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Efficacy Of Dexmedetomidine As An Opioid Sparing Adjunct To Regional Anesthesia For Shoulder Surgery

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Abstract

Regional anesthetics are often the preferred route for patients who are having orthopedic shoulder procedures (Rai & Bhutia, 2017). Traditionally, plain local anesthetics, like bupivacaine or ropivacaine, are used as the local anesthetic of choice because of their fast onset and relatively predictable duration of action. However, several different additives have been trialed to prolong the duration or improve the density of regional blocks. When looking at additives to regional anesthetic techniques, side effects and duration of the block can be unpredictable and unpleasant. For example, additives like fentanyl, morphine, and dexamethasone have been trialed in regional techniques and have been shown to produce itching, nausea and vomiting, respiratory depression, and hemodynamic instability (Rai & Bhutia, 2017). Will adding dexmedetomidine to upper extremity regional anesthetic techniques produce adequate anesthesia while reducing the incidence of side effects and the need for opioids in the postoperative period?

Efficacy of Dexmedetomidine as an Opioid Sparing Adjunct to Regional Anesthesia for Shoulder Surgery

Shoulder surgery is one of the most painful procedures performed in the outpatient setting (Hewson et al., 2019). With 7% of the general population and 26% of people over the age of 70 suffering shoulder pain, procedures on the shoulder are commonly performed to help alleviate discomfort aggravated by strenuous movement, injury, or simple daily activities (Hewson et al., 2019). Surgical intervention is often the optimal treatment when conservative management, like physical therapy, fails to improve movement or pain (Karaman et al., 2018). Pain that occurs in the immediate post-operative period, and the pain that occurs after discharge, can be a significant source of distress and anxiety, which can negatively affect the healing and rehabilitation process (Patel et al., 2020).

With an average numeric pain score of five on a scale of zero to 10, shoulder procedures are notoriously uncomfortable in the post-operative period (Jung et al., 2017). Due to the severity of pain reported, pain management can be challenging. Often, single analgesic regimens do not adequately control the pain associated with recovery from a shoulder procedure (Patel et al., 2020). Therefore, the use of narcotics has been a predominant post-operative pain management technique for many years (Patel et al., 2020). A study by Gil et al. (2019) stated that 42% of orthopedic surgeons prescribe opioids as the primary analgesic choice for post-operative pain. The same study also examined the use of opioids after shoulder arthroscopies. Gil et al. (2019) concluded that as high as 15% of patients remain on opioids to help ease their pain 180 days after the completion of their procedure (Gil et al., 2019).

While opioids may help alleviate pain, these drugs are not free of side effects. Short- and long-term use of opioids can result in adverse side effects such as somnolence, respiratory depression, constipation, nausea and vomiting, urinary retention, and opioid dependence (Patel et al., 2020). Whether patients are younger with acute injuries or elderly with long-standing shoulder pain, patients undergoing shoulder procedures may be opioid naïve, predisposing them to more pronounced adverse side effects like respiratory depression, nausea, and vomiting. In addition, patients who suffer from chronic pain requiring surgical intervention pose a challenge as they may require higher than average dosing of an opioid to control their pain adequately. Despite their pain control ability, the associated adverse effects can result in lengthened stays in inpatient and recovery areas (Patel et al., 2020). Utilizing methods like peripheral nerve blocks to avoid the use of opioids can help mitigate the adverse effects.

As an adjunct or alternative to opioid use, regional nerve blocks are often utilized as both a method of surgical anesthesia and post-operative pain control (Karaman, 2018). When utilized using plain local anesthetics, patients can benefit from an average of eight to 14 hours of pain relief after their procedure (Jung et al., 2017). Single injection regional nerve blocks are good analgesic techniques for short-term use, however, they may be inadequate to control pain that persists for several days following shoulder surgery (Jung et al., 2017).

With success in pain control that nerve blocks provide, different medications have been trialed as additives to extend the duration of these effects, providing more extended pain control and relief after surgery. One medication trialed recently is dexmedetomidine, an alpha-2 receptor agonist. Although dexmedetomidine has not been approved for perineural use by the United States Food and Drug Administration (FDA), studies have shown that it may be efficacious in

prolonging the duration of regional nerve blocks. The goal of this literature review is to examine the efficacy of adjunct perineural dexmedetomidine on the duration of analgesia and the need for opioids in the post-operative period.

Background

Shoulder Anatomy

The shoulder is a large, flexible joint of the upper body that is often prone to injury (Karaman et al., 2018). The shoulder joint comprises two separate mobile joints consisting of three bones and several different muscles that hold the joint together. These bones and muscles work together to allow for a wide range of movements. The scapula and clavicle are articulated, creating the acromioclavicular joint, and the humerus and scapula are articulated together to create the glenohumeral joint. These two joints are held together by a group of four muscles, the infraspinatus, supraspinatus, subscapularis, and teres minor muscles, called the rotator cuff. These four muscles are attached to the humeral head by ligaments and stabilize the shoulder joint. Together this group of muscles allows adduction, abduction, and rotation of the shoulder joint. The deltoid, latissimus, and teres major muscles also facilitate joint mobility and stability (Sheir et al., 2019).

Innervation of the shoulder originates from the anterior divisions of the spinal nerves at the level of C5-T1. This group of nerves, also known as the brachial plexus, is further divided into different sections: roots, trunks, divisions, cords, and branches. At the root level, the brachial plexus is positioned between the anterior and middle scalene muscles, two muscles that are important landmarks in successful regional nerve block placement (Okwumabua & Thompson, 2020). At the trunk level of the brachial plexus, the suprascapular nerve and the axillary nerve

are responsible for both major motor and sensory innervation of the shoulder (Hewson et al., 2019). The supraclavicular nerve, a branch of the cervical plexus at the level of C3-4, is responsible for cutaneous sensory innervation for the shoulder (Hewson et al., 2019). Adequate regional anesthetic techniques aim to block this set of nerves to provide post procedure analgesia.

