Brazilian Journal of Anesthesiology 2023;73(5): 665—675

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SYSTEMATIC REVIEW

Dexmedetomidine versus clonidine as an adjuvant to local anaesthetic in brachial plexus blocks: a meta-analysis of randomised controlled trials

Vijeta Bajpai [a], Tejas K. Patel [b,*], Priyanka Dwivedi [a], Amrita Bajpai[c], Astha Gupta[d], Pradeepika Gangwar[e], Yashpal Singh[f], Richa Agarwal[g], Surekha Kishore[h]

[a] *All India Institute of Medical Sciences, Department of Anaesthesiology, Gorakhpur, India*
[b] *All India Institute of Medical Sciences, Department of Pharmacology, Gorakhpur, India*
[c] *Rajkiya Medical College, Department of Ophthalmology, Badaun, Uttar Pradesh, India*
[d] *B.R.D medical College, Department of Anaesthesiology, Gorakhpur, India*
[e] *Mahamana Pandit Madan Mohan Malviya Cancer Centre, Department of Anaesthesiology, Critical Care and Pain Management, Varanasi, India*
[f] *Banaras Hindu University, Department of Anaesthesiology, Varanasi, India*
[g] *All India Institute of Medical Sciences, Department of Ophthalmology, Gorakhpur, India*
[h] *All India Institute of Medical Sciences, Gorakhpur, India*

Received 3 January 2022; accepted 18 July 2022
Available online 30 July 2022

KEYWORD
Dexmedetomidine;
Clonidine;
Brachial plexus block;
Meta-analysis

Abstract

Objective: This meta-analysis aimed to compare the efficacy and safety of dexmedetomidine and clonidine as an adjuvant to local anesthetics in BPBs.

Methods: Two investigators independently searched databases to identify all RCTs comparing the efficacy and/or safety of dexmedetomidine and clonidine as an adjuvant to local anesthetics in BPBs. All outcomes were pooled using the inverse variance method with a random-effect model. An I^2 test was used to assess heterogeneity. The source of heterogeneity was explored through meta-regression. The quality of the evidence was assessed using the GRADE approach.

Results: Out of 123 full texts assessed, 24 studies (1448 patients) were included in the analysis. As compared to clonidine, dexmedetomidine groups showed significantly longer sensory block duration (MD = 173.31; 95% CI 138.02–208.59; I^2 = 99%; GRADE approach evidence: high); motor block duration (MD = 158.35; 95% CI 131.55–185.16; I^2 = 98%; GRADE approach evidence: high), duration of analgesia (MD = 203.92; 95% CI 169.25–238.58; I^2 = 99%; GRADE approach evidence-high), and provided higher grade quality of block (RR = 1.97; 95% CI 1.60–2.41; I^2 = 0%; GRADE approach evidence: moderate). The block positioning technique (regression coefficient: 51.45, p = 0.005) was observed as a significant predictor of the heterogeneity in the case of sensory

* Corresponding author.
E-mail: dr.tkp2006@yahoo.co.in (T.K. Patel).

https://doi.org/10.1016/j.bjane.2022.07.005
0104-0014/© 2022 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

block duration. No significant difference was observed for the risk of hypotension (RR = 2.59; 95% CI 0.63–10.66; I^2 = %).
Conclusion: Moderate to high-quality evidence suggests dexmedetomidine is a more efficacious adjuvant to local anesthetic in BPBs than clonidine.
© 2022 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Brachial Plexus Blocks (BPBs) are a type of regional nerve block used to provide anesthesia for conducting surgery on upper limbs and to extend analgesia in the postoperative period.[1] Lignocaine and bupivacaine are the commonly used local anesthetics in BPBs. The adjuvant medications are added with the local anesthetic to enhance the quality and efficacy of regional techniques. They work synergistically to quicken the onset, increase the duration of analgesia, improve the quality of analgesia, and limit potential medication-related adverse events. The novel adjuncts used in practice are opioids (morphine, tramadol, fentanyl, sufentanil, and alfentanil), epinephrine, bicarbonate, neostigmine, and alpha-2 agonists.[2] Clonidine and dexmedetomidine are the alpha-2 adrenergic receptor agonists that have been the focus of interest because of their sedative, analgesic, perioperative sympatholytic, and cardiovascular stabilizing effects with reduced anesthetic requirements.[3,4] These pharmacologic properties have been employed clinically to achieve the desired effects in regional anesthesia.[5,6]

Earlier meta-analyses mainly assessed the adjuvant effect of dexmedetomidine as compared to local anesthetic alone in various peripheral nerve block procedures.[7-13] Limited information is available for the comparative effect of dexmedetomidine and clonidine. An earlier meta-analysis of 14 Randomized Controlled Trials (RCTs) compared the adjuvant effect of dexmedetomidine with clonidine in supraclavicular nerve block. The authors explored the source of heterogeneity for the sensory block duration outcome using block localization techniques and doses of dexmedetomidine and clonidine. However, they could not find heterogeneity modifiers due to the small sample size. The authors did not explore the type of local anesthetic as a source of heterogeneity.[14] Subsequently, no large scale RCTs were published comparing dexmedetomidine with clonidine in BPBs. In this updated meta-analysis, we compared the efficacy and safety of dexmedetomidine with clonidine as an adjuvant to local anesthetic in BPB, explored the source of heterogeneity through meta-regression, and assessed the quality of evidence for sensory, motor, and analgesic outcomes.

Methods

The meta-analysis was registered on The International Prospective Register of Systematic Reviews (PROSPERO) – CRD42021249436.

Study identification

Two investigators independently systematically searched the databases: the Cochrane Library, PubMed, PubMed Central, Scopus, LILACS, Google Scholar, Trial registries (clinicaltrial.gov), bibliographies of relevant reviews and systematic reviews. The search terms were: (clonidine and dexmedetomidine) AND (nerve block OR plexus Block OR upper limb block OR lower limb block OR block)) AND (local anesthesia OR bupivacaine OR lignocaine OR lidocaine OR ropivacaine. The last search was run on September 22, 2021. There were no language and time restrictions to include the published articles. Titles, abstracts, and full articles (if required) were assessed for deciding the eligibility of retrieved articles. Any disagreements were resolved by discussion and consensus among the authors.

Selection criteria of studies

All RCTs (open-labelled or blinded) comparing the efficacy and/or safety of dexmedetomidine and clonidine as an adjuvant to local anesthetic in BPBs were included.

The following studies were excluded: studies administering clonidine and dexmedetomidine through neuraxial and other routes (e.g., intravenous administration); studies using autonomic nerve blocks and interfacial plane blocks; observational and non-interventional studies, case series, case reports, review articles; single-arm studies; duplicate studies, retracted articles, studies published in predatory journals.

