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

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**Background and Objectives:** Dexmedetomidine has been thought to be an effective adjuvant to local anesthetics in brachial plexus blockade. We sought to clarify the uncertainty that still exists as to its true efficacy.

**Methods:** A meta-analysis of randomized controlled trials was conducted to assess the ability of dexmedetomidine to prolong the duration and hasten the onset of motor and sensory blockade when used as an adjuvant to local anesthesia for brachial plexus blockade versus using local anesthesia alone (control). A search strategy was created to identify eligible articles in MEDLINE, EMBASE, and The Cochrane Library. The methodological quality for each included study was evaluated using the Cochrane Tool for Risk of Bias.

**Results:** Eighteen randomized controlled trials were included in this meta-analysis (n = 1092 patients). The addition of dexmedetomidine significantly reduced sensory block time onset time by 3.19 minutes (95% confidence interval [CI], −4.60 to −1.78 minutes; F² = 95%; P < 0.00001), prolonged sensory block duration by 261.41 minutes (95% CI, 145.20−377.61 minutes; F² = 100%; P < 0.00001), reduced the onset of motor blockade by 2.92 minutes (95% CI, −4.37 to −1.46 minutes; F² = 96%; P < 0.00001), and prolonged motor block duration by 200.90 minutes (CI, 99.24−302.56 minutes; F² = 99%; P = 0.0001) as compared with control. Dexmedetomidine also significantly prolonged the duration of analgesia by 289.31 minutes (95% CI, 185.97−392.64 minutes; F² = 99%; P < 0.00001). Significantly more patients experienced intraoperative bradycardia with dexmedetomidine (risk difference [RD], 0.06; 95% CI, 0.00−0.11; F² = 72%; P = 0.03); however, there was no difference in the incidence of intraoperative hypotension (RD, 0.01; 95% CI, −0.02 to 0.04; F² = 3%; P = 0.45). It is important to note that all studies reported that intraoperative bradycardia was either transient in nature or reversible, when needed, with the administration of intravenous atropine.

**Conclusions:** Dexmedetomidine has the ability to hasten the onset and prolong the duration of blockade when used as an adjuvant to local anesthesia for brachial plexus blockade. Considering an anesthetic adjuvant to be either decreased pain, a longer duration of analgesic block, or decreased opioid consumption, the addition of dexmedetomidine to local anesthetics for brachial plexus blockade was found to significantly improve analgesia in all 18 included studies. However, patients receiving dexmedetomidine should be continuously monitored for the potentially harmful but reversible adverse effect of intraoperative bradycardia.

**Level of Evidence:** Therapeutic, level I.

(Under-extremity surgeries are a commonly performed procedure in the United States. Most of these surgeries are in the ambulatory setting where pain after surgery and adverse effects of opioid administration remain significant factors in postoperative recovery and discharge. Upper-extremity regional anesthetic techniques, using brachial plexus blockade, have been shown to reduce adverse effects related to opioid administration, improve patient satisfaction, and provide significantly improved analgesia immediately following these surgeries.1

Brachial plexus blockade is typically administered as a single injection or as a continuous peripheral nerve block via a catheter. Continuous peripheral nerve blocks, although effective, have been associated with complications such as pump malfunction, catheter dislodgement, and fluid leakage.2 Thus, they remain unsuitable in many ambulatory surgical settings. While single injections of local anesthetics are free of these complications, they can suffer from suboptimal duration of analgesia and can negatively impact the postoperative experience.3 To remedy this shortcoming, various adjuvant drugs have been used in combination with local anesthetics to prolong the duration of analgesia. The commonly used adjuvants remain clonidine and dexamethasone; however, each of these has also been found to have its own shortcomings.

In comparison to the above, dexmedetomidine has been found to be a more potent and effective adjuvant for brachial plexus blockade.4,5 Its use has been thought to increase the duration of blockade; however, common adverse effects such as bradycardia, hypotension, and significant respiratory depression have been reported.6 The recent increase in use of dexmedetomidine as an adjuvant warrants further investigation into its efficacy and safety in this role.

Abdallah and Brull7 recently conducted a meta-analysis on this topic; however, since that publication, there have been 14 new randomized trials conducted on this popular topic, thus allowing us to gain greater insights into the role of dexmedetomidine as an adjuvant for brachial plexus blockade. Given the continued uncertainty of dexmedetomidine’s ability to prolong the duration of brachial plexus blockade, we undertook this meta-analysis to evaluate current evidence of its efficacy. Therefore, the primary objective of this meta-analysis is to evaluate the effectiveness of dexmedetomidine at prolonging the duration of motor and sensory blockade when used as an adjuvant to local anesthesia for brachial plexus blockade versus using local anesthesia alone (control) in adult patients (≥18 years old) undergoing upper-limb procedures. In addition, we hope to further explore the adverse events profile of dexmedetomidine to gain greater insights into its safety.)
METHODS

Criteria for Study Inclusion
Any clinical trial that randomly allocated adult patients (≥18 years old) to receive dexmedetomidine in addition to local anesthetic in comparison with local anesthetic alone for brachial plexus blockade was considered for inclusion. Because of the high level of expected heterogeneity across clinical outcomes, we included only studies that assessed brachial plexus blockade to ensure consistency. The dose of dexmedetomidine and the type and dose of local anesthetic used were not a consideration for inclusion. In situations where there was no mention of randomization, the corresponding author was contacted for further information. Studies were excluded if dexmedetomidine was used as an adjuvant to local anesthesia for neuraxial blockade.