Shoulder Surgical Procedures

Multiple different surgical approaches can be utilized when shoulder surgery is warranted. Most commonly, arthroscopic procedures are performed as they are less invasive and are thought to have improved outcomes (Karaman et al., 2020). A surgeon can perform several different procedures during an arthroscopic procedure through three to four small incisions around the shoulder. Fluid is instilled into the joint through one of these incisions, inflating the capsule and allowing visualization of structures via an arthroscope. Images are then projected onto a screen where the surgeon and assisting team can surgically alter the shoulder joint and its anatomical structures (Athwal, 2019). Rotator cuff repairs, tendon repairs, and shoulder debridement are often completed via an arthroscopic approach (Athwal, 2019).

When arthroscopic approaches are not sufficient for surgical exposure, fully open or mini-open procedures can be used to better access and visualize the shoulder joint and structures in need of surgical repair. During a mini-open or open procedure, a surgical incision is created over the shoulder joint to directly visualize and access the anatomical structures needed for surgical intervention. Procedures that warrant an open procedure include total shoulder replacements and certain rotator cuff repairs that are more technically challenging and warrant more surgical exposure (Athwal, 2019). Unfortunately, regardless of the surgical approach, many

of these patients suffer significant amounts of pain and often require high doses of opioids to help control their pain level (Karaman et al., 2018).

Regional Nerve Blocks

Brachial Plexus Nerve Blocks

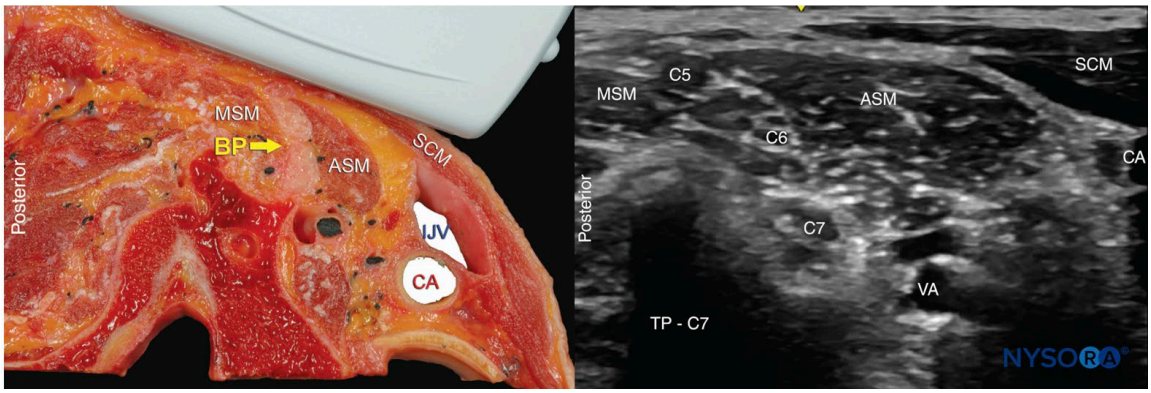
Interscalene blocks have been well studied and are considered the gold standard method of regional anesthesia for upper extremity procedures (Patel et al., 2020). To perform an interscalene block, brachial plexus nerves, which originate from C5-T1, are blocked by local anesthetics at the nerve root level (Grant & Auyong, 2017). The patient is typically positioned with the head of the bed elevated at 30 to 45 degrees. Their head is supported on a pillow and turned facing away from the site of nerve block placement. The shoulder can be supported with a rolled towel or pillow to facilitate extension of the neck and better exposure of procedural field. The skin is then sterilized with a cleaning solution such as 2% chlorhexidine gluconate. Blood pressure, oxygen saturation, and telemetry monitors are utilized throughout the nerve block placement (Grant & Auyong, 2017).

Surgical analgesia and postoperative pain control can be achieved when local anesthetic is deposited in the interscalene groove at the level of C5-C7 (Grant & Auyong, 2017). Under ultrasound guidance, the nerves appear hyperechoic and can be identified in a “stoplight” like arrangement between the anterior and middle scalene muscles (Grant & Auyong, 2017). This can be seen below in Figure 1. Using the midpoint of the clavicle as a landmark, the subclavian artery can be identified and used to help guide the ultrasound probe as it scans cephalad along the neck to identify the brachial plexus. Typically, the brachial plexus is identified as two to

three distinct dark circles surrounded by hyperechoic fascial layers three to five centimeters above the clavicle at the level of the cricoid cartilage (Grant & Auyong, 2017).

Figure 1

Cadaver and Ultrasound Anatomy of Interscalene Regional Nerve Blocks



Note. Adapted from Gautier, P., Vandepitte, C., & Gadsden, J. (2021, October 4). *Ultrasound-guided interscalene brachial plexus nerve block*. NYSORA. Retrieved February 10, 2022, from https://www.nysora.com/techniques/upper-extremity/intescalene/ultrasound-guided-interscalene-brachial-plexus-block/

When the appropriate anatomy is identified, a four-inch echogenic needle is then advanced through the skin and fascial layers in a medial and anterior direction using an in-plane view technique to assure appropriate needle placement. Local anesthetic can be deposited when the needle is appropriately positioned between the nerve roots. Proper needle placement can be confirmed using nerve stimulation. A palpable twitch would be elicited with contact between the nerve fiber and the stimulating needle, demonstrating the appropriate needle location. Ideally, local anesthetic will surround and cause displacement of the nerves (Grant & Auyong, 2017). An average of 20 to 25 milliliters (ml) of chosen local anesthetic is deposited to achieve complete sensory and motor blockade (Ping et al., 2017). Repositioning the echogenic needle may be necessary to thoroughly bathe and surround the nerve roots to achieve complete motor and sensory block (Grant & Auyong, 2017).

Local Anesthetics

Mechanism of Action

Local anesthetics are commonly used to provide anesthesia and analgesia with both surgical and nonsurgical use. There are two distinct classes, aminoamides, and aminoesters. Both local anesthetics create a reversible ion conduction blockade that prevents impulse transmission along central and peripheral nerves. Local anesthetics bind to specific alpha subunits within the voltage gated sodium (Na+) channel to achieve this. When attached, local anesthetics block the Na+ current across the cell membrane, reducing the excitability of the nerve fiber. The inhibited influx of Na+ prevents the cell's ability to achieve threshold and fully depolarize. When unable to reach threshold, the creation of an action potential within a nerve cell is hindered, reducing the nerve cell's ability to propagate action potentials (Rathmell, 2014). The absence of the ability to propagate and transmit nerve impulses results in autonomic, somatic sensory, and somatic motor nerve dysfunction producing the lack of sensation, skeletal muscle paralysis, and autonomic dysfunction distal to the site of injection (Rathmell, 2014).