Participants/population

The adult population of more than 18 years of age undergoing upper limb surgery under nerve block and patients undergoing any BPB techniques (e.g., supraclavicular brachial plexus block) regardless of administration techniques were included.

Exclusion criteria

Patients undergoing BPBs along with general anesthesia; and the pediatric population were excluded.

Types of interventions and control

Dexmedetomidine and clonidine as an adjuvant to local anesthetic in BPB regardless of dosage, volume, or type of local anesthetic.

Risk of bias assessment of included studies

Two investigators assessed the methodological quality of the included RCTs as per revised Cochrane "risk of bias assessment tool for the randomized controlled clinical trials (ROB-II)".[15] Each study was assessed for the possibility of risk of bias in the following five domains: process of randomization, deviations from the intended interventions, missing outcome data, outcome measurement, and selection of the reported results. Each domain was categorized into "low", "high" or having "some concerns" in the risk of bias assessment.[15] Any disagreements were resolved by discussion and consensus among the authors.

Data extraction

The following data were extracted in a Microsoft Excel sheet, 2016: first author, publication year, study design, number of patients in each group, type of surgery, type of local anesthetic, volume and concentration of local anesthetic, method of block localization, analgesic regimen in the perioperative period, baseline data of study population in treatment arms (age, gender, American Society of Anesthesiologists [ASA] physical status, dose of clonidine and dexmedetomidine), safety (adverse events) data and intention to treat analysis. The data were cross-checked to ensure the accuracy of extraction.

Efficacy outcomes

The primary efficacy outcomes were duration of sensory block, motor block and analgesia. The secondary efficacy outcomes were onset of sensory and motor block, sensory block complete, motor block complete, quality of block, rescue analgesic requirement, and sedation score. The included studies defined quality of block using the numeric scale by Memis et al., 2004: Grade IV 4 (excellent) — patients having no complaint; Grade 3 (good) — minor complaint that did not require supplemental analgesics; Grade 2 (moderate) — complaint that required supplemental analgesics; and Grade 1 (unsuccessful) — patient required general anaesthesia.[16]

Safety outcome

The safety outcomes were the number of adverse events between the clonidine and dexmedetomidine groups at the end of the study period. The analyzed adverse events were hypotension, bradycardia, and nausea.

Data synthesis

Outcomes were both continuous and dichotomous variables. The onset of sensory and motor block, duration of sensory and motor block, sensory block complete, motor block complete, and duration of analgesia were summarized as a mean difference (95% CI) of minutes between dexmedetomidine and clonidine treated patients. Sedation scores were summarized as a Risk Difference (RD) with 95% CI. Rescue analgesia requirement was analyzed using standardized mean difference (95% CI). Quality of block and adverse events were summarized as Risk Ratio (RR) with 95% CI. All outcomes were pooled using the inverse variance method. The random model (DerSimonian and Laird method) was used to estimate the meta-analytic summary. In anticipation of substantial heterogeneity, the random effect model was preferred over the fixed effect model. The heterogeneity was assessed using the I^2 test. The heterogeneity was considered as 25% — low; 50% — moderate; and 75% — high. The publication bias was assessed using asymmetry in funnel plot of the primary efficacy outcomes and its standard error using Egger's regression asymmetry test.

The sensitivity analyses of primary efficacy outcomes were performed based on the risk of bias assessment as per ROB-II tool, type of blinding, type of local anesthetic, and surgery. In the case of risk of bias assessment, the meta-analytic summary was estimated by excluding studies showing "some concern" or "high" risk of bias. The open labelled studies were excluded in the case of sensitivity analysis based on the type of blinding. The studies using lidocaine were excluded in the sensitivity analysis based on the type of local anesthetic. The studies including emergency surgeries were excluded in case of sensitivity analysis based on the type of surgery.

The following study characteristics were explored through meta-regression to identify the possible source of heterogeneity: local anesthetics (bupivacaine, levobupivacaine and ropivacaine), block localization techniques (nerve stimulator, paresthesia, and ultrasonography guided techniques), and dose ratio of dexmedetomidine and clonidine (< 1 and 1). The studies that compared same doses of dexmedetomidine and clonidine were assigned dose ratio of one (e.g., 1 $\mu g.kg^{-1}$ dexmedetomidine and 1 $\mu g.kg^{-1}$ of clonidine), while studies who compared lower doses of dexmedetomidine with higher doses of clonidine were assigned dose ratio of less than one (e.g., 1 $\mu g.kg^{-1}$ dexmedetomidine and 2 $\mu g.kg^{-1}$ of clonidine). The univariable meta-regression was conducted to assess the influence of study characteristics on the primary efficacy outcomes. The study variables with a minimum of 4 studies were selected as a moderator for a univariate meta-regression.[17] The study variables showing a significance level of $p < 0.10$ were further explored through multivariable meta-regression.[17] The study variable showing p-value < 0.05 was considered a statistically significant predictor of heterogeneity in the meta-regression model.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the evidence for all efficacy and outcomes. The following parameters were used: study limitations, inconsistency, indirectness of evidence, imprecision, and publication bias.[18] GRADE summary of findings table for all outcomes were prepared using GRADEpro software.[19]

The meta-analysis was performed through "Review manager software version 5.3" and meta-regression was performed using JASP software 0.14.1.0.

Results

Study characteristics

A total of 8248 references were retrieved from the literature search and 123 full-text articles were assessed as per selection criteria. A total of 24 RCTs were included in the analysis (Fig. 1).[20-43] Among 24 included studies, 21 were double-

blind and 2 were open-label. One study did not specify the type of blinding.[32] The general characteristics of all included studies are presented in Table 1. All studies used supraclavicular brachial plexus block. All studies except one had enrolled elective surgery patients. Singh et al.[38] included hemodynamically stable patients undergoing emergency surgeries. The included studies used bupivacaine (11), ropivacaine (09), levobupivacaine (3), and bupivacaine and lignocaine with adrenaline (1). The localization techniques used were nerve stimulator (14), paresthesia (7), and ultrasonography-guided technique (2). The perioperative analgesic regimen is mentioned in Table 1. The demographic profile and dosage of dexmedetomidine and clonidine treated patients among included studies are presented in Supplementary data file (Supplementary Table 1). Twenty studies compared similar doses of dexmedetomidine and clonidine (1 μg.kg^{-1} – 16 studies; 50 μg – 2 studies; 2 μg.kg^{-1} – 1 study; and 0.5 μg.kg^{-1} – 1 study). Four studies used lower doses of dexmedetomidine than clonidine (100 μg versus 150 μg – 3 studies; and 1 μg.kg^{-1} versus 2 μg.kg^{-1} – 1 study). All included studies enrolled patients having American Society of Anesthesiologists (ASA) physical status I and II.

Risk of bias in included studies

The risk of bias assessment in individual RCTs is presented in Supplementary data file (Supplementary Fig. 1). A total of 11 studies were considered as having a "low" risk of bias and 13 were considered as having "some concerns".