Search Methods for Identification of Studies

An evidence-based medicine librarian (L.B.) created a systemic search strategy for each of the following databases: MEDLINE, EMBASE, Cochrane Library, and DARE (Database of Abstracts of Reviews of Effects). A full search strategy was created to identify both published and unpublished articles (Appendix A, Supplemental Digital Content 1, http://links.lww.com/AAP/A192). Two independent reviewers (N.H. and V.P.G.) screened the results from the electronic searches of the various databases from inception to February 10, 2016, for potentially eligible articles. An initial screen was performed in duplicate based on title and abstract. Following this, the full text version of each potentially eligible article was retrieved and evaluated for inclusion. In the case of a disagreement, the 2 reviewers evaluated the full article and discussed until a consensus was reached. If a consensus still could not be reached after discussion, a third reviewer (A.V.) assessed the article for eligibility. The initial agreement between the 2 reviewers for full text eligibility was assessed through the calculation of an unweighted k. The bibliographies and citations of all included articles were also analyzed to ensure completeness in the search. Lastly, the PubMed-related article feature was used throughout the creation and implementation of the search strategy.

Primary and Secondary Outcomes

The primary outcomes of this meta-analysis were to compare the onset and duration of motor and sensory blockade with the addition of dexmedetomidine versus control. The secondary outcomes of this review were adverse events, duration of analgesia, overall postoperative pain at 24-hour follow-up, and postoperative analgesic consumption. The adverse events included in this meta-analysis were hypotension, bradycardia, respiratory depression, and neurological sequelae. These were selected because they were commonly reported by included studies and were considered to be clinically important.

Data Management and Extraction

A data extraction form was created and piloted by an independent reviewer (V.P.G.). The extraction form collected information regarding the clinical setting, demographics, outcome data (eg, duration of motor block, duration of sensory block), and adverse events. Data reported in graphical form were derived from a graph digitizing software (GraphClick; Arizona Software). Two independent reviewers (N.H. and V.P.G.) extracted data to ensure accuracy and minimize risk of error. In the case of disagreement in data extraction, the 2 reviewers discussed until a consensus was reached. If a consensus still could not be reached, a third reviewer (A.V.) was tasked with making the final decision.

Assessment of Methodological Quality and Risk of Bias

Two independent reviewers (N.H. and V.P.G.) evaluated the methodological quality for each included article using The Cochrane Collaboration’s tool for assessing risk of bias.8 Questions in this tool related to randomization, blinding, and outcome data reporting. For each question, the risk of bias was reported as low risk, unclear risk, or high risk of bias. The initial agreement between the 2 reviewers was assessed through the calculation of an unweighted k. In the case of disagreement, the 2 reviewers discussed until a consensus was reached. If an agreement still could not be reached, a third reviewer (A.V.) made the final decision. When necessary, the authors of included articles were contacted to elaborate on the methodology used during their research in order to obtain additional information and ensure an accurate quality assessment.

Statistical Analyses and Measurement of Treatment Effect

The primary outcomes of time to onset and duration of motor and sensory blockade are continuous outcomes that are measured through units of time. All time measures were standardized to a total in minutes. In situations where a median and interquartile range were reported, statistical conversions were made to a mean and SD using the methods described by Wan et al.9 In situations where a mean and confidence interval (CI) were reported, statistical conversions were made to a mean and SD using the methods described by The Cochrane Collaboration.10–12 Overall, a mean difference (MD) in the unit of minutes with a 95% CI was calculated for these primary outcomes to determine the overall effect size.

The secondary outcomes consisted of adverse events, overall postoperative pain at 24-hour follow-up, total analgesic consumption at follow-up 24 hours or more, and duration of analgesia. Adverse events are a dichotomous outcome, and thus, a risk difference (RD) with a 95% CI was calculated. A RD was calculated because it has been found to be more appropriate than a relative risk of examining adverse event data while also incorporating trials with zero reported events.10–13 Postoperative pain is a continuous outcome that could have been measured by a wide range of standardized tools. In the measurement of this outcome, if the same scales were used by at least 2 articles, an MD with a 95% CI was calculated to measure the overall effect; however, in cases where different scales were used, a standardized MD (SMD) with a 95% CI was calculated. Finally, total analgesic consumption and duration of analgesia are continuous outcomes that are measured in units of milligrams and time, respectively. As stated previously, all time measures were standardized to a total in minutes. As such, an MD and 95% CI were calculated for this outcome when possible.

Statistical pooling of data was performed only when there were 2 or more studies for a given outcome. For dichotomous outcome data, a meta-analysis was performed using the Mantel-Haenszel random-effects model because there was expected heterogeneity between the included studies. For continuous outcome data, MDs and SMDs were weighted according to the inverse variance method and pooled using a random-effects model. P < 0.05 was considered to be significant. For continuous outcomes, an MD value less than 0 represented a decrease in value of the specific variable (eg, time, total analgesic consumption, or pain) with the addition of dexmedetomidine. On the other hand, an MD value greater than 0 represented a gain in value of the specific variable with the addition of dexmedetomidine.
Assessment of Heterogeneity

An $I^2$ statistic test was used to calculate heterogeneity. The threshold for conducting subgroup analyses was an $I^2$ greater than 40%. As suggested by The Cochrane Handbook for Systematic Reviews, an $I^2$ greater than 40% suggests that heterogeneity may be present. If heterogeneity was present, a priori subgroup analysis was performed on the basis of dose of dexmedetomidine, type of local anesthetic given with dexmedetomidine, and the location of the block performed. The dose of dexmedetomidine was stratified as being $\leq 50$ µg or $> 50$ µg.

