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Abstract

Regional and neuraxial anesthetic techniques are ever-expanding, and an understanding of the tools, medications, and adjuncts associated with these techniques is prudent for anesthesia providers. One goal of these techniques is to extend pain management beyond the initial surgical phase by using long-acting local anesthetics with or without adjunct medications. The purpose of this review is to detail the clinical utility, benefits, and risks of dexmedetomidine as an adjunct to regional and neuraxial anesthetic techniques. This review includes an analysis of literature of over 20 randomized controlled trials comparing the use of dexmedetomidine to other adjuncts in common regional and neuraxial techniques in adult patients. This expanding body of research suggests dexmedetomidine may exert desirable effects as an adjunct to regional and neuraxial anesthesia.

Keywords: Dexmedetomidine, Intravenous Regional Anesthesia, Peripheral Nerve Block, Regional Anesthesia, Neuraxial Anesthesia

Dexmedetomidine as an Adjunct to Regional and Neuraxial Anesthesia

Regional and neuraxial anesthetic techniques are ever-growing and have become a mainstay in the field of modern anesthesia. These techniques are necessary for the provision of multimodal anesthesia and are often an element of enhanced recovery after surgery (ERAS) protocols (Kukreja, 2019). With this expanding use and popularity, anesthesia providers must maintain a solid foundation of knowledge regarding the methods, medications, and physical anatomy related to regional anesthesia (Butterworth IV et al., 2013). Relative to this understanding, in addition to traditionally used local anesthetics, is the use of adjunct medications to accentuate certain regional anesthesia characteristics.

Adjunct medications may be given to improve the analgesic effect of local anesthetics or to prolong the duration of action of neuronal blockade. With an abundance of adjunct medications from which to choose, anesthesia providers are confronted with choosing the best or most efficacious adjunct possible. A plethora of medications have shown evidence of improving block qualities, though there is no clear leader with ideal characteristics (Kukreja et al., 2019). An ideal additive to local anesthetics quickens the onset of sensory blockade, prolongs sensory blockade without prolonging motor blockade, has little to no adverse effects, and is compatible with local anesthetics (Kukreja et al., 2019). Common adjuncts are often of differing pharmacologic classes and thus have different mechanisms of action and safety profiles (Kukreja et al., 2019).

Dexmedetomidine, an alpha-2 (α-2) adrenoreceptor agonist, contains sedative, anxiolytic, sympatholytic, and analgesic properties. Typically, dexmedetomidine is used for sedation in the intensive care unit (ICU) or for procedural sedation. Dexmedetomidine is not currently Food and Drug Administration (FDA) approved for use as an adjunct to regional anesthesia, however,

there is a growing body of literature regarding its use in these techniques (Marhofer & Brummett, 2016; Weerink et al., 2017). The purpose of this review is to outline the current understanding of dexmedetomidine as an adjunct to regional anesthesia and neuraxial anesthesia. Included in this analysis is a literature review of more than 20 randomized controlled trials that studied the effects of dexmedetomidine as an adjunct to local anesthetics compared to other common adjuncts. The trials reviewed pertain to intravenous regional anesthesia (IVRA), peripheral nerve blockade (PNB), as well as epidural and spinal anesthetic techniques. Limitations of current literature and recommendations for future research are discussed.

Literature Review

Intravenous Regional Anesthesia

Sensory Blockade

When comparing 0.5% lidocaine alone to 0.5% lidocaine with 0.5 mcg/kg dexmedetomidine for IVRA in American Society of Anesthesiologists (ASA) physical class I and II patients undergoing hand or forearm surgeries, Subramanya et al. (2017) noted that the onset of sensory blockade was shortened with statistical significance ($p < 0.001$) when dexmedetomidine was utilized. Similarly, in a comparison between 0.5 mcg/kg dexmedetomidine, 8 mg dexamethasone, and 8 mg lornoxicam (non-steroidal anti-inflammatory drug, NSAID) added to 0.5% lidocaine versus 0.5% lidocaine control in ASA I, II, and III patients undergoing forearm or hand surgery, those who received dexmedetomidine had a statistically significant reduction in the time to onset of sensory blockade ($p < 0.001$). The group that received lornoxicam additive also showed a statistically significant decrease in the time to onset of sensory blockade when compared to the dexamethasone and control groups ($p < 0.001$) (Hamawy & Bestarous, 2019). Modir et al. (2017) also studied IVRA block characteristics by

comparing 1 mcg/kg dexmedetomidine and 30 mg ketorolac added to 0.5% lidocaine in ASA I and II patients admitted for forearm or hand surgery. Those patients who received ketorolac had a reduction in the time to onset of analgesia when compared to the dexmedetomidine group, albeit non-significant. However, both the ketorolac group and the dexmedetomidine group showed a statistically significant reduction in the time to onset of analgesia ($p < 0.001$) (Modir et al., 2017). Modir et al. (2017) did not delineate what specifically constituted the onset of analgesia, only that this was a recorded data point. Lornoxicam is not currently available in the United States, however, comparing it to other additives is useful for reference.