Duration of sensory block

A total of twenty-one studies contributed to the duration of sensory block data analyses (Fig. 2). Patients treated with dexmedetomidine showed a significantly longer duration of the sensory block than those treated with clonidine (MD = 173.31; 95% CI 138.02–208.59; I^2 = 99%). The GRADE approach suggested the high quality of evidence for this outcome (Table 2). No significant asymmetry in the funnel plot was observed (Egger's regression asymmetry test: Z = 1.509, p = 0.131). Sensitivity analysis did not affect this outcome (Supplementary Table 2). Only block localization technique was the significant predictor of the heterogeneity in the case of sensory block duration (Supplementary Table 3).

Duration of motor block

A total of 23 studies contributed to the duration of motor block data analyses (Fig. 3). Patients treated with dexmedetomidine showed significantly longer duration of the motor block than those treated with clonidine (MD = 158.35; 95% CI 131.55–185.16; I^2 = 98%; GRADE approach evidence: high). No significant asymmetry in the funnel plot was observed (Egger's regression asymmetry test: Z = 1.123, p = 0.261). Sensitivity analysis did not affect this outcome

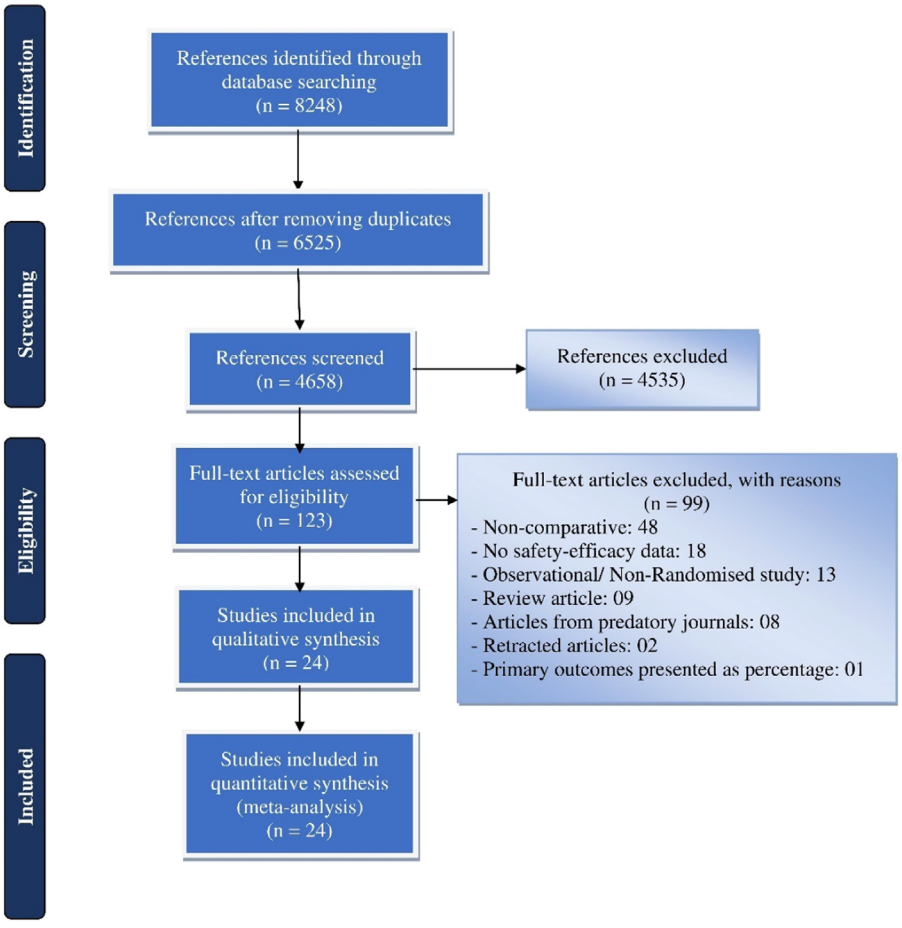

Figure 1 Prisma flow diagram showing the study selection process.

Table 1 General characteristics of the included studies.