Assessment of Publication Bias

A funnel plot was created and visually inspected to assess for publication bias in each of the primary outcomes. In the absence of bias, the plot should generally take the shape of a symmetrical, inverted funnel.

Data Management

All forest and funnel plots were generated using Review Manager Software (RevMan version 5.2; Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Agreement between the reviewers, as assessed through the unweighted $\kappa$, was calculated using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, New York). Finally, all tests of significance were 2-tailed, and $P < 0.05$ was considered significant.

RESULTS

Study Characteristics

The primary literature search identified a total of 384 articles. After the initial title and abstract screen, a total of 35 articles were assessed for full text eligibility. Of these articles, 18 articles were included in this meta-analysis. Articles were excluded because of their nonrandomized nature, lack of brachial plexus blockade, or lack of live human study subjects. The raw agreement between the independent reviewers was found to be 88.6%, and the unweighted $\kappa$ was calculated to be 0.77, which represents excellent agreement. The full flow diagram of study inclusion is shown in Figure 1.

A detailed description of all the included studies is shown in Table 1. Furthermore, a summary table of their results is shown in Appendix B, Supplemental Digital Content 2, http://links.lww.com/AAP/A193. All of the included studies were published between the years 2010 and 2015. The vast majority of the studies were conducted at international centers in Asia and Europe. Across all included studies, a total of 1092 patients were assessed. In regard to the type of brachial plexus block used, a total of 10 studies utilized a supraclavicular block, 4,15,18,19,22,25,27,30 3 used an axillary block, 20,26,29 3 used an interscalene block, 14,17,21 14,19,21 23,24,27,29,29 30 and 2 used an infraclavicular block. 16,28 Dexmedetomidine was used as an adjuvant to several different local anesthetics, which included levobupivacaine, 17,18,20,25,28 ropivacaine, 14,19,21,23,24,27,29,30 bupivacaine, 15,16,22 and mepivacaine. 28 Across the studies, the dose of dexmedetomidine ranged from 0.5 µg/kg to a total of 150 µg. Local anesthetic dosages also varied across the studies.

Risk-of-Bias Assessment of Included Studies

The risk-of-bias assessment for all included studies was conducted by 2 independent reviewers (N.H. and V.P.G.). The overall agreement between the reviewers, as represented through an unweighted $\kappa$, was calculated to be 0.71, which represents substantial agreement. The vast majority of the studies had an unclear risk of bias due to the lack of sufficient methodological reporting.

Several studies were classified as high risk of bias for allocation concealment due to the lack of clarity in methods used. A full risk-of-bias summary for all included studies is shown in Figure 2. Visual inspection of the funnel plot for all primary outcomes (sensory block duration, sensory block onset time, motor block duration, and motor block onset time) did not suggest publication bias; however, there were very few studies with large effect sizes (Appendix C, Supplemental Digital Content 3, http://links.lww.com/AAP/A194). Because of this, publication bias could not entirely be ruled out.