The clinical relevance of the onset of sensory blockade with IVRA is far surpassed by the clinical relevance of the duration of sensory blockade. Subramanya et al. (2017) showed that patients who received the additive dexmedetomidine with 0.5% lidocaine for IVRA had a mean duration of postoperative analgesia of 30.16 minutes, while those who received 0.5% lidocaine alone had a mean postoperative analgesia duration of 7.3 minutes ($p < 0.001$). Quality of sensory blockade was also reported in this study. Patients who received dexmedetomidine for IVRA showed a higher incidence of "excellent" quality of sensory blockade, while those who received lidocaine alone showed a higher incidence of "moderate" quality ($p < 0.001$) (Subramanya et al., 2017). Comparing fentanyl supplementation intraoperatively, patients in the lidocaine control group had a mean dose of 21.66 mcg [Standard Deviation (SD) 12.68 mcg] fentanyl, whereas those in the dexmedetomidine group had a mean dose of 1.66 mcg (SD 6.34 mcg) fentanyl ($p < 0.001$) (Subramanya et al., 2017).

Modir et al. (2017) reported that adding dexmedetomidine or ketorolac to 0.5% lidocaine significantly lengthened the average time to initial onset of pain after tourniquet deflation when compared to lidocaine control. In this study, a significant increase of average time to initial onset

of pain after tourniquet deflation was also noted of ketorolac in comparison to dexmedetomidine, with mean durations until initial pain onset of 52.53 and 55.70 minutes, respectively ($p < 0.0001$) (Modir et al., 2017). This data is similar to that of Hamawy & Bestarous (2019), who showed the additives dexmedetomidine or lornoxicam in 0.5% lidocaine significantly increased the duration of sensory blockade, significantly prolonged the first postoperative request for analgesia, and significantly decreased the amount of postoperative analgesic utilization when compared to additive dexamethasone or lidocaine control ($p < 0.001$).

Discomfort at the level of the tourniquet is a time-limiting factor of IVRA (Barash et al., 2017). When dexmedetomidine was added to lidocaine for IVRA, Subramanya et al., (2017) found that visual analog scale (VAS) scores for tourniquet pain intraoperatively and pain for the first 6-hours postoperatively were significantly lower compared to the lidocaine control group ($p < 0.001$). In a comparison of ketorolac, dexmedetomidine, or lidocaine control, VAS scores intraoperatively at 15 and 30 minutes after block placement were found to be significantly lower in the ketorolac and dexmedetomidine groups compared to control (Modir et al., 2017). However, at 45 minutes after block placement, VAS scores were significantly lower in the ketorolac, dexmedetomidine, and control groups, respectively (Modir et al., 2017). Alternatively, Hamawy & Bestarous (2019) reported no significant difference in the intraoperative incidence of tourniquet pain requiring supplemental fentanyl between dexamethasone, dexmedetomidine, lornoxicam, and lidocaine control groups.

Motor Blockade

Onset and duration of motor blockade are also relevant block characteristics with IVRA. During a surgical procedure, motor blockade can facilitate a smoother procedure, but a prolonged motor blockade postoperatively may impact early mobilization or raise a concern of

potential nerve injury. Studies have failed to outline consistent differences among additives to IVRA, including dexmedetomidine. For instance, when using 0.5 mcg/kg dexmedetomidine additive to 0.5% lidocaine, researchers reported a significantly faster time to onset of motor blockade compared to lidocaine control ($p < 0.001$) (Subramanya et al., 2017). However, in a comparison of additive 0.5 mcg/kg dexmedetomidine, 8 mg dexamethasone, 8 mg lornoxicam, and 0.5% lidocaine control, the authors showed no statistical difference in time to onset or duration of motor blockade between groups (Hamawy & Bestarous, 2019).

Adverse Effects

Intravenous Regional Anesthesia is a generally safe, technically easy, and usually rapid method to provide anesthesia for surgical procedures to the extremity (Nagelhout & Elisha, 2018). When using local anesthetic alone, the biggest risk is Local Anesthetic Systemic Toxicity (LAST), which can stem from tourniquet failure leading to systemic administration of a large amount of local anesthetic (Nagelhout & Elisha, 2018). In addition to LAST, adverse outcomes can arise from utilization of additives to local anesthetics.

Hamawy & Bestarous (2019) reported with statistical significance that at three minutes after tourniquet release, both heart rate and mean arterial blood pressure (MAP) were lower in patients who received dexmedetomidine additive versus lornoxicam ($p < 0.001$), dexamethasone ($p < 0.01$), or control ($p < 0.01$). For those who received dexmedetomidine, data showed an average heart rate of 85.1 beats per minute (bpm) (SD 5.6 bpm) and an average MAP of 63.4mmHg (SD 5.8 mmHg) and authors noted that no patients required treatment for bradycardia or hypotension. Heart rate and MAP differences at baseline, immediately after tourniquet inflation, and immediately before surgical incision were not significant (Hamawy & Bestarous, 2019). Modir et al. (2017) reported no significant differences in heart rate, systolic blood

pressure (SBP), or diastolic blood pressure (DBP) after tourniquet deflation between dexmedetomidine, ketorolac, and control groups. The authors failed to report the time interval from tourniquet deflation to measurement of these hemodynamic parameters (Modir et al., 2017). While no statistical comparison of heart rate or MAP data was shown, Subramanya et al. (2017) reported that two patients in the dexmedetomidine group required atropine for bradycardia upon deflation of the tourniquet. Additionally, the dexmedetomidine group was noted to have significantly higher sedation scores during the first two hours after tourniquet deflation ($p < 0.001$) (Subramanya et al., 2017). Modir et al. (2017) measured respiratory status as a function of arterial oxygen saturation and found no significant differences between groups. The incidence of nausea, vomiting, shivering, and pruritus was not discussed in any of the aforementioned articles.