Author	N° of patients/ study design	Types of surgery	Type of local anesthetic with concentration and volume	Type of blocks/ technique localization	Scale for sensory block	Scale for motor block	Scale for analgesia	Scale for sedation	Analgesic regimen			Efficacy outcomes
									Preoperative	Intra operative	Post operative	
Bafna[20]	80/ RCT-Double blind	Upper limb surgery	0.50% Ropivacaine 30 mL	SCBP/ Paresthesia	3-point pin prick scale	Modified Bromage Scale	VAS	Four-point Scale	ND	ND	Tramadol 100 mg iv	SBO, MBO, SBD, MBD, DA, SS
Channabasappa[21]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Ropivacaine 35 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	NRS	Ramsay Sedation Score	ND	IV midazolam 0.02 mg.kg^{-1}+ fentanyl 1 μ. kg^{-1}	Diclofenec 1.5 mg.kg^{-1} im	SBO, MBO, SBD, MBD, DA, QB
Harshvardhana[22]	50/ RCT-Double blind	Upper limb orthopedic surgery	0.50% Ropivacaine 29 mL	SCBP/ Paresthesia	Spirit Swab method	Modified Bromage Scale	Not Mentioned	Ramsay Sedation Score	ND	ND	ND	SBO, MBO, SBD, MBD, DA
Jinjil[23]	60/ RCT-Double blind	Upper limb arm and forearm surgery	0.25% Ropivacaine 20 mL	SCBP/ USG	Hollmen Score	Modified Bromage Scale	VAS	5-point sedation scale.	Alprazolam 0.25 mg p.o.	ND	Diclofenec 75 mg im	SBO, MBO, SBD, MBD, DA
Kakad[24]	68/ RCT-Double blind	Upper limb orthopedic surgery	0.38% Bupivacaine 40 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	ND	University of Michigan Sedation Scale (UMSS)	ND	ND	ND	SBO, MBO, SBD, MBD, AC
Kalyanam[25]	60/ RCT-Double blind	Forearm and Hand surgery	0.25% Bupivacaine 35 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	loss of motor function of any nerve	ND	Modified Ramsay sedation score. (12)	ND	ND	Paracetamol 1 gm iv	SBO, MBO, SBD, MBD, DA, SS
Kanvee[26]	50/ RCT-Double blind	Upper limb surgery	0.50% Ropivacaine 30 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	ND	Midazolam 0.02 mg.kg^{-1} iv	ND	Diclofenec 75 mg im	SBO, MBO, SBD, MBD, DA
Karthik[27]	50/ RCT-Double blind	Upper limb orthopedic surgery	0.50% Levobupivacaine 30 mL	SCBP/ Paresthesia	3-point pin prick scale	Modified Bromage Scale	VAS	ND	ND	ND	ND	SBO, MBO, SBD, MBD, DA, SS
Kataria[28]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.50% Levobupivacaine 30 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	3-point pin prick scale	VAS	ND	Alprazolam 0.25 mg	IV Ketamine- 0.5 mg.Kg^{-1}	ND	MBD, DA
Kirubhar[29]	60/ RCT- Open label	Upper limb orthopedic Surgery	0.38% Bupivacaine 35 mL	SCBP/ Paresthesia	Hollmen Score	Modified Bromage Scale	ND	ND	ND	ND	ND	SBO, MBO, SBD, MBD, DA
Munshi [30]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Bupivacaine 30 mL	SCBP/ Paraesthesia	3-point pin prick scale	Modified Bromage Scale	NRS	Ramsay Sedation Score	ND	ND	Diclofenec 75 mg im	SBO, MBO, SBD, MBD, DA, QB
Narolia[31]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.75% Ropivacaine 30 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	Ramsay Sedation Score	Alprazolam 0.5 mg and ranitidine 150 mg p.o. at night	ND	Paracetamol iv	SBO, MBO, SBD, MBD, DA, SS, CSB
Nazir[32]	50/ RCT-Not specified blinding	Upper limb surgery	0.50% Ropivacaine 30 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	ND	ND	ND	ND	SBO, MBO, SBD, MBD, DA, AC
Palai[33]	60/ RCT-Double blind	Forearm surgery	0.5% + 2% Bupivacaine + Lignocaine with Adrenaline 2 mg.kg^{-1} + 5 mg. kg^{-1}	SCBP/ ND	Hollmen Score	Modified Bromage Scale	VAS	Ramsay Sedation Score	Alprazolam 0.5 mg and ranitidine 150 mg p.o. at night	ND	ND	SBO, MBO, SBD, MBD, DA, CSB, CMB
Rao[34]	60/ RCT-Double blind	Upper limb surgery	0.25% Bupivacaine 38 mL	SCBP/ Paresthesia	Cold Alcohol Swabs	Modified Bromage Scale	VAS	ND	ND	ND	Diclofenec 1–5 mg.kg^{-1} im	SBO, MBO, SBD, MBD, DA
Reddy[35]	60/ RCT-Double blind	Upper limb surgery	0.33% Bupivacaine 30 ml	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	NRS	Modified Ramsay Sedation Score RSS	ND	IV midazolam 0.02 mg.kg^{-1}+ fentanyl 1 μ. kg^{-1}	Diclofenec 1.5 mg.kg^{-1} im	SBO, MBO, SBD, MBD, DA, QB
Sebastian[36]	60/ RCT-Double blind	Upper limb urgery	0.50% Ropivacaine 29 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	ND	ND	ND	Tramadol 100 mg iv	SBO, MBO, SBD, MBD, DA
Sharma[37]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Bupivacaine 35 mL	SCBP/ Paresthesia	3-point pin prick scale	Modified Bromage Scale	VAS	ND	Alprazolam 0.5 mg	IV midazolam 0.02 mg.kg^{-1}+ fentanyl 1 μ. kg^{-1}	ND	SBO, MBO, SBD, MBD, DA, AC
Singh[38]	60/ RCT-Open label	[a]Upper limb surgery excluding shoulder surgery	0.50% Ropivacaine 30 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	ND	No premedication given	ND	Diclofenec 1.5 mg.kg^{-1} im	SBO, MBO, SBD, MBD, DA, CSB, CMB
Sinha[39]	80/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Bupivacaine 38 mL	SCBP/ Nerve Stimulator	3-point pin prick scale	Modified Lovett Rating Scale.	VAS	Modified Ramsay Sedation Score RSS	Alprazolam 0.25 mg and	ND	Diclofenec 3 mg.kg^{-1} im	SBO, MBO, DA

Table 1 (*Continued*)

Author	N° of patients/ study design	Types of surgery	Type of local anesthetic with concentration and volume	Type of blocks/ technique localization	Scale for sensory block	Scale for motor block	Scale for analgesia	Scale for sedation	Analgesic regimen			Efficacy outcomes
									Preoperative	Intra operative	Post operative	
									omeprazole 20 mg p. o. at bedtime			
Spurthi[40]	60/ RCT-Double blind	Upper limb surgery	0.38% Bupivacain 25 mL	SCBP / USG	3-point pin prick scale	Modified Bromage	Not Mentioned	Ramsay Sedation Score	ND	ND	ND	SBO, MBO, SBD, MBD, DA, SS
Swami[41]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Bupivacaine 35 mL	SCBP / Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	NRS	Ramsay Sedation Score	ND	IV midazolam 0.02 mg·kg^{-1}+ fentanyl 1 μ.. kg^{-1}	Diclofenec 1.5 mg·kg^{-1} im	SBO, MBO, SBD, MBD, DA, QB
Tandon[42]	60/ RCT-Double blind	Upper limb surgery	0.50% Levobupivacaine 30 mL	SCBP / Nerve Stimulator	3-point pin prick scale	Modified Lovett Rating Scale.	VAS	Chernik Sedation Score	ND	ND	ND	SBO, MBO, SBD, MBD
Tripathi[43]	60/ RCT-Double blind	Upper limb orthopedic surgery	0.25% Bupivacaine 39 mL	SCBP / Nerve Stimulator	3-point pin prick scale	Modified Bromage Scale	VAS	ND	Midazolam 2 mg iv	ND	Diclofenec 75 mg im	SBO, MBO, SBD, MBD, DA, QB

[a] Emergency hemodynamically stable patients were also included.
RCT, Randomized Controlled Trial; SCBP, Supraclavicular Brachial Plexus; ND, Not Defined; p.o., per orally; iv, intravenous; im, intramuscular; SBO, Sensory Block Onset; MBO, Motor Block Onset; SBD, Sensory Block Duration; MBD; Motor Block Duration; DA, Duration of Analgesia; SS, Sensory Block; QB, Quality of Block; CSB, Complete Sensory Block; CMB, Complete Motor Block; AC, Analgesic Consumption; VAS, Visual Analogue Score; NRS, Numerical Rating Scale.

(Supplementary Table 2). No factors significantly predicted the heterogeneity in the case of motor block duration (Supplementary Table 3).

Duration of analgesia

A total of 22 studies contributed to the duration of analgesia data analyses (Fig. 4). Patients treated with dexmedetomidine showed significantly longer duration of analgesia than those treated with clonidine (MD = 203.92; 95% CI 169.25–238.58; I^2 = 99%; GRADE approach evidence: high). No significant asymmetry in the funnel plot was observed (Egger's regression asymmetry test: Z = 1.598, p = 0.110). Sensitivity analysis did not affect this outcome (Supplementary Table 2). No factors significantly predicted the heterogeneity in the case of analgesia duration (Supplementary Table 3).