Onset & Duration

The duration of action of local anesthetics is directly correlated with lipid solubility and the degree of protein binding (Irene et al., 2021). When a local anesthetic has a high degree of lipid solubility and protein binding, the medication crosses a cell's protective lipid bilayer more readily. After crossing into the cell, local anesthetics with a high degree of protein binding more readily attach themselves to the structures of the voltage gated sodium channels, producing a more prolonged blockade. For example, 0.5% ropivacaine and 0.5% bupivacaine, two medications commonly used in peripheral nerve blocks, are 94 and 97% protein bound,

respectfully, and produce a sensory nerve block duration of roughly eight to 14 hours (Ping et al., 2017; Jung et al., 2017). This is in comparison to chloroprocaine, which has the lowest degree of protein binding and lipophilicity, with an average action duration of two hours (Irene et al., 2021).

Dexmedetomidine

First approved for intravenous use by the FDA in 1999, dexmedetomidine has become a popular medication in both the intensive care unit and anesthesia practice. When given intravenously, dexmedetomidine produces sedation and hypnosis that closely mimics natural sleep without the respiratory depressive effects seen with other commonly used sedatives (Weerink et al., 2017). However, several off-label uses have been described, including intranasal use in pediatric sedation and perineural use in regional and neuraxial anesthesia techniques (Weerink et al., 2017).

Dexmedetomidine is classified as a highly selective alpha-2 adrenergic receptor agonist with sedative, sympatholytic, anxiolytic, and analgesic-sparing properties (Weerink et al., 2017). With a half-life of two to three hours, the effects of dexmedetomidine are shorter than clonidine, another alpha-2 agonist commonly used in anesthesia practices. Yet, the selectivity for alpha-2 receptors arguably makes the effects of dexmedetomidine more profound than clonidine Weerink et al., 2017). Dexmedetomidine is greater than 90% protein bound and undergoes metabolism almost exclusively in the liver.

Mechanism of Action

When used intravenously, dexmedetomidine produces analgesia and mild sedation by directly stimulating alpha-2 receptors both centrally and peripherally. With an alpha-2 to alpha-1

selectivity ratio of 220:1, dexmedetomidine has an extremely high affinity for alpha-2 receptor mediated effects such as sedation and analgesia. Sedation is achieved through central stimulation of alpha-2 stimulation in the locus coeruleus, which decreases norepinephrine release from the presynaptic cleft via a negative feedback loop. Reduced levels of free norepinephrine result in a reduced level of cyclic AMP, resulting in sympathetic nervous system depression and decreased arousal (Weerink et al., 2017). In addition, alpha-2 stimulation inhibits the release of nociceptive pain transmitters, like substance P and glutamate, in neurons at the dorsal root level, inhibiting the nociceptive pathway preventing the transmission and amplification of pain signals traveling to the brain (Weerink et al., 2017).

The mechanism of action of perineural dexmedetomidine is not well understood but is thought to be multifactorial (Tripathi et al., 2016). When used peripherally, the stimulation of the alpha-2 receptor by dexmedetomidine decreases the release of norepinephrine at the synaptic cleft. This decrease in free norepinephrine produces an inhibitory effect on nerve action potential transmission independent of the alpha-2 receptor itself (Tripathi et al., 2016). As the levels of free norepinephrine decrease, the nerve's ability to reach threshold and produce an action potential is impaired, reducing the body's ability to transmit pain signals from the periphery to the brain (Weerink et al., 2017). Additionally, dexmedetomidine is described to produce analgesia via directly binding to alpha-2 receptors in the central nervous system and spinal cord. Hyperpolarization of sensory C, pain transmission alpha delta, and motor alpha-alpha fibers by perineural dexmedetomidine suppress the ability to transmit pain impulses between nerve cells (Weerink et al., 2017). Direct central stimulation of the locus coeruleus by dexmedetomidine is

also thought to play a role in the analgesic effects of perineural dexmedetomidine (Weerink et al., 2017).

Side Effects of Dexmedetomidine

Hemodynamic changes are commonly noted as side effects of intravenous dexmedetomidine administration (Weerink et al., 2017). Hypertension is often seen with rapid bolus administration. Bradycardia and hypotension are most described with continuous infusions. These side effects are direct results of both pre-and postsynaptic alpha-2 receptor stimulation, which causes vasoconstriction, vasodilatation, and reflex bradycardia (Weerink et al., 2017). Decreased salivation, myocardial contractility, insulin release, and GI motility, have also been described in the literature. The side effects noted with the perineural administration of dexmedetomidine will be discussed later.

Literature Review

Methods

A literature search was performed on the following major databases: CINHAL, PubMed, Cochrane Library, and Google Scholar. Randomized control trials (RCT), systemic reviews of RCTs, and experimental studies published within the last five years, 2016-2021, were preferentially selected. The search also revealed articles with lower levels of evidence, such as quasi-experimental and non-experimental studies, literature reviews, case studies, and review articles that were utilized to support the literature found. Initially, 25 articles were selected for review. However, five articles were excluded due to duplicate studies and low levels of evidence.

Keywords for the initial search included “dexmedetomidine and shoulder surgery” which provided various articles and multiple uses of dexmedetomidine used throughout the

perioperative period. Further search terms were more specific and related to “dexmedetomidine and brachial plexus block,” “perineural dexmedetomidine,” “interscalene + dexmedetomidine,” “opioid + dexmedetomidine + shoulder surgery” which yielded more specific results related to the research question.

From the literature review, several common themes were examined by various authors. When analyzing the effectiveness of dexmedetomidine as an adjunct to local anesthetics used for regional nerve blocks, the onset and duration of both sensory and motor blockade were heavily scrutinized. The dosing of dexmedetomidine and the associated adverse side effects were also reviewed extensively. Studies included in the literature review also examined the subjective quality of sensory and motor block, pain scores, and opioid consumption in the post-operative period, which will be explored in the following section.