Peripheral Regional Anesthesia

Sensory Blockade

Time to onset of sensory block with PNB is not often clinically relevant, as regional anesthesia and general anesthesia are commonly used in conjunction to provide balanced anesthesia (Nagelhout & Elisha, 2018). However, in a double-blind randomized control trial (RCT) of ASA I and II patients undergoing elective upper extremity surgery with infraclavicular brachial plexus blockade (IBPB) using 0.5% ropivacaine with either 150 mg magnesium or 100 mcg dexmedetomidine additive, the dexmedetomidine group had a significantly shorter time to onset of sensory blockade ($p < 0.000$) (Abu Elyazed & Mogahed, 2018). In a double-blind RCT of ASA I and II patients undergoing elective upper limb orthopedic surgeries with supraclavicular brachial plexus blockade (SBPB) using 0.5% bupivacaine with either 50 mcg

fentanyl or 75 mcg dexmedetomidine, those in the dexmedetomidine group had a faster time to onset of sensory blockade ($p < 0.001$) (Lotfy et al., 2020).

Yet, in an RCT comparing α-2 agonists clonidine (1 mcg/kg) and dexmedetomidine (1 mcg/kg) in 0.25% bupivacaine for SBPB in patients undergoing orthopedic surgery of the upper limb, authors found no significant difference in the time to onset of sensory blockade (Tripathi et al., 2016). Tripathi et al. (2016) did find a significant difference in the duration of sensory blockade, with significant prolongation in the dexmedetomidine group compared to the clonidine group, with mean durations of 502.66 and 316.67 minutes respectively ($p < 0.001$). These findings were consistent with the data presented by Abu Elyazed & Mogahed (2018) and Lotfy et al. (2020), which also showed significant prolongation of sensory blockade with the addition of dexmedetomidine ($p < 0.000$). Lotfy et al. (2020) noted a significant difference in the duration of sensory blockade not only between the dexmedetomidine group versus the fentanyl and control groups but also between the fentanyl group versus the control group ($p < 0.001$).

Analgesia is the basis for, and a critical component of PNB. In a double-blind RCT of patients undergoing elective thyroid surgery using bilateral cervical plexus blockade (CPB), patients who received 40 mcg dexmedetomidine in 0.35% bupivacaine with 1:200,000 epinephrine showed statistically significant decreases in the 24-hour meperidine consumption compared to patients who received 0.35% bupivacaine with 1:200,000 epinephrine control. The dexmedetomidine group also had significantly lower postoperative VAS scores between the six- and 16-hour time points, as well as significantly increased time to first opioid request postoperatively ($p < 0.001$) (Elmaddawy & Mazy, 2018). Manzoor et al. (2018) conducted a double-blind RCT of ASA I, II, and III female patients undergoing breast surgery utilizing pectoral nerve block type I and II (PECS I & II) with bupivacaine alone or with

dexmedetomidine additive. The dexmedetomidine group showed significantly lower postoperative VAS scores at rest and with the abduction of the ipsilateral arm ($p < 0.001$) (Manzoor et al., 2018). This correlated to a 40% increase in the duration of complete analgesia (VAS 0) in the dexmedetomidine group, a significantly prolonged time to the first administration of rescue analgesia, and a significantly lower 24-hour diclofenac requirement ($p = 0.003$) (Manzoor et al., 2018). Abu Elyazed & Mogahed (2018) and Tripathi et al. (2016) also showed significant prolongation of the duration of analgesia in patients who received dexmedetomidine additive. Lotfy et al. (2020) reported a significantly prolonged time to the first request of rescue analgesics between dexmedetomidine, fentanyl, and control groups ($p < 0.001$). Researchers also recorded a significant decrease in 24-hour diclofenac consumption in the dexmedetomidine group, as well as a significant decrease in 24-hour meperidine consumption in both the dexmedetomidine and fentanyl groups ($p < 0.001$) (Lotfy et al., 2020).

Motor Blockade

A common goal with regional anesthesia is to prolong sensory blockade without significantly prolonging motor blockade. Motor blockade can improve surgical conditions and the onset and duration are important considerations when planning regional anesthesia, especially when considering additives. When magnesium was added to local anesthetic and compared to dexmedetomidine, both the time to onset and the duration of motor blockade were prolonged in the dexmedetomidine group (Abu Elyazed & Mogahed, 2018). When comparing the magnesium group to the 0.5% ropivacaine control group, there was no significant difference in time to onset of motor blockade, however, a significant prolongation of motor blockade in the magnesium group was reported (Abu Elyazed & Mogahed, 2018). In another comparison of two different additives, dexmedetomidine or fentanyl versus 0.5% bupivacaine control, the

dexmedetomidine group was found to have a significantly faster time to onset and longer duration of motor blockade ($p < 0.001$) (Lotfy et al., 2020). Though the fentanyl group did not show significance in time to onset of motor blockade, there was a significant motor blockade prolongation versus control ($p < 0.001$) (Lotfy et al., 2020). In an evaluation of either dexmedetomidine or clonidine at a dose of 1 mcg/kg each added to local anesthetic for SBPB, the time to onset of motor blockade was not significant between these two α-2 agonists, while the duration of motor blockade was significantly prolonged in the dexmedetomidine group ($p < 0.001$) (Tripathi et al., 2016). Table 1 below outlines various adjunct medications used for PNB compared to dexmedetomidine.