Onset of sensory block

A total of 23 studies contributed to the onset of sensory block data analyses (Supplementary Fig. 2). Patients treated with dexmedetomidine showed significantly earlier onset of the sensory block than those treated with clonidine (MD = -1.58; 95% CI -2.18–-0.99]; I^2 = 97%). The GRADE approach suggested moderate quality of evidence (Supplementary Table 4). An I^2 of 97% suggested a high degree of between-trial heterogeneity.

Onset of motor block

A total of 23 studies contributed to the onset of motor block data analyses (Supplementary Fig. 3). Patients treated with dexmedetomidine showed significantly earlier onset of motor block than those treated with clonidine (MD = -1.46; 95% CI -2.38–-0.54; I^2 = 98%; GRADE approach evidence: low).

Sensory block complete

A total of three studies contributed to sensory block complete data analyses (Supplementary Fig. 4). Patients treated with dexmedetomidine showed significantly earlier onset of complete sensory blockade than those treated with clonidine (MD = -3.20; 95% CI -4.01–-2.39]; I^2 = 51%). The GRADE approach suggested low quality of evidence (Supplementary Table 4).

Motor block complete

A total of two studies contributed to motor block complete data analyses (Supplementary Fig. 5). Patients treated with dexmedetomidine showed significantly earlier onset of complete motor blockade than those treated with clonidine (MD = -2.75; 95% CI -4.95–-0.54; I^2 = 89%; GRADE approach evidence: very low).

Sedation score

A total of two studies contributed to sedation score data analyses (Supplementary Fig. 6). We found no difference in sedation score in patients treated with dexmedetomidine than clonidine.

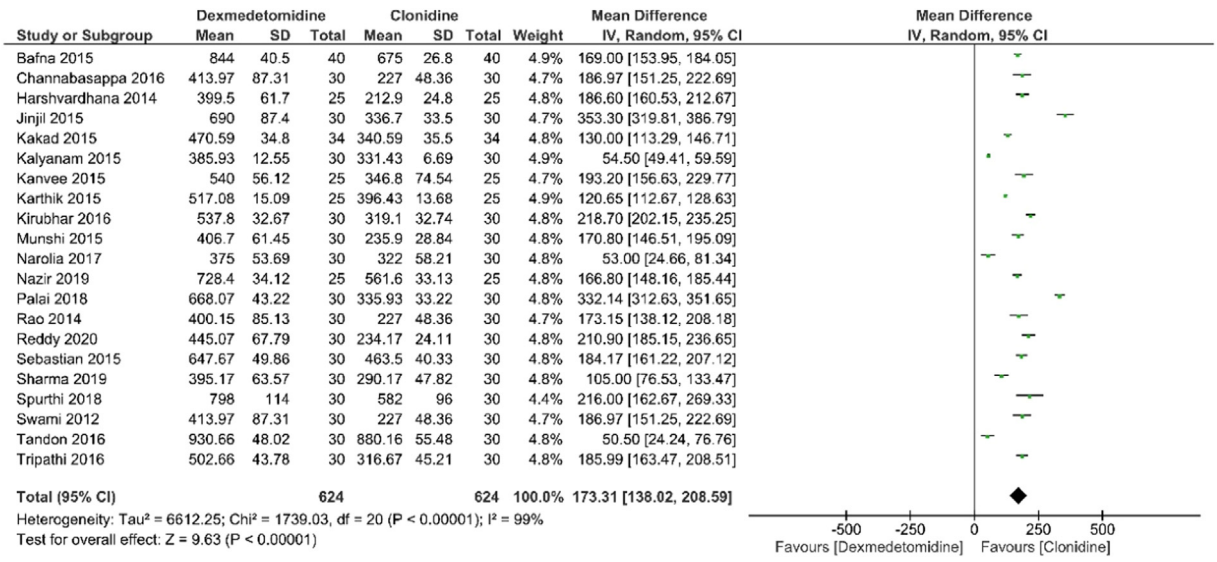

Figure 2 Meta-analytic summary of the sensory block duration through a random effect model.

Rescue analgesic requirement

Two studies contributed to rescue analgesic requirement data analyses (Supplementary Fig. 7). Patients treated with dexmedetomidine showed significantly less rescue analgesic requirement than those treated with clonidine (SMD = -1.40; 95% CI -2.44–-0.35; I^2 = 86%).

Quality of block

A total of five studies contributed to the quality of block data analyses (Supplementary Fig. 8). Patients treated with dexmedetomidine showed significantly higher-Grade IV quality of block than those treated with clonidine (1.97 [95% CI 1.60–2.41]; I^2 = 0%). An I^2 of 0% suggested a low degree of between-trial heterogeneity. The GRADE approach suggested moderate quality of evidence (Supplementary Table 4)

Adverse events

A total of two studies contributed to adverse event data analyses. The meta-analysis was conducted only for hypotension (Supplementary Fig. 9). No significant difference was observed for hypotension (2.59 [95% CI 0.63–10.66]; I^2 = 0%).

Discussion

This meta-analysis confirms the clinical superiority of dexmedetomidine over clonidine as an adjunct to local anesthetics for BPBs. The GRADE approach analysis suggested high quality of evidence for the better effect of dexmedetomidine over clonidine on the duration of sensory block, motor block, and analgesia. A similar trend was observed in the sensitivity analysis. The findings also suggest no significant differences in the safety profile between two alpha 2 adrenoreceptor agonists.

Our findings suggest that dexmedetomidine prolongs the duration of sensory (~3 h) and motor block (~2h30) significantly as compared to clonidine. The use of dexmedetomidine is also associated with the early achievement of onset of sensory and motor block as well as complete block compared to clonidine. However, the time difference may not be clinically significant for the onset and compete block parameters. The quality of block during the intraoperative period was found to be better with dexmedetomidine than clonidine. In an earlier meta-analysis by El-Boghdadly et al., dexmedetomidine showed better sensory and motor block characteristics than clonidine as an adjunct to local anesthetic in a supraclavicular block. El-Boghdadly et al. could not find the significant predictors of heterogeneity in case of sensory block duration. This may be due to inclusion of only one study that used ultrasound to locate the supraclavicular block.[14] We observed the block localization technique as a significant predictor of heterogeneity in the case of sensory block duration. Block localization techniques are ultrasound-guided, nerve stimulator-guided, or paresthesia techniques. The nerve stimulator and paresthesia are the blind needle placement techniques for PNBs. This increases risk of too far or too close dispersion of local anesthetics leading to block failure and nerve injury, respectively.[44] Use of more specific techniques such as ultrasound may result in a better local anesthetic allocation and influence the duration of sensory block. Ultrasound allows anesthesiologists to visualize the needle, nerve, and spread of local anesthetic agents.[45] Ultrasound facilitates detection of anatomical variations in the architecture of brachial plexus.[46] This minimizes procedure-related pain and complications by reducing multiple trial-and-error needle attempts.[47] In an earlier meta-analysis by Zhang et al., dexmedetomidine showed superior findings for sensory block outcomes and trend to faster onset and longer duration for motor block outcomes as compared to clonidine in the case of intrathecal anaesthesia.[48] Vorobeichik et al. conducted a meta-analysis of 32 RCTs comparing the adjuvant effect of dexmedetomidine to local anesthetic alone in PNBs. The authors observed the superior effect of dexmedetomidine for motor and sensory blockade

Table 2 GRADE approach evidence of primary efficacy outcomes.