Sensory Block Time at Onset

A total of 15 studies assessed sensory block onset time; however, 13 studies (n = 739) had sufficient information to allow for pooling. 4,15–17,19,20,22–27,29 The addition of dexmedetomidine significantly reduced sensory block onset time by an average of 3.19 minutes in comparison to control (MD, $-3.19$ minutes; 95% CI, $-4.60$ to $-1.78$ minutes; $P = 0.0001$) (Fig. 3). Subgroup analyses were performed because the heterogeneity was above our predefined cutoff (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). Studies were grouped according to dosage of dexmedetomidine. Doses greater than 50 µg 4,14,16,19,20,25–27 led to a significant reduction in sensory block onset time (MD, $-2.61$ minutes; 95% CI, $-3.93$ to $-1.30$ minutes; $P = 0.0044$; $I^2 = 94%$; $P < 0.0001$); however, no significance was observed at doses 50 µg or less 17,22–24,29 (MD, $-5.07$ minutes; 95% CI, $-11.93$ to 1.78 minutes; $P = 0.15$). The data were also stratified according to location of the overall block. Dexmedetomidine, when given as an adjuvant for supraclavicular 4,15,19,22–25,27 (MD, $-3.20$ minutes; 95% CI, $-5.13$ to $-1.27$ minutes; $P = 0.001$), infraclavicular 16 (MD, $-6.20$ minutes; 95% CI, $-7.45$ to $-4.95$ minutes; $P = 0.001$).
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<tr>
<th>Study</th>
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<th>Sensory Outcomes Reported</th>
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<tr>
<td>Abdallah et al, 2015</td>
<td>Upper limb</td>
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<td>-Duration of analgesia</td>
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<td>Bharti et al., 2015</td>
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<td>0.75% Ropivacaine</td>
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<td>-Duration time of sensory block</td>
<td>-Onset time of motor block</td>
<td>-Duration time of motor block</td>
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<td>Supraclavicular</td>
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<td>-Duration time of sensory block</td>
<td>-Onset time of motor block</td>
<td>-Duration time of motor block</td>
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<td>-Duration time of sensory block</td>
<td>-Onset time of motor block</td>
<td>-Duration time of motor block</td>
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<td>Supraclavicular (forearm and hand)</td>
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<td>(1) 1 μg/kg Dex + ropivacaine (30) (2) 0.01 mL/kg NS + ropivacaine (30)</td>
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<td>-Duration time of sensory block</td>
<td>-Onset of time motor block</td>
<td>-Duration of analgesia</td>
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<td>Infraclavicular</td>
<td>30</td>
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<td>20 mL 2.0% Mepivacaine</td>
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<td>-Duration time of sensory block</td>
<td>-Duration time of motor block</td>
<td>-Duration of analgesia</td>
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<td>-Onset time of sensory block</td>
<td>-Duration time of sensory block</td>
<td>-Onset of time motor block</td>
<td>-Duration of analgesia</td>
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<tr>
<td>Bengisu et al (^{17}) 2014</td>
<td>Upper limb (shoulder)</td>
<td>Interscalene</td>
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<td>(1) 20 mL mixture of 10 μg Dex + 50 μg Epinephrine + 10 μg Levobupivacaine (23)</td>
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<td>-Duration time of motor block</td>
<td>-Postoperative analgesic requirement</td>
<td>-Adverse events</td>
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<td>Biswas et al (^{16}) 2014</td>
<td>Upper limb (forearm and hand)</td>
<td>Supraclavicular</td>
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<td>(1) 100 μg Dex in 1 mL + levobupivacaine (30) (2) 1 mL NS + levobupivacaine (30)</td>
<td>35 mL 0.5% Levobupivacaine</td>
<td>-Duration time of sensory block</td>
<td>-Duration time of motor block</td>
<td>-Duration time of motor block</td>
<td>-Adverse events</td>
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<td>Zhang et al (^{20}) 2014</td>
<td>Upper limb (forearm and hand)</td>
<td>Axillary</td>
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<td>(1) 50 μg Dex in 1 mL + ropivacaine (15) (2) 100 μg Dex in 1 mL + ropivacaine (15) (3) 1 mL NS + ropivacaine (15)</td>
<td>40 mL 0.33% Ropivacaine</td>
<td>-Onset time of sensory block -Duration time of sensory block</td>
<td>-Onset time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<td>Supraclavicular</td>
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<td>(1) 100 μg Dex in 1 mL + bupivacaine (25) (2) 1 mL NS + bupivacaine (25)</td>
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<td>-Onset time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<td>Fritsch et al (^{21}) 2014</td>
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<td>-Duration time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<td>Infraclavicular</td>
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<td>(1) 0.75 μg/kg (100 μg in 1 mL) Dex + bupivacaine (30) (2) NS + bupivacaine (25)</td>
<td>30 mL 0.33% Bupivacaine</td>
<td>-Onset time of sensory block -Duration time of sensory block</td>
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<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<td>Swami et al (^{7}) 2012</td>
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<td>Supraclavicular</td>
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<td>35 mL 0.25% Bupivacaine</td>
<td>-Onset time of sensory block -Duration time of sensory block</td>
<td>-Duration time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<td>60</td>
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<td>5 mg/mL Levobupivacaine</td>
<td>-Onset time of sensory block -Duration time of sensory block</td>
<td>-Duration time of motor block -Duration time of motor block</td>
<td>-Post operative analgesic requirement -Duration of analgesia</td>
<td>-Adverse events</td>
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<td>-Duration time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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<tr>
<td>Esmagul et al (^{21}) 2010</td>
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<td>40 mL 0.5% Levobupivacaine</td>
<td>-Onset time of sensory block -Duration time of sensory block</td>
<td>-Duration time of motor block -Duration time of motor block</td>
<td>-Duration of analgesia</td>
<td>-Adverse events</td>
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</table>

*Study by Song et al\(^{28}\) did report block onset time; however, they did not stratify data based on sensory and motor block onset times.

NS indicates normal saline; IV, intravenous; NRS, numeric rating scale; VRS, verbal rating scale.
Sensory Block Duration

A total of 16 studies assessed the duration of sensory blockade; however, 14 studies (n = 771) had sufficient information to allow for pooling. The addition of dexmedetomidine significantly prolonged the duration of sensory blockade by an average of 261.41 minutes in comparison to control (MD, 261.41 minutes; 95% CI, 145.20–377.61 minutes; \( \bar{F} = 100\% \); \( P < 0.0001 \)) (Fig. 4).

The heterogeneity was above our predefined cutoff, and thus, subgroup analysis was performed (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). The addition of dexmedetomidine significantly prolonged duration of sensory blockade irrespective of the dosage (≤50 \( \mu \text{g} \)) to >50 \( \mu \text{g} \)), location of block (eg, supraclavicular, \( I^2 = 15\% \)) to infracavicular, \( I^2 = 16\% \)), or the local anesthetic given (eg, ropivacaine, \( I^2 = 10\% \)) to levobupivacaine, \( I^2 = 8\% \)) or mepivacaine, \( I^2 = 0\% \).

Motor Block Time at Onset

The time at onset of motor blockade was assessed by 14 studies; however, 12 studies (n = 692) had sufficient information to allow for pooling. Overall, it was found that the addition of dexmedetomidine significantly reduced motor block onset time by an average of 2.92 minutes in comparison to control (MD, −2.92 minutes; 95% CI, −4.37 to −1.46 minutes; \( F = 96\% \); \( P < 0.0001 \)) (Fig. 5).