Table 1

Medication Doses and Associated Sensory Blockade and Analgesia Duration

Medication	Dose	Local Anesthetic Used	Sensory Block Duration (minutes)	Duration of Analgesia (minutes)
Ropivacaine	175 mg (35 ml, 0.5%) + 4 ml NS	-	362 +/- 53.6[a]	403 +/- 53.4[a]
Magnesium	150 mg	Ropivacaine (35 ml, 0.5%)	550 +/- 47.6[a]	598 +/- 51.4[a]
Dexmedetomidine	100 mcg	Ropivacaine (35 ml, 0.5%)	636 +/- 54.8[a]	684 +/- 51.5[a]
Bupivacaine	150 mg (30 ml, 0.5%)	-	307 +/- 23.8[b]	249 +/- 37[b]
Fentanyl	50 mcg	Bupivacaine (30 ml, 0.5%)	360 +/- 20.3[b]	361 +/- 20.7[b]
Dexmedetomidine	75 mcg	Bupivacaine (30 ml, 0.5%)	459 +/- 49.3[b]	485 +/- 13.1[b]
Clonidine	1 mcg/kg	Bupivacaine (39 ml, 0.25%)	316 +/- 45.2[c]	349 +/- 42.9[c]
Dexmedetomidine	1 mcg/kg	Bupivacaine (39 ml, 0.25%)	502 +/- 43.7[c]	525 +/- 42.8[c]
Dexamethasone	4 mg	Bupivacaine (18 ml, 0.5%)	512 +/- 36.8[d]	635 +/- 38.6[d]
Dexamethasone	8 mg	Bupivacaine (18 ml, 0.5%)	604 +/- 48.9[d]	1074 +/- 94[d]

Note: Data adapted from [a]Abu Elyazed & Mogahed (2018); [b]Lotfy et al., (2020); [c]Tripathi et al., (2016); & [d]Arjun, B.K. et al., (2019)

Patient Satisfaction

In assessing patient satisfaction, Manzoor et al. (2018) reported that more patients in the dexmedetomidine group rated postoperative analgesia at the top tier of the rating scale as excellent when compared to the plain bupivacaine control group for PECS I and II block. Abu Elyazed & Mogahed (2018) reported similarly, adding that both dexmedetomidine and magnesium as additives increased patient satisfaction when compared to ropivacaine alone for IBPB. Although patient satisfaction was not specifically addressed, Tripathi et al. (2016) discussed the quality of anesthesia as it related to the amount of postoperative supplemental analgesia required by the patient. Eighty percent of the patients in the dexmedetomidine group were rated at the top tier of the anesthesia quality scale as excellent, whereas 40% of patients who received clonidine were rated as excellent and this finding was statistically significant ($p < 0.001$) (Tripathi et al., 2016).

Adverse Effects

Dexmedetomidine, when administered intravenously, can cause hemodynamic changes including hypertension, hypotension, and bradycardia. Abu Elyazed & Mogahed (2018) reported a statistically significant decrease in both heart rate and MAP in patients who received dexmedetomidine additive for IBPB, however, authors failed to report clinical significance or treatments of these altered hemodynamics. In another study, patients who received dexmedetomidine additive for SBPB showed significantly decreased heart rate and MAP from initial block placement to the 90-minute mark (Tripathi et al., 2016). Authors discussed that none of these patients required treatment for hypotension or bradycardia and that beyond the 90-minute mark, heart rate and blood pressure data were comparable between control and study groups (Tripathi et al., 2016). In patients who received dexmedetomidine additive for PECS I

and II blockade, statistically significant reductions in blood pressure measurements were noted at the 10-minute post-surgical incision point as well as the 1-hour postoperative point compared to 0.25% bupivacaine control ($p < 0.001$) (Manzoor et al., 2018). These reductions were not clinically significant as none of the participants required hemodynamic support in the form of vasopressors (Manzoor et al., 2018). Whether in the control group or the study group, none of the patients had any incidence of bradycardia or hypotension (Manzoor et al., 2018). Furthermore, after receiving dexmedetomidine additive for superficial cervical plexus blockade, patients were noted to have significantly lower heart rates at 60, 75, 90, and 105 minutes after block placement (Elmaddawy & Mazy, 2018). The clinical significance of this finding was not acknowledged. Authors reported comparable MAP statistics between the control and study groups (Elmaddawy & Mazy, 2018).

In patients who received dexmedetomidine additive for SBPB, Ramsay Sedation Scores (RSS) were higher, suggesting increased sedation, at the 15- and 30-minute post-block time points, compared to fentanyl additive or control (Lotfy et al., 2020). The authors reported no significant difference in RSS between those who received fentanyl and the control group (Lotfy et al., 2020). Authors failed to report the clinical significance of this higher degree of sedation described with dexmedetomidine additive (Lotfy et al., 2020). Outcomes of nausea, vomiting, hematoma, hoarseness, and nerve injury were addressed by Elmaddawy & Mazy (2018) where authors found no significant differences in these postoperative complications between control and study groups.