Certainty assessment		Effect	Certainty							N° of patients
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomidine	Clonidine	Absolute (95% CI)	
Sensory block duration										
21	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	Strong association	624	624	MD 173.31 Minutes higher (138.02 higher to 208.59 higher)	⊕⊕⊕⊕ High
Motor block duration										
23	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	Strong association	684	684	MD 158.35 Minutes higher (131.55 higher to 185.16 higher)	⊕⊕⊕⊕ High
Duration of analgesia										
22	Randomized trials	Not serious	Serious[c]	Not serious	Not serious	Strong association	690	690	MD 203.92 Minutes higher (169.25 higher to 238.58 higher)	⊕⊕⊕⊕ High

[a] Heterogeneity (I^2 = 99%).
[b] Heterogeneity (I^2 = 98%).
[c] Heterogeneity (I^2 = 99%).
CI, Confidence Interval; MD, Mean Difference.

as well as analgesic outcomes.[9] Abdallah et al. observed superiority of dexmedetomidine as an adjunct to local anesthetic over the local anesthetic alone group for the prolongation of motor block duration in case of brachial plexus block. The authors did not observe expedition of the onset of sensory and motor block effects in case of brachial plexus block. The outcome was based on 4 RCTs with a total sample size of 125.[7] A small sample size could have missed the significant difference.

Dexmedetomidine prolongs the duration of analgesia (~3 h) and reduces the requirement of rescue analgesics in comparison to clonidine. This is in line with the earlier meta-analysis suggesting a longer duration of the analgesic effect of dexmedetomidine in peripheral nerve block or intrathecal anesthesia as compared to clonidine[14,49] or local anesthetic alone.[7-12]

Our findings suggest no significant difference in the sedation scores and risk of hypotension between dexmedetomidine and clonidine. We could not evaluate the risk of bradycardia as only one trial provided the outcome. In an earlier meta-analysis, El-Boghdadly et al. suggested a significantly higher risk of perioperative sedation and bradycardia in patients who received dexmedetomidine than those who received clonidine.[14] Zhang et al. did not observe a difference in the rate of adverse events among patients treated with dexmedetomidine and clonidine.[49] Abdallah et al. observed a higher incidence of bradycardia in patients who received dexmedetomidine for brachial plexus block but found no difference with intrathecal administration as compared to patients who received local anesthetic alone.[7,49] In a systematic review, Kirksey et al. observed that both clonidine and dexmedetomidine can cause bradycardia and hypotension in higher doses. They should be used cautiously. However, the authors did not statistically pool the results to derive a meta-analytic summary.[50] All these meta-analyses had only a few trials in the safety analysis. Our findings should not be considered confirmatory for absence of risk of hypotension due to the wide confidence interval and based on inclusion of only two studies with a total sample of 160 patients.

Our meta-analysis has several limitations. We acknowledge that some of the published literature could have been missed due to lack of literature search on EMBASE and CINAHL databases. There was no restriction on the type of blinding for the RCTs. Two open-labeled studies and one study with unspecified nature of blinding were included in our meta-analysis. However, sensitivity analysis on the exclusion of these trials did not affect the primary outcomes. A total (of) 13 studies were considered to have "some concerns" on the risk of bias assessment for the measurement of the outcome. However, sensitivity analysis did not suggest any difference in the primary outcomes. Our findings on efficacy outcomes should be interpreted cautiously due to the presence of high statistical heterogeneity. This could be due to methodological variability among included studies. The studies differed in terms of type of surgeries (upper limb and forearm surgeries), doses of dexmedetomidine and clonidine (absolute [50–150 μg] and body weight [0.5–2 $\mu g.kg^{-1}$] basis), local anesthetics (types, volumes and concentration), block localization techniques (paresthesia, nerve stimulator and ultrasound), scales used to measure sensory block, motor block and analgesia.

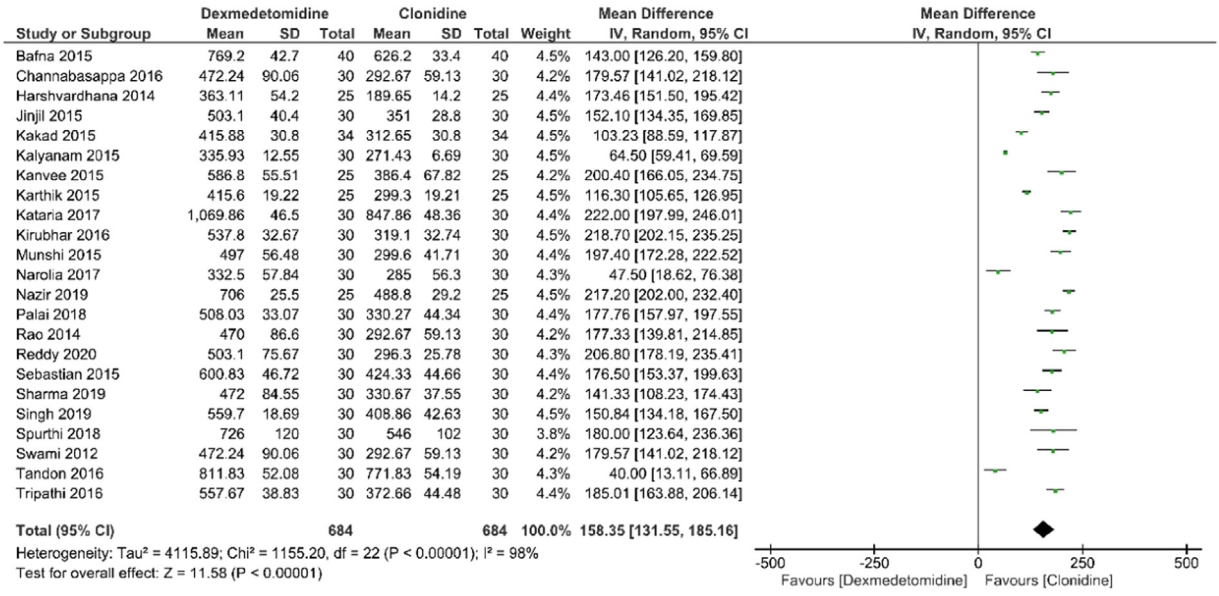

Figure 3 Meta-analytic summary of the motor block duration through a random effect model.