Onset & Duration of Nerve Blocks with Dexmedetomidine

The onset of sensory and motor blocks has been well studied over the last five to 10 years. Dai et al. (2018) conducted a systematic review and meta-analysis of 12 different independent studies that examined the efficacy of dexmedetomidine used in conjunction with ropivacaine in brachial plexus blocks. From their review, Dai et al. (2018) elucidated that the addition of dexmedetomidine hastened the onset of both sensory and motor block. The study showed that sensory block onset was decreased by an average of 3.86 minutes (CI = 95% -5.45 to -2.27 minutes, I=85%, p <0.00001), and motor block onset time was decreased by 5.21 minutes (CI =95%, 7.48 to 2.94 minutes, I2 = 94%; p < .0001) (Dai et al., 2018).

The study also examined each nerve block approach (interscalene, supraclavicular, infraclavicular) that was utilized and determined from the data that despite the different

approaches, the addition of dexmedetomidine consistently decreased the time to onset (Dai et al., 2018).

As mentioned above, Dai et al. (2018) examined multiple aspects of the benefits of adding dexmedetomidine to brachial plexus blocks. Their study also examined the duration of both sensory and motor block duration. When added to 0.5% ropivacaine, dexmedetomidine facilitated an average of 228.7 minutes of additional sensory block (CI=95% 187.87–269.52 minutes, I2 = 93%; $p < .0001$) (Dai et al., 2018). Similarly, motor block duration was also extended by dexmedetomidine. Motor blockade was shown to have been prolonged by an average of 191.7 minutes (CI=95 152.48–230.91 minutes, I2 = 92%; $p < .0001$) (Dai et al., 2018).

Interestingly, the block approach with the most significant extension of motor blockade was noted to be the supraclavicular approach more than any other approach studied. Also, the data from Dai et al. (2018) showed that dosing of 50 micrograms (mcg) of dexmedetomidine or higher, prolonged motor blockade, but not as effectively as dosing less than 50 mcg (165.2 minutes vs. 337.2 minutes respectively) (Dai et al., 2018). The authors further say that this significant difference may be related to the amount of 0.5% ropivacaine utilized more than the dosing of dexmedetomidine as an adjunct (Dai et al., 2018).

Somsunder et al. (2019) conducted a study comparing the effects of intravenous dexmedetomidine and perineural dexmedetomidine used in combination with 0.5% levobupivacaine administered in a brachial plexus block. The study examined a difference in the onset and duration of both sensory and motor deficits. The study concluded that intravenous dexmedetomidine at 1 mcg/kg was administered 10 minutes before block placement and

perineural dexmedetomidine administered at 1 mcg/kg in the brachial plexus block produced similar results. The intravenous group produced sensory and motor blocks at 7.58 ± 1.6 min and 9.22 ± 2.6 min, respectively (Somsunder et al., 2019). The perineural group produced a mean duration of sensory and motor blocks onset of 7.06 ± 2.0 min and 10.10 ± 2.83 min, respectively (Somsunder et al., 2019). The marginal difference in recorded times to onset was deemed statistically insignificant by the authors, signifying that the two methods of administration were comparable in their effects, and one was not superior to the other (Somsunder et al., 2019).

Hussain et al. (2017) also examined the effects of dexmedetomidine on the onset of sensory block. Their meta-analysis reviewed 18 different randomized control trials with 1092 patients enrolled. Their analysis of the data also showed an average decrease in the time to sensory block of 3.19 minutes (Hussain et al., 2017). The time to motor block onset was also shorted by an average of 2.92 minutes (Hussain et al., 2017). The data further supports the idea that that as an adjunct, dexmedetomidine decreases the time to sensory and motor blockade. Hussain et al. (2017) also examined the overall duration of sensory and motor block with dexmedetomidine utilized as an additive to local anesthetics. Their study showed that adding dexmedetomidine to local anesthetic to be administered into a brachial plexus blocks significantly prolonged the duration of both sensory and motor block by as much as 261.41 minutes and 200.9 minutes, respectively (Hussain et al., 2017).

Ping et al. (2017) conducted a meta-analysis of 18 studies, with a total of 1015 patients, that examined the duration of sensory block. Total time was calculated as the time from administration of local anesthetic with complete sensory block to complete sensory recovery. The study revealed an estimated prolongation of sensory block by 282.65 minutes when

dexmedetomidine was used as an adjunct to long-acting local anesthetics and 60.16 minutes with intermediate-acting local anesthetics (Ping et al., 2017). The study also showed that the nerve block type showed some heterogenicity. The infraclavicular nerve block technique showed that the duration of sensory prolongation was predictable and reproducible with a heterogenicity of I2=0% (Ping et al., 2017). Axillary and supraclavicular approaches showed prolongation of sensory block, but with heterogenicity of I2=68.4% and I2=95.9%, respectively (Ping, 2017). The variation in results is considerable, yet further examination and meta-analysis of bias and effects by Ping et al. (2017) determined the heterogenicity did not affect the quality and predictability of the results. From the data, Ping et al. (2017) concluded that despite the block technique, dosing, and local anesthetic of choice, dexmedetomidine prolonged the analgesic effects of peripheral nerve blocks by as much as seven hours, producing a total time of analgesia as long as 24 hours, compared to the estimated eight to 14 hours of when plain local anesthetic is administered (Ping et al., 2017).

Similarly, Agarwal et al. (2014) studied the effects of dexmedetomidine as an adjunct to local anesthetics in brachial plexus blocks. Their study produced similar results to the studies mentioned above. The control group of 25 patients received plain 0.325% bupivacaine in their study. The experimental group of 25 patients received 0.325% bupivacaine and a standard dose of 100 mcg of dexmedetomidine. The onset of both sensory and motor block was significantly shorter in the experimental group when compared to the control group (Agarwal et al., 2014). The time to onset of sensory block in the experimental group was nearly eight minutes shorter (13.20±1.848, t= -7.911, $p < 0.001$) than the plain local anesthetic control group (19.04±3.195) (Agarwal et al., 2014). Similarly, the onset to motor block in the experimental group was shorted

by almost 10 minutes (16.3±1.7, t= -9.6, $p < 0.001$) when compared to the control group time to motor block onset (22.7±2.8) (Agarwal et al., 2014).