Epidural Anesthesia

Sensory Blockade

When dexmedetomidine was compared to clonidine as an adjuvant for epidural anesthesia in patients undergoing lower limb orthopedic surgery, those who received dexmedetomidine showed faster onset of sensory analgesia to the T10 level ($p < 0.00001$) (Shaikh & Mahesh, 2016). This finding was similar to that of Kiran et al. (2018), who studied the adjuvants fentanyl and dexmedetomidine for epidural anesthesia in patients undergoing infraumbilical surgeries. In this study, the authors found that the onset of sensory blockade to the T10 level was significantly faster when 10 mcg dexmedetomidine was added to 18 ml of 0.5% ropivacaine on the initiation of epidural anesthesia, as compared to 20 mcg fentanyl ($p < 0.003$) additive or ropivacaine control ($p < 0.001$) (Kiran et al., 2018). Fentanyl with ropivacaine was also significantly faster in providing sensory blockade than ropivacaine alone ($p < 0.001$) (Kiran et al., 2018). In comparing 0.5% ropivacaine or 0.5% bupivacaine, dexmedetomidine additive to either local anesthetic did not lead to any significant differences in onset of sensory blockade for patients undergoing lower abdominal or lower limb surgery, nor did authors show any differences in regression time of sensory blockade to the level of S1 (Srinivas Rao et al., 2016).

The addition of epidural dexmedetomidine leads to faster onset of sensory blockade, helps to achieve analgesia faster, and increases the duration of analgesia as well. This is described by Shaikh & Mahesh (2016), where the addition of 1 mcg/kg dexmedetomidine to 0.5% bupivacaine not only led to faster onset of sensory blockade but also aided in attaining the maximum level of analgesia in a shorter time compared to 2 mcg/kg clonidine. Although verbal rating scale (VRS) scores were comparable immediately after epidural placement up to the 220-minute mark, at each time interval beyond 220 minutes, patients who received clonidine reported

significantly higher VRS scores than those who received dexmedetomidine ($p < 0.0001$). Additionally, the duration of analgesia for the dexmedetomidine group was significantly prolonged and those who received clonidine required significantly earlier rescue analgesia (Shaikh & Mahesh, 2016). Similarly, when the epidural adjuvants dexmedetomidine or fentanyl were compared to ropivacaine alone, there were significant differences between all groups in the time from epidural placement to rescue analgesia, with the dexmedetomidine group showing the greatest prolongation of analgesia. The quality of anesthesia was similar between the fentanyl and dexmedetomidine groups. The total number of times the epidural was re-dosed was significantly lower in the dexmedetomidine, fentanyl, and control groups, respectively. (Kiran et al., 2018).

Motor Blockade

Dexmedetomidine also led to a faster onset and deeper level of motor blockade, as assessed by the Modified Bromage Scale (MBS) (Kiran et al., 2018). On the MBS, a score of 0 relates to no motor blockade, while a score of 3 is equivalent to a complete motor blockade (Miller et al., 2015). Kiran et al. (2018) not only reported that motor blockade onset was significantly faster, but also that an MBS score of 3 was attained in 100% of patients who received dexmedetomidine as an epidural additive to 0.5% ropivacaine, as compared with 80% and 0% in the fentanyl and ropivacaine control groups, respectively ($p < 0.001$). In comparing the motor blockade onset times between α-2 agonists clonidine or dexmedetomidine, patients who received 1 mcg/kg dexmedetomidine as an epidural adjuvant to 0.5% bupivacaine attained an MBS score of 3 significantly earlier than those who received 2 mcg/kg clonidine. Patients who received dexmedetomidine were also reported to have significantly increased time to

regression back to an MBS score of 1, indicating prolongation of motor blockade (Shaikh & Mahesh, 2016).

Adverse Effects

Dizziness, headache, nausea, vomiting, shivering, respiratory depression, and dry mouth were all noted adverse effects in the study by Shaikh & Mahesh (2016). When comparing the clonidine/bupivacaine group to the dexmedetomidine/bupivacaine group, there were no significant differences in the incidence of these adverse effects (Shaikh & Mahesh, 2016). In a comparison between epidural fentanyl/ropivacaine, dexmedetomidine/ropivacaine, or ropivacaine control, Kiran et al. (2018) reported no significant differences in the incidence of nausea, vomiting, pruritus, or shivering between groups. Though the fentanyl group had a higher incidence of pruritus, it was not statistically significant (Kiran et al., 2018). This study also reported that the incidence of hypotension and bradycardia was significantly higher in the dexmedetomidine group when compared to both the ropivacaine control and the fentanyl group (Kiran et al., 2018). These patients required treatment of hypotension with intravenous fluids or vasopressors, but it was not severe enough to warrant prolonged treatment (Kiran et al., 2018). The authors did not discuss the clinical significance of the higher incidence of bradycardia or whether anticholinergic treatment was required (Kiran et al., 2018). When comparing the α-2 agonists clonidine and dexmedetomidine as adjuvants to epidural bupivacaine, no significant differences in blood pressure or heart rate were noted between groups (Shaikh & Mahesh, 2016). Authors also reported that there was no clinically significant incidence of bradycardia or hypotension at any time in either of the groups (Shaikh & Mahesh, 2016).