Subgroup analysis was performed because the heterogeneity was above our predefined cutoff (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). Studies were grouped according to dosage of dexmedetomidine. Doses greater than 50 \( \mu \text{g} \) led to a significant reduction in motor block onset time (MD, −2.32 minutes; 95% CI, −3.69 to −1.05 minutes; \( \bar{F} = 95\% \); \( P = 0.0004 \)); however, no significant difference was observed at doses less than 50 \( \mu \text{g} \) (MD, −6.98; 95% CI, −15.69 to 1.74; \( \bar{F} = 97\% \); \( P = 0.12 \)). The data were also stratified according to location of the overall block. The addition of dexmedetomidine significantly reduced motor block onset time in comparison to control irrespective of the location (eg, supraclavicular, \( I^2 = 19\% \)) to infracavicular, \( I^2 = 28\% \)) or axillary \( I^2 = 24\% \). Finally, when the data were stratified according to location of the overall block where the addition of dexmedetomidine was given with ropivacaine \( I^2 = 19\% \)) to levobupivacaine, \( I^2 = 20\% \)) or mepivacaine, \( I^2 = 25\% \) (Fig. 6).

Motor Block Duration

All 18 studies assessed motor block duration. Seventeen studies (n = 938) had sufficient reporting to allow for pooling. The addition of dexmedetomidine significantly prolonged the duration of motor blockade by an average of 200.90 minutes in comparison to control (MD, 200.90 minutes; 95% CI, 99.24–302.56 minutes; \( \bar{F} = 99\% \); \( P = 0.0001 \)) (Fig. 6).

Subgroup analyses were performed as the heterogeneity was above our predefined cutoff (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). The addition of dexmedetomidine significantly increased motor block duration in comparison to control irrespective of the dosage (≤50 \( \mu \text{g} \)) to >50 \( \mu \text{g} \)). When the data were stratified by location of block, it was found that dexmedetomidine, when
given as an adjuvant for supraclavicular, infracclavicular, and axillary blockade, significantly prolonged motor block duration in comparison to control; however, no significant difference was observed for interscalene blockade (MD, −145.59 minutes; 95% CI, −557.09 to 265.91; I² = 74%; P = 0.49).

Finally, when the studies were categorized according to local anesthetic, it was found that giving dexmedetomidine as an adjuvant to blockade with ropivacaine (MD, 236.16 minutes; 95% CI, 124.53–347.79 minutes; I² = 94%; P = 0.0002), bupivacaine (MD, 320.52; 95% CI, 24.21–616.84 minutes; I² = 74%; P = 0.03), and mepivacaine (MD, 66.20 minutes; 95% CI, 33.97–98.43 minutes; I² = N/A; P < 0.0001) significantly prolonged the duration of motor block in comparison to control; however, no significant difference was seen when it was given with levobupivacaine (MD, 74.07 minutes; 95% CI, −65.68 to 331.83 minutes; I² = 100%; P = 0.54).

Duration of Analgesia

The duration of analgesia was assessed by 14 studies. Thirteen of these studies (n = 720) had data that were permissive to pooling. It was found that the addition of dexmedetomidine significantly prolonged the duration of analgesia by an average of 289.31 minutes in comparison to control (MD, 289.31 minutes; 95% CI, 185.97–392.64 minutes; I² = 99%; P < 0.0001) (Fig. 7).

Subgroup analyses were performed because the heterogeneity was above our predefined cutoff (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). The duration of analgesia was significantly prolonged irrespective of dexmedetomidine dosage (≤50 μg or >50 μg).

Upon stratification of the data based on location of blockade, it was found that there was no significant difference in duration of analgesia between supraclavicular, infracclavicular, and interscalene blocks significantly prolonged duration of analgesia in comparison to control; however, axillary blocks failed to show significance (MD, 335.06 minutes; 95% CI, −77.67 to 747.79 minutes; I² = 98%; P = 0.11). The data were then stratified according to local anesthetic. It was found that using dexmedetomidine as an adjuvant with ropivacaine (MD, 346.88 minutes; 95% CI, 184.90–508.86 minutes; I² = 95%; P = 0.0001), bupivacaine (MD, 351.63 minutes; 95% CI, 145.68–557.58 minutes; I² = 99%; P < 0.0008), and mepivacaine (MD, 63.20 minutes; 95% CI, 23.88–102.52 minutes; I² = N/A; P = 0.002) led to a significantly prolonged duration of analgesia in comparison to control; however, no significant difference was seen when given with levobupivacaine (MD, 74.07 minutes; 95% CI, −65.68 to 331.83 minutes; I² = 100%; P = 0.54).