Duration of action was also assessed in the study by Agarwal et al. (2014). The data collected from the 50 patient, randomized control trial showed sensory and motor blockade lasting an average of 700 minutes in the experimental group (Agarwal et al., 2014). The control group duration was noted as an average of 200 minutes (Agarwal et al., 2014). Duration of analgesia was also examined and showed similar results. Duration of analgesia in the experimental group lasted almost 500 minutes longer, clocking at 776.4 minutes compared to the plain local anesthetic group averaging 241.4 minutes (Agarwal et al., 2014). Again, that data supports the idea that dexmedetomidine helps prolong regional blocks' analgesic effects. However, limitations of the study were the small sample size and patient population without significant comorbidities, warranting additional research in a wider variety of patients to help further validate the results of the study.

A study of a similar design to Agarwal et al. (2014) was conducted by Manjunatha et al. (2020). In the Manjunatha et al. (2020) trial, 70 patients were enrolled. Each patient received an ultrasound-guided supraclavicular block for an upper extremity surgery. The experimental group received 20 ml of 0.25% bupivacaine with 1 mcg/kg of dexmedetomidine. The control group received 20 ml of 0.25% bupivacaine only. Similar results were yielded. Onset was noted to be quicker with the addition of dexmedetomidine; however, the study does not delineate specific measurements (Manjunatha et al., 2020).. In addition, the duration of both sensory and motor block was substantially prolonged almost twice as long in the experimental group (863.8 ± 106.8

min and 758. 5 ± 121.6 min) compared to the control group (335.6 ± 58.6 min and 308.4 ± 71.8 min) (Manjunatha et al., 2020).

Dosing of Dexmedetomidine in Nerve Blocks

Several studies examined the dosage of dexmedetomidine as an adjunct to regional anesthetic techniques. When examining non-weight-based dosing, several studies investigated the effects of dexmedetomidine in doses less than or greater than 50 mcg per regional block. Dai et al. (2018) completed a systematic review of 12 different studies, with a patient population of 617, that analyzed the effects of dexmedetomidine as an adjunct to upper extremity regional anesthetic techniques. From the pooled data, Dai et al. (2018) elicited dosing of dexmedetomidine greater than 50 mcg added to ropivacaine produced a longer duration of both sensory and motor block when compared to doses of 50 mcg or less. The study also stated that the duration of analgesia was prolonged with a mean difference of an additional 303.04 minutes with a confidence interval of 95% (228.84–377.24 minutes) and a degree of heterogenicity of 85% (Dai et al., 2018).

Like Dai et al. (2018), Hussain et al. (2017) investigated the efficacy of dexmedetomidine as an adjunct of regional anesthesia. They examined dosing in increments of less than or greater than 50 mcg compared to a control group with plain local anesthetics. The study shows that doses greater than 50 mcg added to various local anesthetics prolonged sensory and motor block and decreased the onset of both sensory and motor blocks, leading to an overall increase in the duration of regional block compared to plain local anesthetics (Hussain et al., 2017). The study also showed that hemodynamic effects were more prevalent in the group with dosing greater than

50 mcg. Still, the hemodynamic changes were not significant enough that additional or more invasive hemodynamic monitoring was necessary (Hussain et al., 2017).

Two independent studies by Vorobeichik et al. (2017) and Rao & Rajan (2021) investigated the use of dexmedetomidine in regional anesthetic techniques and yielded similar results. Vorobeichik et al. (2017) conducted a systematic review and meta-analysis of 32 different trials examining the effects of perineural dexmedetomidine. Their study supports the idea that dexmedetomidine added to regional blocks increased duration of action and decreased time to onset of both motor and sensory block. The study concluded that a dose between 50 and 60 mcg maximized the benefits of dexmedetomidine as an additive while mitigating the adverse hemodynamic effects, like bradycardia and hypotension, reported with greater dosing (Vorobeichik et al., 2017).

Rao & Rajan (2021) also examined the effects of dexmedetomidine in peripheral nerve blocks. They analyzed data from 34 studies with a pool of 2007 patients. Their research and analysis supported the dosing of 50 to 60 mcg of dexmedetomidine used as an adjunct in peripheral nerve blocks. Their examination of the available data also showed that 50 to 60 mcg added to peripheral nerve blocks maximized the sensory blockade without hemodynamic instability reported with higher dosing (Rao & Rajan, 2021).

Jung et al. (2017) examined the effects of various weight-based dosing of dexmedetomidine as an additive to interscalene blocks for patients undergoing arthroscopic shoulder surgery. Ninety-seven patients were enrolled in a trial and then divided into four test groups. The control group was administered 20 ml of 0.5% ropivacaine with 2 ml of normal saline. The three trial groups were administered 20 ml of 0.5% ropivacaine with weight-based

dosing of 1 mcg/kg, 1.5 mcg/kg, and 2 mcg/kg of dexmedetomidine, respectively. Dosing calculations utilized ideal body weight via the Broca calculation of IBW= Height (cm) – x, where x = 100 for men and 105 for women. In this study, brachial plexus blocks were utilized as postoperative pain control rather than the primary anesthetic technique as each patient underwent general anesthesia after regional block placement.

The study by Jung et al. (2017) revealed incremental increases in dosing produced hemodynamic changes that were more significant in the trial dexmedetomidine groups versus the control groups. From the study, there was no significant difference in the block duration in groups one and two, 1 mcg/kg and 1.5 mcg/kg. Group three, which received 2 mcg/kg of dexmedetomidine, showed more significant, transient episodes of hypotension; however, the duration and pain control quality of the block lasted as much as three hours longer than group two (1.5 mcg/kg) and the overall duration of the block lasted up to 20 hours (Jung et al., 2017). The authors identified several limitations to this study. They mention that the American Society of Anesthesiology (ASA) physical status classification and total body weight were higher in the trial group than in the control group. With higher ASA physical status classifications in the control group, patients typically have significant comorbidities, like obesity, that may affect the metabolism of medications used in the trial. To help negate that observation, ideal body weight was used to calculate all perineural dexmedetomidine administrations (Jung et al., 2017).

