lower in DEX group. Hemodynamic param-

First	Out	com	es	O						
Author	PAC	PP	HP	ients						
Agarwal S [32]			*	HR, SBP, and DBP in GD at 15, 30, 45, 60, 90, and 120 min were significantly lower than in GC (P<0.001).						
Ammar AS [33]	*	*		1. GD had a lower morphine rescue requirement for 48 h after surgery [4.9 mg (0-8.0) vs 13.6 mg (4.0-16.0) mg, $P = 0.005$ ]. 2. Verbal rating scale in GD at 1, 2, 12, 24, 36, and 48 hour postoperative were significantly lower than in GC (P<0.05).						
Biswas S [35]			*	SBP in GD at 15, 60, 90, 120 minutes were significantly lower than in GC (P<0.05). DBP in GD at 60, 90, 120 minutes were significantly lower than in GC (P<0.05). HR in GD, except basal measurements were significantly lower than in GC (P<0.05).						
Das A [27]	*	*		1. GD required less number of diclofenac sodium injection as rescue analgesics than patients in GC in first 24 hours postoperative, and the difference is statistically highly significant (P<0.01). 2. Postoperative VAS value at 12 hour were significantly lower in GD (P<0.05).						
Esmaoglu A [36]			*	SBP in GD at 10, 15, 30, 45, 60, 90, and 120 minutes were significantly lower than in GC (P<0.05). DBP in GD at 60, 90, and 120 minutes were significantly lower than in GC (P<0.05). HR in GD, except basal measurements, were significantly lower than in GC (P<0.05).						
Kathuria S [29]	*			The total analgesic consumption in 24 hour postoperative was significantly higher in GC than GD.						
Kaygusuz K [37]	*	*	*	1. The total need for analgesics was lower in GD (P< $0.05$ ). 2. Intraoperative 5- and 10-minute VAS values and postoperative VAS value at 12 hours were significantly lower GD (P< $0.05$ ). 3. Intraoperative MAP and HR values, except at 5 minutes and postoperative at 10 and 30 minutes and 1 and 2 hours, were significantly lower in GD (P< $0.01$ ).						
Kwon Y [30]			*	MAP in GD at 0, 10, 20, 30, 40, 50, 60 min were significantly lower than in GC (P<0.001). HR in GD at 10, 20, 30, 40, 50, 60 min were significantly lower than in GC (P<0.001).						
MirkheshtiA [39]			*	GD shows the most reduction in diastolic blood pressure (P<0.001). HR in GD was significantly lower than DC (P = $0.043$ ).						
Song JH [38]			*	HR in GD was significantly lower compared to GC at 40 minute after drug injection (P<0.05).						
PCA = nostonerative	analgee	ic con	cumnt	ion PP = postonerative pain HP = bemodynamic parameters HP = beart rate SPP = systelic arterial blood pressure DPP =						

## Table 3. Qualitatively outcomes

PCA = postoperative analgesic consumption, PP = postoperative pain, HP = hemodynamic parameters, HR = heart rate, SBP = systolic arterial blood pressure, DBP = diastolic arterial blood pressure, MAP = mean arterial blood pressure, GD = group dexmedetomidine, GC = group control, VAS = visual analog scale, \* = Study reported the outcome.

eters such as MAP, HR, SAB, and DAB were also lower in DEX group, and the difference reached the statistical significance at some time points.

Most of our results were in agreement with a previous meta-analysis [40] except the duration of sensory block and onset of both sensory and motor block. The limited number of included trials of the previous meta-analysis may cause the difference, for most trials included in our study were published in recent two years, which were not included in the previous study. However, our results also have limitations. First, the quality of included trials of our meta-analysis was generally low. Only one trial had low risk of bias of all elements of the Cochrane Collaboration's Risk of Bias Tool. Six trials had 1-3 unclear risk of bias. And the remaining six trials had one element judged at high risk of bias. Second, three out four primary outcomes of our meta-analysis were pooled with significant heterogeneity. Although we performed subgroup analysis to identify the source of heterogeneity, there was still high heterogeneity in long-acting LAs group. And eleven trials included in our meta-analysis used long-acting LAs. That makes the subgroup analysis failed to identify the heterogeneity source. As a result, the generalizability of the results of our study was limited. A variety of DEX doses including 100  $\mu$ g, 50  $\mu$ g, 30  $\mu$ g, 1  $\mu$ g/kg, and 0.75  $\mu$ g/kg; the use of premedication in some included trails; the techniques used to locate the nerve (ultrasound or nerve stimulator) and the type of surgery may contribute to the heterogeneity together. More trials designed strict and consistent are needed.

The safety of patients should be always considered seriously. The pooled results of our metaanalysis indicated that the risk of hypotension and bradycardia was increased. Previous studies largely focused on transient and reversible side effects such as bradycardia, hypotension, vomiting and nausea. However, that is not enough. One study showed that DEX may have a harmful effect on the myelin sheath when administered via the epidural route in rabbits [41]. That remind us the same injury may occur when DEX used perineural in BPBs. More attention should be paid to investigate neurological side effects and long-term outcomes of patients. The concern was also delivered in previous meta-analysis [40].

# Conclusion

The results of our meta-analysis showed that perineural DEX combined with LA may prolong the duration of analgesia, motor block duration and sensory block duration and decrease onset time in brachial plexus blocks. However, perineural DEX may increase the risk of bradycardia at the same time. The future study should focus on the neurological side effects and longterm outcomes of patients.

# Disclosure of conflict of interest

None.

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