Total Analgesic Consumption at 24 Hours or More

A total of 8 studies reported postoperative analgesic consumption at 24 hours or more (n = 506) (Table 2). The...
choice of analgesia varied among the studies, with 4 utilizing diclofenac, 
1,21,24,25,30 1 using piritramide, 21 1 using lornoxicam, 17 and 2 using morphine. 14,16 Because of the different analgesics used and the lack of sufficient reporting to allow for pooling, we were unable to create an estimate of effect for this outcome. Overall, 5 studies reported that the addition of dexmedetomidine significantly decreased postoperative analgesic requirement at 24 hours or more in comparison to control. 14,16,17,19,24,30 On the other hand, 3 studies reported no significant difference between the 2 groups. 14,21,25

Overall Postoperative Pain at 24-Hour Follow-Up

Eight studies assessed postoperative pain at 24-hour follow-up (n = 461) (Table 3). 14,16,17,18,21,23,30 Six of these studies assessed pain using the verbal analog scale (VAS), 14,17,18,21,23,30 1 used the verbal rating scale, 16 and 1 utilized the numeric rating scale. 21 Two studies reported mean values but no SD, 16,19 and 2 studies stated that they measured postoperative pain; however, their results were not reported. 16,21 One study reported insufficient graphical information to allow for extraction. 30 Finally, 1 study reported mean and CI, which was then converted to mean and SD. 14 Thus, of the 8 studies, 3 had adequate reporting to allow for statistical pooling. 14,17,22 No significant difference in postoperative pain was found with the addition of dexmedetomidine at 24-hour follow-up (SMD, −0.15; 95% CI, −0.66 to 0.35; I² = 65%; P = 0.55) (Fig. 8). Because of the limited number of studies included in this analysis, subgroup analysis was not performed.

Intraoperative Adverse Events

The 2 most commonly reported intraoperative adverse events were hypotension and bradycardia. No study reported any cases of respiratory depression. In regard to intraoperative hypotension, there was 1 additional case per 100 patients receiving dexmedetomidine in comparison to control; however, this was not found to be significant (RD, 0.01; 95% CI, −0.02 to 0.04; I² = 3%; P = 0.45) (Fig. 9). On the other hand, there were 6 additional cases of intraoperative bradycardia per 100 patients receiving dexmedetomidine in comparison to control, and this was found to be significant (RD, 0.06; 95% CI, 0.00–0.11; I² = 72%; P = 0.03) (Fig. 10). It is important to note that all studies reported that intraoperative bradycardia was either transient in nature or reversed, when needed, with the administration of intravenous atropine. The I² for bradycardia was above our predefined cutoff, and thus, subgroup analysis was performed (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). Subgroups were categorized on the basis of dexmedetomidine dosage. When the dose of dexmedetomidine was greater than 50 μg, 15,16,19,20,25,27–30 there were significantly more cases of intraoperative bradycardia when compared with control (RD, 0.07; 95% CI, 0.00–0.14; I² = 75%; P = 0.04); however, doses of 50 μg or less 14,17,22–24 failed to show significance in cases of bradycardia in comparison to control (RD, 0.04; 95% CI, −0.06 to 0.15; I² = 75%; P = 0.41).

Even though the heterogeneity for hypotension was below our predefined cutoff, we performed an analysis based on the dose

FIGURE 5. Mean time to onset of motor blockade in minutes with 95% CI in patients receiving dexmedetomine versus control.

FIGURE 6. Mean duration of motor blockade in minutes with 95% CI in patients receiving dexmedetomine versus control.
of dexmedetomidine (Appendix D, Supplemental Digital Content 4, http://links.lww.com/AAP/A195). Irrespective of dosage (≤50 μg14,17,22–24,29 and >50 μg15,18,20,26,30), the occurrence of intraoperative hypotension was nonsignificant (P > 0.05) with the addition of dexmedetomidine in comparison with control.

### Neurological Sequelae

Neurological adverse effects were assessed by 7 studies.4,14,16,21,23,24,30 Various neurological sequelae were assessed including paresthesias, hand/arm weakness, and sensory loss. Although the reporting of this outcome varied across several studies, no significant difference in neurological adverse events was reported during the intraoperative period,4 immediate postoperative period,4,14,21,30 7-day follow-up,4,14,21,30 14-day follow-up,4,14 1-month follow-up,21 and 3-month follow-up.14 One study23 reported no neurological adverse effects for the duration of the hospital stay. Lastly, 2 studies16,24 did not specify a time frame for their assessment of neurological adverse events; however, none were reported.

### DISCUSSION

The results of our systematic review and meta-analysis suggest that the use of dexmedetomidine, particularly at doses greater than 50 μg, significantly prolongs both sensory and motor block duration, provides significantly quicker sensory and motor block onset times, and leads to an overall increase in the duration of analgesia when used as an adjuvant to local anesthesia for brachial plexus blockade. Furthermore, we found that the majority of studies reported that the addition of dexmedetomidine significantly reduces postoperative analgesic consumption but fails to significantly reduce postoperative pain scores at 24-hour follow-up. However, our review also suggests that dexmedetomidine can lead to a significantly greater occurrence of transient or reversible adverse events, namely, intraoperative bradycardia. As suggested by subgroup analysis, the effects of bradycardia appear to be dose dependent since studies that used doses greater than 50 μg had significantly more events in comparison with control; however, this effect was not seen with doses 50 μg or less. It is equally important to note that the adverse event of respiratory depression was not reported by any study and that the risk of intraoperative hypotension did not differ between patients on dexmedetomidine in comparison with control. Overall, when considering an analgesic effect to be either decreased pain, a longer duration of analgesic block, or decreased opioid consumption, the addition of dexmedetomidine to local anesthetics for brachial plexus blockade significantly improved analgesia.