A study by Thakur et al. (2017) examined the effects of dexmedetomidine at doses of 0.5 and 1 mcg/kg added to 2% lidocaine for patients receiving axillary nerve blocks. Their study enrolled 104 patients divided into three equal-sized groups: one control and two trial groups. When looking at the data gathered from the study, the addition of both 0.5 and 1 mcg/kg of

dexmedetomidine used in conjunction with 2% lidocaine prolonged the duration of analgesia by as much as 395.9 minutes (Thakur et al., 2017). When comparing the control group, that received plain 2% lidocaine to the two trial groups that received 0.5 and 1 mcg/kg of dexmedetomidine, the study showed that the addition of dexmedetomidine prolonged the time until the request for the first dose of supplemental analgesics in both experimental groups. In the 0.5 mcg/kg group, 30% required additional analgesia in the first six hours after their procedure (Thakur et al., 2017). Eighty percent of patients who received 1 mcg/kg of dexmedetomidine as an additive to their axillary block required analgesics in the six-hour post-operative period. Despite the need for rescue analgesics, both groups required less than the plain 2% lidocaine group, where 100% of patients in that group analgesics needed within the first six hours post operatively (Thakur et al., 2017). A limitation of this study was the lack of ultrasound. The authors noted that ultrasound may have helped facilitate a better block placement and a reduction in the total volume of 2% lidocaine used to achieve adequate analgesia (Thakur et al., 2017).

Quality of Analgesia

In a study by Tripathi et al. (2016), perineural dexmedetomidine was compared to perineural clonidine in ultrasound-guided brachial plexus blocks. In this study, 60 patients were enrolled and divided randomly into two, 30 patient groups. The control group received 1 mcg/kg of clonidine, and the experimental group received 1 mcg/kg of dexmedetomidine. Both groups received 39 ml of 0.25% bupivacaine as a local anesthetic in the peripheral block. Tripathi et al. (2016) defined the quality of analgesia on a one to four scale with the following score definitions: a score of one signified unsuccessful block placement, a score of two was correlated with moderate pain complaints from the patient that required supplemental analgesia, a score of

three was correlated with minor complaints of discomfort that required supplemental analgesia, and a score of four was associated with no complaints and 'excellent analgesia' (Tripathi et al., 2016). Data from the study suggests that the addition of dexmedetomidine to 0.25% bupivacaine produced more satisfactory and higher quality analgesia, with 80%, 24 of the 30 participants, scoring a four on the quality scale (Tripathi et al., 2016). A total of six members of the dexmedetomidine group scored a three on the quality scale. In comparison, members of the clonidine group did not score as highly, with 60%, 18 of 30 participants, scoring a three on the quality scale. The remaining 40%, 12 of 30 participants, did score a four. Although the study's sample size was small, the data collected supports dexmedetomidine as the superior additive choice to help improve the overall quality of peripheral nerve block anesthesia (Tripathi et al., 2016).

Rao & Rajan (2021) examined the efficacy of dexmedetomidine as an additive to peripheral and neuraxial nerve blocks. A meta-analysis of 18 independent studies supported that the addition of dexmedetomidine to peripheral nerve blocks improved the overall quality and analgesia of peripheral nerve blocks compared to plain local anesthetics (Rao & Rajan, 2021). However, criteria to define the quality of peripheral nerve blockade were not defined by the study.

Pain Scores & Rescue Analgesic Use

Hussain et al. (2017) examined the total analgesic consumption during the 24-hour period following a patient's procedure. Their meta-analysis uncovered that the need for rescue or supplemental analgesics in the immediate postoperative period was reduced in the dexmedetomidine trial group compared to plain local anesthetics (Hussain et al., 2017). Hussain

et al. (2017) demonstrated data extracted from several studies included in their meta-analysis, showing the difference in analgesic consumption over the first 24-hour postoperative period in Table 1 below.

Table 1.

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

Study	Sample Size Used for Data Analysis	Analgesic Used	Analgesic Consumption With Dexmedetomidine	Analgesic Consumption With Control	*P*
Ammar and Mahmoud,[16] 2012	60	Morphine	4.9 (0–8.0) mg*	13.6 (4.0–16.0) mg*	$P = 0.005$
Bengisun et al,[17] 2014	50	Lornoxicam	8 (11.8) mg†	20.2 (17.5) mg†	$P = 0.01$
Das et al,[19] 2014	80	Diclofenac	11 of 40‡	25 of 40‡	$P < 0.01$
Fritsch et al,[21] 2014	61	Piritramide	19.4 (15.7) mg†	23.3 (19.8) mg†	$P = 0.38$
Abdallah et al,[14] 2015	65	Morphine	49.9 (40.1–59.7)§	58.9 (50.8–67.1)§	$P = 0.326$
Bharti et al,[30] 2015	54	Diclofenac	2 doses (0–3 doses)‖	2 doses (0–3 doses)‖	$P < 0.0001$
Kathuria et al,[24] 2015	40	Diclofenac	60.00 (39.25) mg‡	120.00 (56.55) mg‡	$P = 0.001$
Kaur et al,[25] 2015	90	Diclofenac	5 of 45†	12 of 45†	$P = 0.059$

*Median 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.

Note. Adapted from "Optimal Dose of Perineural Dexmedetomidine for Interscalene Brachial Plexus Block to Control Postoperative Pain in Patients Undergoing Arthroscopic Shoulder Surgery. A Prospective, Double-Blind, Randomized Controlled Study" by Hussain et al., 2017, *Regional anesthesia and pain medicine*, *42*(2), 184–196.

As shown in Table 1 above, several studies examined by Hussain et al. (2017) supported the idea that using dexmedetomidine as an adjunct to peripheral nerve blocks reduced the overall consumption of analgesics 24 hours after surgery. However, the studies examined by Hussain et al. (2017) utilized several different postoperative analgesics and pain rating scales, making it challenging to conclude dexmedetomidine's effectiveness at decreasing pain scores and the need for rescue analgesics in the postoperative period. Despite being unable to pool the data they collected, Hussain et al. (2017) mentioned in their analysis that five of their 12 selected studies show a decreased requirement for postoperative analgesics in the 24 hours post-procedure in the

trial groups that received dexmedetomidine as an adjunct to local anesthetic when compared to the control of plain local anesthetics (Hussain et al., 2017). Three of the 12 studies showed no difference in pain scores or need for analgesics between trial and control groups (Hussain et al., 2017).