However, these study variabilities are likely to affect degree of benefits (small versus large effect) rather than direction of benefits (benefit versus harm). All included studies used supraclavicular block techniques, and most were conducted in elective settings. This limits the generalizability of our findings to other techniques and setup.

In conclusion, dexmedetomidine quickens the onset and prolongs the duration of sensory and motor block, increases the duration of analgesia, and provides higher grade quality of block in comparison to clonidine. There was no significant difference in risk of adverse events between dexmedetomidine and clonidine. Block localization techniques are the important study characteristics affecting sensory block duration outcomes. Use of ultrasound may result in a better local anesthetic allocation in brachial plexus blocks and influence the duration of sensory blocks.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.07.005.

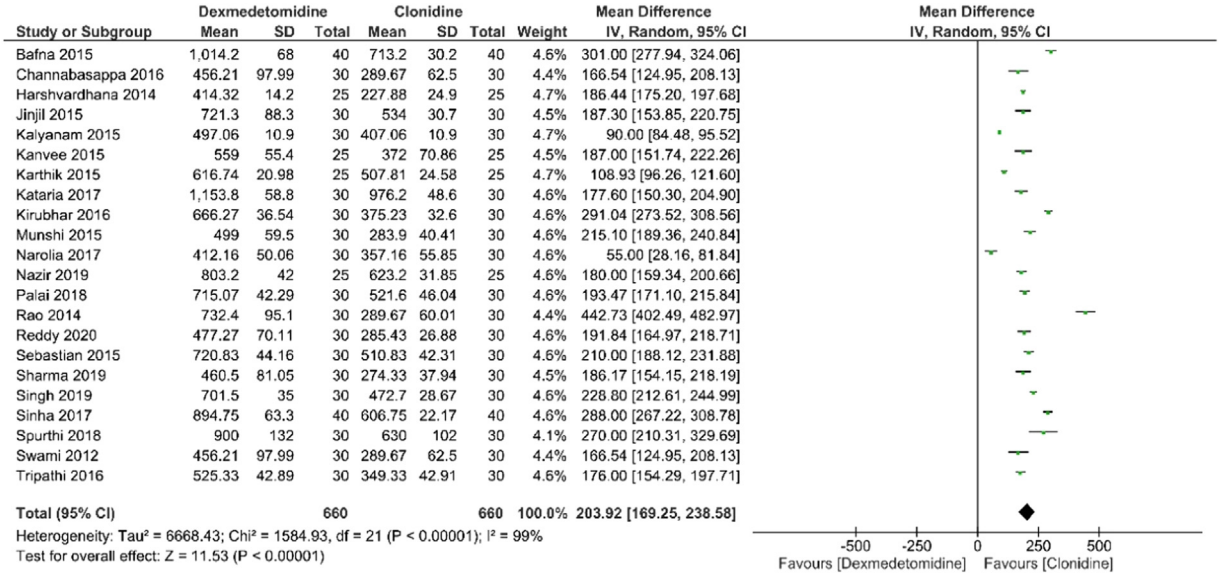

Figure 4 Meta-analytic summary of the duration of analgesia through a random effect model.

References

1. Fischer HBJ. Brachial plexus anaesthesia. In principles and practice of regional anaesthesia. London: Churchill Livingstone; 2003. p. 193—204.
2. Damien B, Murhy Collin JL, Cartney Vincent WS. Novel analgesic adjuvants for brachial plexus block: A systemic review. Anesth Analg. 2000;90:1122—8.
3. El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS. Addition of Clonidine or Dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth. 2009;103:268—74.
4. Popping DM, Elia N, Marret E, Wenk M, Tramèr MR. Clonidine as an adjuvant to local anaesthetic for peripheral nerve and plexus blocks: A meta-analysis of randomized trials. Anesthesiology. 2009;111:406—15.
5. Virtanein R, Savola JM, Saanov Nyman L. Characterization of the selectivity, specificity, and potency of dexmedetomidine as an alpha -2 adrenoceptor. Eur J Pharmacol. 1998;150:194.
6. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anaesth Analg. 2010;111:1548—51.
7. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2013;110:915—25.
8. Schnabel A, Reichl SU, Weibel S, et al. Efficacy and safety of dexmedetomidine in peripheral nerve blocks: A meta-analysis and trial sequential analysis. Eur J Anaesthesiol. 2018;35:745—58.
9. Vorobeichik L, Brull R, Abdallah FW. Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth. 2017;118:167—81.
10. Hussain N, Grzywacz VP, Ferreri CA, et al. Investigating the Efficacy of Dexmedetomidine as an Adjuvant to Local Anesthesia in Brachial Plexus Block: A Systematic Review and Meta-Analysis of 18 Randomized Controlled Trials. Reg Anesth Pain Med. 2017;42:184—96.
11. Dai W, Tang M, He K. The effect and safety of dexmedetomidine added to ropivacaine in brachial plexus block: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97:e12573.
12. Ping Y, Ye Q, Wang W, Ye P, You Z. Dexmedetomidine as an adjuvant to local anesthetics in brachial plexus blocks: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96:e5846.
13. Wang K, Wang LJ, Yang TJ, Mao QX, Wang Z, Chen LY. Dexmedetomidine combined with local anesthetics in thoracic paravertebral block: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97:e13164.
14. El-Boghdadly K, Brull R, Sehmbi H, Abdallah FW. Perineural dexmedetomidine is more effective than clonidine when added to local anesthetic for supraclavicular brachial plexus block: a systematic review and meta-analysis. Anesth Analg. 2017;124:2008—20.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;28(366):l4898.
16. Memiş D, Turan A, Karamanlioğlu B, Pamukçu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg. 2004;98:835—40.
17. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: ahrq and the effective health care program. 2010 Oct 25. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. RockvilleMD: Agency for Healthcare Research and Quality (US); 2008. Available from: https://www.ncbi.nlm.nih.gov/books/NBK49407/.
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924—6.
19. GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. McMaster University; 2020 (developed by Evidence Prime, Inc.). Available from gradepro.org.
20. Bafna U, Sharma G, Sapru S, Khandelwal M, Kothari V, Mathur R. Comparison of clonidine and dexmedetomidine as an adjuvant to 0.5% ropivacaine in supraclavicular brachial plexus block: a prospective, randomized, double-blind and controlled study. J Recent Adv Pain. 2015;1:73—7.
21. Channabasappa SM, Shruthi DK, Shobha MM. A comparative study between dexmedetomidine and clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block: a prospective study. J Evolution Med Dent Sci. 2016;5:433—7.
22. Harshavardhana HS. Efficacy of dexmedetomidine compared to clonidine added to ropivacaine in supraclavicular nerve blocks: a prospective, randomized, double blind study. Int J Med Health Sci. 2014;3:127—32.
23. Jinjil K, Bhatnagar V, Swapna P, Tandon U. Comparative evaluation of alpha two agonists dexmedetomidine with clonidine as adjuvants to 0.25% ropivacaine for ultrasound guided supraclavicular block: a randomised double-blind prospective study. Int J Healthc Biomed Res. 2015;3:20—31.
24. Kakad RR, Chaudhari DR, Lawhale SS, Ghodki SG, Bite BM. Comparative study between dexmedetomidine and clonidine as an adjunct to bupivacaine in brachial plexus block in orthopaedic surgeries. J Cont Med A Dent. 2015;3:39—43.
25. Kalyanam P, Julakanti M, Babu BS, Kiran M, Raghuram CG. A prospective randomized study to compare dexmedetomidine with clonidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block. J Evol Med Dent Sci. 2015;4:15289—97.
26. Kanvee V, Patel K, Doshi M, Vania M, Gandha K. Comparative study of clonidine and dexmedetomidine as an adjuvant with inj. ropivacaine in supraclavicular brachial plexus block for upper limb surgery. J Res Med Den Sci. 2015;3:127—30.
27. Karthik GS, Sudheer R, Sahajananda H, Rangalakshmi S, Kumar R. Dexmedetomidine and clonidine as adjuvants to levobupivacaine in supraclavicular brachial plexus block: a comparative randomised prospective controlled study. J Evol Med Dent Sci. 2015;4:3207—21.
28. Kataria AP, Jarewal V, Singh G, Attri JP. Comparison of dexmedetomidine and clonidine as an adjuvant to levobupivacaine in supraclavicular brachial plexus block. Int J Med Res Rev. 2017;5:399—404.
29. Kirubahar R, Bose S, Kanna V, Murugadoss K. Comparison of clonidine and dexmedetomidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block for upper limb orthopedic procedures. Int J Res Med Sci. 2016;4:1172—6.
30. Munshi FA, Bano F, Khan AA, Saleem B, Rather MA. Comparison of dexmedetomidine and clonidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block: a randomised double-blind prospective study. J Evol Med Dent Sci. 2015;4:7263—78.
31. Narolia AK, Bhati K, Saini K, Pareek A, Kumari K. To Compare the effect of dexmedetomidine and clonidine as adjuvant to ropivacaine in supraclavicular brachial plexus block for upper limb surgery. IAIM. 2017;4:82—90.
32. Nazir O, Bhat AH, Sharma T, Khatuja A, Misra R. Comparison of clonidine and dexmedetomidine as adjuvants for ropivacaine in supraclavicular brachial plexus block. Sri Lankan J Anaesthesiol. 2019;27:53—8.
33. Palai PK, Soren DK, Panda P, Das SK. A comparative study of clonidine and dexmedetomidine as an adjuvant in supraclavicular brachial plexus block. J Evol Med Dent Sci. 2018;7:1806—10.