### TABLE 2. Individual Study Data for Postoperative Analgesic Requirement at 24 Hours or More in Patients Receiving Dexmedetomidine Versus Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size Used for Data Analysis</th>
<th>Analgesic Used</th>
<th>Analgesic Consumption With Dexmedetomidine</th>
<th>Analgesic Consumption With Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammar and Mahmoud,16 2012</td>
<td>60</td>
<td>Morphine</td>
<td>4.9 (0–8.0) mg*</td>
<td>13.6 (4.0–16.0) mg*</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>Bengisu et al,17 2014</td>
<td>50</td>
<td>Lornoxicam</td>
<td>8 (11.8) mg†</td>
<td>20.2 (17.5) mg†</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Das et al,19,20 2014</td>
<td>80</td>
<td>Diclofenac</td>
<td>11 of 40‡</td>
<td>25 of 40‡</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Fritsch et al,21 2014</td>
<td>61</td>
<td>Piripiramide</td>
<td>19.4 (15.7) mg‡</td>
<td>23.3 (19.8) mg‡</td>
<td>P = 0.38</td>
</tr>
<tr>
<td>Abdallah et al,21,22 2015</td>
<td>65</td>
<td>Morphine</td>
<td>49.9 (40.1–59.7)§</td>
<td>58.9 (50.8–67.1)§</td>
<td>P = 0.326</td>
</tr>
<tr>
<td>Bhati et al,23 2015</td>
<td>54</td>
<td>Diclofenac</td>
<td>2 doses (0–3 doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kathuria et al,24,25 2015</td>
<td>40</td>
<td>Diclofenac</td>
<td>60.00 (39.25) mg‡</td>
<td>120.00 (56.55) mg‡</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Kaur et al,26 2015</td>
<td>90</td>
<td>Diclofenac</td>
<td>5 of 45§</td>
<td>12 of 45§</td>
<td>P = 0.059</td>
</tr>
</tbody>
</table>

*Mean amount of analgesic used (interquartile range) reported.†Mean (SD) reported.‡Number of patients who required injections.§Mean (CI) reported.||Median number of doses of analgesic required (interquartile range) reported.\NR indicates not reported.
in all 18 of the studies included. Future studies should focus on definitively identifying the possibility of a dose-dependent effect, as was seen in the study conducted by Zhang et al.29

A previous meta-analysis conducted by Abdallah and Brull7 found similar results to ours; however, their findings were nonsignificant with regard to motor and sensory block onset times due to the limited number of studies published at the time of their review. The results of our meta-analysis are the first to suggest the potential significance of dexmedetomidine in these aspects. Additionally, in contrast to the previous review, we were able to further analyze the effects of dexmedetomidine based on dosage, location of the block performed, and the local anesthetic given. This was again due in part to the larger number of studies published at the time of this meta-analysis in comparison to the prior review.27 On these aspects, our review suggests that dexmedetomidine significantly prolongs the duration of motor and sensory blockade irrespective of dosage; however, motor and sensory block onset times appear to be significantly quicker among studies that utilized larger doses (>50 μg). The onset and duration of blockade were also significantly prolonged irrespective of whether supraclavicular, infraclavicular, or axillary blockade was used. Finally, our review suggests that the effects of dexmedetomidine also differ on the basis of which local anesthetic is administered. Specifically, the combination of dexmedetomidine with ropivacaine was the only treatment regimen that led to both significantly prolonged block duration and significantly quicker block onset time in comparison to using ropivacaine alone. However, we were unable to determine why this may be the case. A summary table of all subgroup effects is shown in Table 4. We generated this table to provide clinicians with a quick reference tool to help guide decision making.

Over the past decade, there have been several adjuvants used for peripheral nerve blockade including epinephrine, clonidine hydrochloride, dexamethasone, and, now more recently, dexmedetomidine. Peripheral nerve blockade with the use of dexmedetomidine represents an excellent opportunity to quicken the onset of anesthesia and prolong its duration while also potentially reducing postoperative opioid consumption. Despite these benefits, there are drawbacks. Because dexmedetomidine also prolongs the duration of motor blockade, there is a potential risk of delayed rehabilitation. Furthermore, patients administered dexmedetomidine should be continuously monitored intraoperatively and postoperatively for potential adverse effects, the most important of which is bradycardia. It is important to also note that the systemic use of dexmedetomidine in conjunction with peripheral nerve blockade may not be as effective as perineural administration, as shown in both animal31 and human volunteer14 studies. This may be due to the mechanism of action of perineural administration of dexmedetomidine, which is thought to be related to the inhibition of hyperpolarization-activated cation currents rather than its effects on α2 adrenergic receptors.32

### Strengths and Limitations

Our review comes with several strengths and potential limitations. First, ours is the first review to pool a large number of studies on the topic and provide greater insights into the benefits of dexmedetomidine. While the prior review27 included 4 randomized controlled trials, we were able to include an additional 14. There was also substantial to a high level of agreement between reviewers on all parameters of this meta-analysis. Finally, we were able to successfully analyze the effects of dexmedetomidine on

![FIGURE 8. Standardized mean pain score at 24-hour follow-up with 95% CI in patients receiving dexmedetomidine versus control.](image)

**TABLE 3.** Individual Study Data for Postoperative Pain with the Use of Dexmedetomidine Versus Control at 24-Hour Follow-Up