As an epidural adjuvant to bupivacaine, 1 mcg/kg dexmedetomidine was associated with a statistically significant increase in the level of sedation when compared to patients who

received 2 mcg/kg clonidine ($p < 0.00001$) (Shaikh & Mahesh, 2016). This difference was noted from the time of epidural placement to 60-minute post-block placement, from which point the sedation scores were comparable between the two groups. The clinical significance of this sedation is not discussed, and authors failed to report if the sedation scale used was previously validated (Shaikh & Mahesh, 2016). Other studies fail to mention or compare sedation levels between study groups, which identifies a limitation of such studies (Kiran et al., 2018; Srinivas Rao et al., 2016).

Spinal Anesthesia

Sensory Blockade

In a spinal anesthesia comparison between 5 mcg dexmedetomidine, 100 IU calcitonin, or 25 mcg fentanyl additive to 0.5% bupivacaine for spinal anesthesia in patients undergoing lower limb surgeries, no significant differences in sensory blockade onset time were noted between any of the study groups or bupivacaine control (Jandial et al., 2018). There was statistically significant prolongation in the time to two-segment sensory regression, sensory regression to S1 from max sensory block height, and time to first rescue analgesia in patients who received dexmedetomidine, calcitonin, fentanyl, or plain bupivacaine, respectively ($p < 0.000$) (Jandial et al., 2018). Liu et al. (2019) reported similar results in a dose-finding study comparing intrathecal hyperbaric bupivacaine to intrathecal hyperbaric bupivacaine with dexmedetomidine additive in parturients undergoing elective cesarean section, showing no difference in the time to onset of sensory blockade to the T10 level. The duration of sensory blockade was significantly longer, and the overall consumption of postoperative narcotic was significantly less in those who received dexmedetomidine additive to hyperbaric bupivacaine ($p < 0.05$) (Liu et al., 2019).

Two separate studies by Sharma et al. (2020) and Sudhakar et al. (2017) researched the use of IV dexmedetomidine infusions as a supplement to spinal anesthesia compared to intrathecal addition of dexmedetomidine to hyperbaric bupivacaine. Sharma et al. (2020) administered 0.5 mcg/kg IV dexmedetomidine over 15 minutes to ASA I and II patients undergoing distal lower extremity orthopedic surgery 20 minutes before placement of subarachnoid blockade with 0.5% hyperbaric bupivacaine and compared to those who received 3 mcg dexmedetomidine as an additive to 0.5% hyperbaric bupivacaine for subarachnoid blockade. The time to regression of the sensory blockade to level S1 and the duration of analgesia were significantly prolonged in the group which received intrathecal dexmedetomidine, though the time to onset of sensory blockade was similar between groups (Sharma et al., 2020). Sudhakar et al. (2017) administered a 1 mcg/kg IV dexmedetomidine bolus over 10 minutes followed by 0.25 mcg/kg/hr IV infusion as a supplement to subarachnoid blockade using 0.5% hyperbaric bupivacaine and compared this to subarachnoid blockade using 16 mcg dexmedetomidine added to 0.5% hyperbaric bupivacaine in ASA I and II patients undergoing various lower abdominal and lower limb surgeries. The group that received intrathecal dexmedetomidine showed a consistently higher max height of sensory blockade, which was a statistically significant finding ($p = 0.02$), as well as a shorter time to onset of sensory blockade ($p = 0.03$), and a prolonged time to first rescue analgesic postoperatively ($p < 0.01$), which was also a statistically and clinically significant finding (Sudhakar et al., 2017).

Motor Blockade

In ASA I and II parturients undergoing cesarean section, the onset of motor blockade was not significantly affected when dexmedetomidine was added to subarachnoid blockade with hyperbaric bupivacaine compared to hyperbaric bupivacaine control (Liu et al., 2019). Jandial et

al. (2018), when comparing intrathecal additives dexmedetomidine, calcitonin, fentanyl, and 0.5% bupivacaine control, similarly reported no difference in onset of motor blockade. In this study, dexmedetomidine as an additive to 0.5% bupivacaine showed a prolonged time to regression to an MBS score of 0. There was no significant difference in prolongation of motor blockade between the calcitonin, fentanyl, and control groups (Jandial et al., 2018). Intrathecal bupivacaine with 16 mcg dexmedetomidine additive was associated with a shorter mean time to onset ($p = 0.01$) and a prolonged mean time of duration ($p < 0.01$) of motor blockade compared to bupivacaine spinal anesthesia with supplemental IV infusion of dexmedetomidine (listed previously). These findings were statistically and clinically significant (Sudhakar et al., 2017).

Patient Satisfaction

Patient satisfaction is briefly discussed by Liu et al. (2019), assessing whether patients who received intrathecal bupivacaine/dexmedetomidine had higher satisfaction scores compared to those who received intrathecal bupivacaine control. In the intrathecal dexmedetomidine versus hyperbaric bupivacaine control groups, 63% and 55% of patients, respectively, rated their satisfaction of analgesia as excellent. The remainder of the patients in each group, 37%, and 45%, respectively, rated their satisfaction with analgesia as good. Statistical analysis showed that these findings were not statistically significant (Liu et al., 2019).