Jung et al. (2017) also assessed pain scores and the need for rescue analgesia in the postoperative period. From their study of 90 patients, the data collected showed that pain scores on the numeric pain scale were lower in the trial groups treated with perineural dexmedetomidine compared to the placebo control group treated with plain local anesthetics at 12 and 18 hours after surgery. However, there was no reported difference in pain scores or need for analgesics 24 and 36 hours postoperatively (Jung et al., 2017). They concluded that although perineural dexmedetomidine extended the duration of action and sensory blockade, numeric pain scores in both the trial and control group were similar at the 24-hour mark and that multimodal analgesia should be utilized before the pain control efficacy of the nerve block wears off (Jung et al., 2017).

Vorobeichik et al. (2017) conducted a systematic review of 34 separate studies, with a patient population of 2007 patients, investigating the efficacy of dexmedetomidine as an adjunct to brachial plexus blocks. Of those 34 examined trials, 26 trials examined local anesthetic/dexmedetomidine peripheral nerve block analgesic outcomes. Cumulative 24-hour analgesic consumption was reported directly in eight of the 34 trials. When combined with local anesthetics, dexmedetomidine decreased the oral morphine equivalent consumption by an average of 10.2 milligrams (mg) (95% CI [-15.3, -5.2], ($p < 0.0001$, I2 1⁄4 83%) (Vorobeichik et al., 2017).

Pain rating scores were also scrutinized by Vorobeichik et al. (2017). Seven of the 34 trials looked at pain scores 24 hours after surgery. The limited number of studies reported a slight decrease, less than one point on a zero to 10 pain rating scale (Vorobeichik et al., 2017). Overall, there were several limitations to the study by Vorobeichik et al. (2017). The definition of duration of analgesia varied, including time to first analgesic request, time to pain score greater than three or four on a scale of 0-10, or time to patient reporting surgical site pain. The inconsistency in measurement scales was a limitation of the study as the frank variation from study to study made it difficult to draw concrete conclusions (Vorobeichik et al., 2017).

El-Boghdadly et al. (2017) also included an examination of the postoperative analgesic requirement. Their study examined the difference between clonidine and dexmedetomidine used perineurally in brachial plexus blocks. Their meta-analysis of 14 different studies examined a patient population of 868 patients. Like the studies mentioned above, El-Boghdadly et al. (2017) found inconsistencies in how the individual studies reviewed report pain scores and analgesic consumption, proving a limitation of the overall study. However, the duration of analgesia was assessed in 12 of the 14 studies included in their meta-analysis. El-Boghdadly et al. (2017) concluded that compared to clonidine, dexmedetomidine prolonged total analgesic effect by a factor of 1.2 providing a longer duration of complete analgesia ($p < .00001$). The authors inferred that the prolonged analgesic effects might reduce the overall need for rescue and supplemental analgesics in the postoperative period (El-Boghdadly et al., 2017).

Dai et al. (2018) also examined pain scores in the postoperative period. Unfortunately, the data pool utilized multiple different pain rating scales. The authors felt that not enough data was collected using one pain scale to conduct an appropriate comparison, proving to be a

limitation of the study. However, the overall trend from the data examined does reflect the idea dexmedetomidine reduced pain scores and the consumption of postoperative opioids (Dai et al., 2018).

Side Effects of Dexmedetomidine in Nerve Blocks

As an alpha two adrenoceptor agonist, dexmedetomidine's side effect profile has been well described. Intravenous dexmedetomidine has the potential to cause transient hypertension with rapid bolus administration, bradycardia, and hypotension (Weerink et al., 2017). Asku & Bicer (2017) examined the off-label use of dexmedetomidine as an additive to brachial plexus blocks as a means of reducing the total volume of local anesthetic needed to achieve surgical anesthesia. From their study of 50 patients, several different side effects were recorded. Between the control and the trial group, changes in heart rate and blood pressure were noted in the trial group only. Heart rates were recorded in five, 10, and 15-minute intervals for the first 120 minutes after block placement. In the trial group, statistically significant decreases in heart rate from basal heart rate were noted for the first 90 minutes after block placement ($p < 0.05$) (Asku & Bicer, 2017). In the trial group, heart rates were reported to decrease from 77.5 ± 14.5 to a range of 66.5 ± 8.9 at the 60-minute mark. Heart rates averaged in the mid 60's for the first 90 minutes after block placement (Asku & Bicer, 2017). No significant changes in heart rate were observed in the control group (Asku & Bicer, 2017).

Mean arterial blood pressure (MAP) values were recorded at similar intervals, however statistically significant decreases in MAP were not as prevalent ($p <0.1$). The basal MAP reading for both the control and the experimental group averaged 100 ± 16.0 (Asku & Bicer, 2017). With the addition of dexmedetomidine, MAP readings dipped slightly to 92.1 ± 14.8, at the 15-, 60-,

and 90-minute intervals after block placement (Asku & Bicer, 2017). At no point were these hemodynamic changes noted to be outside of normal hemodynamic parameters but were decreased from the basal readings before placement of the brachial plexus block (Asku & Bicer, 2017).

Another study that examined the hemodynamic effects of dexmedetomidine as an additive to regional anesthetics was by Nazir & Jain (2016). Their study consisted of 70 patients, all of whom were ASA I or II, undergoing upper extremity surgeries. All 70 patients received an ultrasound-guided supraclavicular block with 38 ml of 0.25% bupivacaine. The control group received plain local anesthetic and the experimental group 1 mcg/kg of dexmedetomidine in addition to the 0.25% bupivacaine. Basal heart rates were recorded before block placement in each member of both groups. Heart rates were measured at various intervals for the first 150 minutes after block placement. In the experimental group, heart rates were noted to be decreased from baseline as many as 15 to 20 beats per minute at the 15 through 90-minute measurements (Nazir & Jain, 2016). During the study, no patient became dangerously bradycardic necessitating emergent intervention as noted in other studies, such as the study by Ping et al. (2017). At the 120-minute measurements, heart rates in both the experimental group returned to near basal rates and were similar to those documented in the control group. No significant changes in heart rate were noted in the control group (Nazir & Jain, 2016).