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size Used for Data Analysis</th>
<th>Pain Scoring System Used</th>
<th>Mean Pain Score With Dexmedetomidine (SD)</th>
<th>Mean Pain Score With Control (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammar and Mahmoud16 2012</td>
<td>60</td>
<td>VRS*</td>
<td>1.7</td>
<td>3.3</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Bengisu et al17 2014</td>
<td>50</td>
<td>VAS†</td>
<td>0.76 (0.76)</td>
<td>1.5 (1.27)</td>
<td>P = 0.004</td>
</tr>
<tr>
<td>Biswas et al18 2014</td>
<td>60</td>
<td>VAS†</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Das et al19 2014</td>
<td>80</td>
<td>VAS†</td>
<td>5.0</td>
<td>5.5</td>
<td>NR</td>
</tr>
<tr>
<td>Fritsch et al20 2014</td>
<td>61</td>
<td>NRS‡</td>
<td>2.68 (2.93)</td>
<td>2.1 (2.2)</td>
<td>P = 0.38</td>
</tr>
<tr>
<td>Abdallah et al21 2015</td>
<td>65</td>
<td>VAS†</td>
<td>5.5 (2.53)</td>
<td>5.6 (2.49)</td>
<td>P = 0.87</td>
</tr>
<tr>
<td>Bharti et al22 2015</td>
<td>54</td>
<td>VAS†</td>
<td>IR</td>
<td>IR</td>
<td>NR</td>
</tr>
<tr>
<td>Gurajala et al23 2015</td>
<td>31</td>
<td>VAS†</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Mean pain scores are reported with SD. If an SD was not reported by a study, then only the mean is listed.

NR indicates not reported; IR, insufficient information to allow for conversion to mean and SD; VRS, verbal rating scale; NRS, numeric rating scale.

*Rating scale is from 0 to 10, with a higher score representing more pain.
†Rating scale is from 0 to 10, with a higher score representing more pain.
‡Rating scale is from 0 to 10, with a higher score representing more pain.
the basis of several factors including dosage, location of block, and the local anesthetic administered; however, this analysis comes with an inherent risk of bias because these factors were not randomized among the included studies. As such, they should be validated by future randomized trials.

Notable among the limitations of our review is the high level of heterogeneity present across the pooled clinical outcomes, such as block duration and postoperative pain. Furthermore, the heterogeneity was unsuccessfully resolved even with subgroup analyses, which may reduce the external validity of our results. This suggests that there may have been other, unaccounted-for factors, which may have affected these results. The high level of heterogeneity could have been due to a myriad of factors including the smaller sample sizes of individual studies, the potential variation in the study populations, differences in the standard of care in the wide range of regions where the studies were conducted, and the different methods that could have been used to measure the outcomes in question. These factors, along with other intrinsic factors, could have led to the large variation in the magnitude of effect across all included studies. In relation to this, the definition for duration of analgesia and the adverse event of hypotension varied greatly across the studies, which may have affected the pooled estimate for these outcomes. Particularly for hypotension, there currently exists no standard measure of hemodynamic instability with the use of dexmedetomidine.34 As such, our finding of no significant difference in events between patients receiving dexmedetomidine in comparison to control may be a function of this lack of clarity. There is also the potential for publication bias because the majority of studies originated from journals with potentially less stringent editorial policies. The majority of the studies in this review had an unclear or high risk of bias due to their methodological inadequacies. This may reduce the external validity and overall generalizability of the results. Finally, we were unable to provide rationale as to why the effects of dexmedetomidine varied based on local anesthetic given. Although the differences may have been a function of the methodological quality of the included trials, future studies should evaluate a potential for biochemical interactions.

CONCLUSIONS

Overall, the results of our systematic review and meta-analysis suggest that dexmedetomidine, particularly at doses greater than 50 μg, holds a great potential for clinicians wishing to quicken the onset and prolong the duration of anesthesia; however, the results of our review are dampened by the poor quality of evidence on the topic. As such, in order to optimize outcomes associated with brachial plexus blockade, physicians may consider utilizing dexmedetomidine as an adjuvant to local anesthesia. Furthermore, its use may also decrease postoperative analgesia consumption. In light of these benefits, physicians should also
### TABLE 4.
Summary Guide of Subgroup Effects From the Results of the Meta-Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dose of Dexmedetomidine</th>
<th>Location of Block</th>
<th>Local Anesthetic Type</th>
<th>Sensory block duration</th>
<th>Motor block duration</th>
<th>Analgesia duration</th>
<th>Sensory block onset time</th>
<th>Motor block onset</th>
<th>Adverse event: bradycardia</th>
<th>Adverse event: hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50 μg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*†</td>
<td>*†</td>
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<tr>
<td>&gt; 50 μg</td>
<td>*</td>
<td>*†</td>
<td>*†</td>
<td>*</td>
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<td>*†</td>
<td>*†</td>
<td>*†</td>
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<tr>
<td>Supraclavicular</td>
<td>*†</td>
<td>Infraclavicular</td>
<td>Axillary Interscalene</td>
<td>Bupivacaine</td>
<td>Ropivacaine</td>
<td>Levobupivacaine</td>
<td>Mepivacaine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sensory block duration</th>
<th>Sensory block onset time</th>
<th>Motor block duration</th>
<th>Motor block onset</th>
<th>Analgesia duration</th>
<th>Sensory block onset time</th>
<th>Motor block onset</th>
<th>Adverse event: bradycardia</th>
<th>Adverse event: hypotension</th>
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<td>*†</td>
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</tbody>
</table>

*Favors dexmedetomidine.†No significant difference between dexmedetomidine and control. NA indicates not applicable.

continuously monitor patients for the potentially harmful, but reversible, adverse effect of intraoperative bradycardia.

### REFERENCES