34. Rao KG, Kapoor P, Chaurasiya MK, Shukla A. A Randomised double blind prospective study to compare clonidine and dexmedetomidine as an adjuvant in supra-clavicular brachial plexus block. Indian J Fundamental Appl Life Sci. 2014;4:226—9.
35. Reddy MS, Bhaskar KU, Paturu M, Srinivasan KV. A comparative study of the efficacy of dexmedetomidine and clonidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block. Indian J Anesth Analg. 2020;7:562—9.
36. Sebastian D, Ravi M, Dinesh K, Somasekharam P. Comparison of dexmedetomidine and clonidine as adjuvant to ropivacaine in supraclavicular brachial plexus nerve blocks. J Dent Med Sci. 2015;14:91—7.
37. Sharma A, Sharma A, Sharma A, Sood A, Sharma G, Thakur A. Comparison of clonidine with dexmedetomidine as an adjuvant to local anesthetic agent in supraclavicular brachial plexus block. Indian J Anesth Analg. 2019;6:1889—93.
38. Singh R, Singam A. Comparative evaluation of dexmedetomedine versus clonidine as an adjuvant in supraclavicular brachial plexus block. J Krishna Inst Med Sci Univ. 2019;8:2231—4261.
39. sur S Sinha S, Pal S, Chaterjee S, Pahari S. Comparative evaluation of efficacy and duration of analgesia of clonidine and dexmedetomidine as adjuvant to bupivacaine in supraclavicular brachial plexus nerve block in upper limb orthopaedic surgery. Int Res J Nat Appl Sci. 2017;4:231—44.
40. Spurthi George B, Lagoo J. Comparison of low dose dexmedetomidine and clonidine as additives to bupivacaine in ultrasound directed supraclavicular blocks. Indian J Clin Anaesth. 2019;6:134—9.
41. Swami SS, Keniya VM, Ladi SD, Rao R. Comparison of dexmedetomidine and clonidine (a2 agonist drugs) as an adjuvant to local anaesthesia in supraclavicular brachial plexus block: A randomised double-blind prospective study. Indian J Anaesth. 2012;56:243—9.
42. Tandon N, Gupta M, Agrawal J, et al. A comparative clinical study to evaluate the efficacy of levobupivacaine with clonidine and levobupivacaine with dexmedetomidine in supraclavicular brachial plexus block. J Evol Med Dent Sci. 2016;5:925—9.
43. Tripathi A, Sharma K, Somvanshi M, Samal RL. A comparative study of clonidine and dexmedetomidine as an adjunct to bupivacaine in supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol. 2016;32:344—8.
44. Helen L, O'Donnell BD, Moore E. Nerve localization techniques for peripheral nerve block and possible future directions. Acta Anaesthesiol Scand. 2015;59:962—74.
45. Kapral S, Krafft P, Eibenberger K. Ultrasound guided supraclavicular approach for regional anaesthesia of the brachial plexus. Anesth Analg. 1994;78:507—13.
46. Bansal T, Jain M, Singh S. Anatomical variations in brachial plexus on ultrasound: Reason for failure of supraclavicular block – Nerve stimulator along with ultrasound can play a major role for success. J Anaesthesiol Clin Pharmacol. 2019;35:135—6.
47. Fanelli G, Casati A, Garancini P, Torri G. Nerve stimulator and multiple injection technique for upper and lower limb blockade:failure rate, patient acceptance, and neurologic complications – Study Group on Regional Anaesthesia. Anesth Analg. 1999;88:847—52.
48. Zhang C, Li C, Pirrone M, Sun L, Mi W. Comparison of dexmedetomidine and clonidine as adjuvants to local anesthetics for intrathecal anesthesia: a meta-analysis of randomized controlled trials. J Clin Pharmacol. 2016;56:827—34.
49. Lundblad M, Trifa M, Kaabachi O, et al. Alpha-2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children: a meta-analysis. Paediatr Anaesth. 2016;26:232—8.
50. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative review. PLoS One. 2015;10:e0137312.