Discussion

As an adjunct to regional anesthesia for shoulder surgery, the literature supports dexmedetomidine as a method of extending both the sensory and motor blockade achieved by local anesthetics used in regional anesthesia. Dai et al. (2018), Ping et al. (2017), and Hussain et

al. (2017) all concluded that the inclusion of dexmedetomidine in regional blocks both hastened the onset of motor and sensory block by an average of three minutes, and it extended the duration of both blocks by an average of 220 minutes. Agarwal et al. (2014) conducted a similar experiment which concluded that using dexmedetomidine and 0.325% levobupivacaine extended the duration of regional blocks by an average of 500 minutes, for a total duration of 700 minutes. Each study yielded evidence supporting dexmedetomidine's efficacy for extending the period of sensory and motor blocks and providing extended pain relief for patients.

The dose of dexmedetomidine did influence the duration of pain relief gained. Dai et al. (2018) and Hussain et al. (2017) examined dosing less than and greater than 50 mcg of dexmedetomidine in a regional block. The study showed that dosing above 50 mcg had a better efficacy for extending the durational analgesic effect. A meta-analysis by Vorobeichik et al. (2017) also supported dosing above 50 mcg. Vorobeichik et al. (2017) concluded that the optimal dose to achieve the maximal prolongation of pain relief without adverse side effects is 50 to 60 mcg. Weight based dosing was also examined. Jung et al. (2017) examined weight-based dosing in increments of 1.0, 1.5, and 2.0 mcg/kg added to regional blocks. The study concluded that the optimal dose to achieve the maximal benefits of dexmedetomidine was 1.5 mcg/kg, which produced pain relief for an additional three hours without negative side effects such as hypotension and bradycardia (Jung et al., 2017).

Several studies examined the efficacy of perineural dexmedetomidine as an opioid sparing technique. For example, Hussain et al. (2017) examined the total consumption of analgesics in the 24-hour post-operative period in patients who received dexmedetomidine as an adjunct to their regional nerve blocks. Their meta-analysis concluded that the experimental

groups that received adjunct dexmedetomidine consistently consumed a lower amount of both opioid and non-opioid rescue analgesics immediately after the procedure and in the first 24 hours post procedure. Vorobeichik et al. (2017) also supported dexmedetomidine as an opioid sparing technique. They determined that in the 24 hour post-operative period that perineural dexmedetomidine decreased the oral morphine equivalent consumption by an average of 10.2 mg (Vorobeichik et al., 2017).

Limitations & Literature Gaps

When comparing the studies above, several limitations are noted: the first is the small sample sizes. Studies by Manjunatha et al. (2020), Agarwal et al. (2014), and Somsounder et al. (2019) all enrolled small cohorts with populations of less than 100 participants, making the results difficult to apply to the public. Other limitations in the data are the variation in technique, local anesthetics used, and dosing of dexmedetomidine utilized as an adjunct. These noted variations can produce substantial differences in the data collected as there was no standardization in study methods across each of the studies included in the literature review.

Many studies focus heavily on the onset and duration of the peripheral nerve block more than the prolongation of pain control. Several studies touched upon 24-hour post-operative pain scale ratings and the need for rescue narcotics or analgesics a day out from surgery. Yet, there was limited data collected about hours zero – 24. The lack evidence makes drawing conclusions about the efficacy of pain control during the first 24 hours difficult.

Another variable that created a gap in the literature was the local anesthetic used in brachial plexus blocks. Each study described a different local anesthetic of choice, and sometimes multiple local anesthetics were examined within a single meta-analysis. Although the

drug class is the same, the effects of each individual drug may play an influential role in the effects of adjunct perineural dexmedetomidine.

With less than 100 participants, multiple small studies examined dexmedetomidine as an adjunct to local anesthetics. These small sample size randomized control trials, each with a different local anesthetic studied, make the generalizability of the results difficult to apply to all patient populations. Also, patients enrolled in these trials mainly were ASA class I or II patients without significant comorbidities. This also makes applying the results to the public difficult as many patients presenting for surgery often have significant comorbidities. More research is warranted with larger patient populations and patients with varying ASA classifications to better understand the use of perineural dexmedetomidine as an opioid/narcotic sparing technique.

Recommendations

The literature supports the use of dexmedetomidine to prolong the duration of sensory and motor blockade in regional nerve blocks. The data supports the idea that as sensory block is prolonged, the need for rescue analgesics and opioids in the post-operative period is consistently reduced when dexmedetomidine is utilized as an adjunct with plain local anesthetics. When utilized, the most efficacious dose of perineural dexmedetomidine ranges from 50 to 60 mcg, with the effects being achieved using both weight-based and non-weight-based dosing calculations (Jung et al., 2017; Vorobeichik et al., 2017; Dai et al., 2018). When examining current practice, the use of perineural dexmedetomidine does appear to be a viable and effective adjunct to plain local anesthetics and can pragmatically be utilized as a means of sparing opioids in the post-operative period.

Conclusion

Regardless of the chosen technical approach, brachial plexus peripheral nerve blocks are widely accepted forms of surgical anesthesia and post pain control measures for patients undergoing upper extremity procedures (Urits et al., 2020; Hewson et al., 2019). Plain, long-acting local anesthetics such as 0.5% ropivacaine and 0.5% bupivacaine are often the chosen agents to provide anesthesia and analgesia for as long as 14 hours after an upper extremity procedure (Hewson et al., 2019; Ding et al., 2017). As discussed above, dexmedetomidine used as an adjunct to plain local anesthetics can prolong the analgesic effect of regional nerve blocks utilized for shoulder surgery by as long as 24 hours. Studies have concluded that including dexmedetomidine as an adjunct to regional anesthesia has decreased the need for opioids in the post-operative period by as much as 64% (Trop & McClain, 2020).

By increasing the duration of motor and sensory blockade, perineural dexmedetomidine extends the pain control benefits on regional blocks utilized for shoulder surgery. The longer the nerve block lasts, the lesser the need for opioids to help with pain control in the post-operative period. As the consumption of opioids decreases, the potential risk of suffering adverse reactions to such medications is also lessened. The literature does support the use of dexmedetomidine as an adjunct to regional anesthesia and the potential opioid-sparing benefits. However, more organized research is warranted to support further dexmedetomidine's effect as an opioid-sparing technique.

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