Adverse Effects

Nausea, vomiting, hypotension, bradycardia, oxygen desaturation, pruritus, shivering, sedation, abdominal pain, and restlessness were described by Jandial et al. (2018) as authors compared the additives dexmedetomidine, calcitonin, fentanyl, and control for spinal anesthesia. Patients who received 100 IU calcitonin with 0.5% bupivacaine showed a higher incidence of nausea, vomiting, shivering, abdominal pain, and restlessness whereas those who received

fentanyl additive had a higher incidence of pruritus (Jandial et al., 2018). However, the authors failed to compare the incidence of each adverse event between groups, a critical limitation of this study. Similarly, Liu et al. (2019) described the adverse events of hypotension, bradycardia, nausea, vomiting, shivering, pruritus, and respiratory depression (arterial oxygen saturation less than 90% or a respiratory rate less than 12) in cesarean section patients undergoing spinal anesthesia with 5 mcg dexmedetomidine in hyperbaric bupivacaine. Statistical analysis revealed no significant differences in these adverse events compared to hyperbaric bupivacaine control (Liu et al., 2019). Sedation was listed as a secondary outcome measure in this study, but the authors failed to report on this data (Liu et al., 2019).

In a meta-analysis and trial sequential analysis of six RCT's, including 360 patients undergoing cesarean section with spinal anesthesia using intrathecal dexmedetomidine additive, Miao et al. (2018) reported on the incidence of shivering, post-operative nausea and vomiting (PONV), hypotension, and bradycardia. Shivering, the primary outcome of this meta-analysis, was significantly reduced when intrathecal dexmedetomidine was administered compared to other additives. There was no significant difference in the incidence of shivering with either 5 mcg or 10 mcg dexmedetomidine, suggesting a dose of 5 mcg may be sufficient to prevent shivering. Researchers found no significant differences in the incidence of PONV, hypotension, or bradycardia when using intrathecal dexmedetomidine versus other additives. Authors determined from the trial sequential analysis that no firm conclusions could be made until further research is completed on this topic (Miao et al., 2018).

The adverse effects of intrathecal dexmedetomidine and those from IV infusion of dexmedetomidine as a supplement to spinal anesthesia have also been compared. In Sharma et al. (2020), authors measured blood pressure, MAP, heart rate, respiratory rate, and arterial oxygen

saturation and found comparable data intraoperatively between intrathecal and IV dexmedetomidine. Statistical analysis was not completed, however. Increased sedation intraoperatively was seen in 33% of patients who received an intravenous infusion of 0.5 mcg/kg dexmedetomidine over 15 minutes, 20 minutes before spinal anesthesia, whereas none of the patients who received 3 mcg intrathecal dexmedetomidine exhibited intraoperative sedation. At 3 hours after subarachnoid block, none of the patients in either group exhibited sedation (Sharma et al., 2020). Comparing 16 mcg intrathecal dexmedetomidine additive or 1 mcg/kg IV dexmedetomidine over 10 minutes with 0.25 mcg/kg/hr IV maintenance, authors reported no clinically or statistically significant difference in the MAP or the incidence of hypotension between groups (Sudhakar et al., 2017). Patients who received IV bolus and infusion of dexmedetomidine showed a lower heart rate intraoperatively, a clinically and statistically significant finding. No significant difference in the incidence of bradycardia between groups was noted (Sudhakar et al., 2017).

Discussion

Regional anesthesia is an ever-growing and popular aspect of the total anesthesia landscape. Regional anesthesia encompasses PNB, IVRA, as well as spinal and epidural techniques collectively referred to as central neuraxial blockade (CNB). Modern regional anesthetic techniques are the result of evolution and enhancement from the late 1800s when regional anesthesia was first described (Miller et al., 2015). The injection of cocaine into peripheral areas for minor surgery in the 1880s was described by two American surgeons, William Halsted and Richard Hall (Miller et al., 2015). In 1898, cocaine was again described, along with its potential for use in surgical anesthesia, for injection into the spinal column by Augustus Bier and Theodor Tuffier (Nagelhout & Elisha, 2018). Regional anesthesia has been

shown to decrease postoperative pain, decrease the need for postoperative rescue pain medications, lower the incidence of nausea, shorten postanesthesia unit length-of-stay, and is associated with higher patient satisfaction (Miller et al., 2015).

While also providing analgesia, regional anesthesia may modulate the stress response, decrease systemic analgesic requirements and their associated adverse effects, lower general anesthesia requirements, and possibly reduce the development of chronic pain (Butterworth IV et al., 2013). With the gold-standard use of ultrasound technology, literature shows a higher success rate, shorter time to onset of blocks, better quality sensory blockade, reduction in pneumothorax incidence, and reduction in systemic toxicity (Lotfy et al., 2020). Today, as regional anesthesia gains popularity, a solid understanding of the methods, medications, and physical anatomy of regional anesthesia is essential for the comprehensive anesthesia provider (Butterworth IV et al., 2013). Relative to this understanding, along with a deep understanding of local anesthetics, is the knowledge of adjunct medications to potentiate the effects of local anesthetics.

Local Anesthetics

Local anesthetics are the foundation of regional anesthesia. There are two separate classes of local anesthetics used clinically for regional anesthesia: aminoamides and aminoesters. There are three structural segments to a local anesthetic: a lipophilic benzene ring, an intermediate ester or amide chain, and a hydrophilic amine end (Nagelhout & Elisha, 2018). With perineural local anesthetic administration, a specific region of the alpha subunit of the membrane-bound sodium channel is bound, inhibiting voltage-gated sodium channels, preventing channel activation, and thus, preventing sodium influx required for cell membrane depolarization (Butterworth IV et al., 2013).

The duration of action of a local anesthetic correlates with lipid solubility and protein binding (Nagelhout & Elisha, 2018). Local anesthetics with high lipid solubility and protein binding attach with more affinity to these structures in the area of the voltage-gated sodium channel, producing a prolonged blockade (Nagelhout & Elisha, 2018). Protein binding for mepivacaine, ropivacaine, and bupivacaine is approximately 65%, 94%, and 97%, respectively (Nagelhout & Elisha, 2018). Clinically, the duration of action of these local anesthetics increases as the percentage of protein binding increases (Nagelhout & Elisha, 2018). However, central nervous system toxicity and cardiovascular toxicity are also closely related to lipid solubility, and thus bupivacaine carries a higher risk of toxicity (Barash et al., 2017). An ideal local anesthetic for use in regional anesthesia provides a long duration of action, while also having little risk of systemic toxicity (Kukreja et al., 2019).

Local anesthetic adjuvants or additives are sometimes utilized to modulate the effects of local anesthetics. As previously stated, an ideal additive to local anesthetics quickens the onset of sensory blockade, prolongs sensory blockade without prolonging motor blockade, has few to no adverse effects, and is compatible with local anesthetics. Common adjuvants are often of differing pharmacologic classes and thus have different mechanisms of action and safety profiles (Kukreja et al., 2019). Local anesthetic additives commonly used for regional anesthesia include epinephrine, dexamethasone, fentanyl, morphine, tramadol, ketorolac, clonidine, dexmedetomidine, midazolam, ketamine, neostigmine, and magnesium (Stuart, 2011). It should be added that currently, epinephrine is the only FDA approved local anesthetic additive for regional anesthesia (Kukreja et al., 2019).

Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenoreceptor agonist (Nagelhout & Elisha, 2018). Stimulation of α-2 adrenoreceptors by dexmedetomidine leads to calcium channel inhibition, potassium channel activation, and protein release modulation which results in cellular hyperpolarization (Nagelhout & Elisha, 2018). The resultant clinical effect is sedation, anxiolysis, sympatholysis, and analgesia, all while exerting little effect on the respiratory drive (Nagelhout & Elisha, 2018). Dexmedetomidine is highly potent and selective for the α-2 receptor, with an α-2:α-1 ratio of 1620:1 (Weerink et al., 2017). In comparison, clonidine, a closely related α-2 agonist, has an α-2:α-1 ratio of 220:1 (Weerink et al., 2017). The most common side effects of dexmedetomidine include hypertension, hypotension, and bradycardia which are related to its effect on vasoconstriction, sympatholysis, and baroreceptor-mediated parasympathetic activation (Weerink et al., 2017).

Pharmacokinetics

Absorption rate of dexmedetomidine is highly dependent on administration route (Weerink et al., 2017). Extravascular administration of dexmedetomidine, as is the case with peripheral regional blockade and neuraxial techniques, avoids high peak plasma levels normally seen with intravenous administration (Weerink et al., 2017). Dexmedetomidine is 95% protein-bound in the plasma, primarily metabolized and eliminated through hepatic biotransformation, and has an elimination half-life of 2.1-3.1 hours in healthy patients (Weerink et al., 2017).

Clinical Utilization

Currently, dexmedetomidine is FDA approved for intravenous sedation of mechanically ventilated patients in the intensive care unit (ICU), as well as for procedural intravenous sedation of non-intubated patients (Nagelhout & Elisha, 2018). Sedation produced by dexmedetomidine

closely resembles natural sleep and patients usually remain arousable (Nagelhout & Elisha, 2018). Dexmedetomidine use for off-label indications is often reported in the literature (Weerink et al., 2017). The addition of dexmedetomidine to regional anesthesia has shown promise in extending block duration (Weerink et al., 2017). Though not completely understood, the extension of neural blockade is thought to occur by prolonged hyperpolarization of sensory C-fibers as well as motor A-fibers, however to a lesser degree (Weerink et al., 2017). Central effects on the locus coeruleus may be a factor as well (Weerink et al., 2017).

Intravenous Regional Anesthesia

Intravenous Regional Anesthesia is used for surgical procedures of the forearm, wrist, or hand but can be utilized for lower extremity procedures as well (Nagelhout & Elisha, 2018). IVRA is used for shorter procedures, as durations longer than one hour are often met with increased patient discomfort related to the tourniquet used to initiate and maintain the block (Nagelhout & Elisha, 2018). The greatest concern with IVRA is related to the intravascular administration of a large amount of local anesthetic and the potential for tourniquet failure or improper use leading to LAST (Nagelhout & Elisha, 2018).

After exsanguination of the extremity and the application of a tourniquet, generally, a 3 mg/kg volume of 0.5% lidocaine is delivered through a distal intravenous catheter (Miller et al., 2015). Rapid recovery from local anesthetics with deflation of the tourniquet can lead to undesirable postoperative pain (Miller et al., 2015). Compared to other regional anesthetic techniques, it is relatively difficult to provide ongoing postoperative analgesia with the use of IVRA (Subramanya et al., 2017). For this reason, adjuncts have been added to local anesthetics in an attempt to not only hasten the onset of analgesia, but also prolong analgesia beyond the deflation of the tourniquet (Subramanya et al., 2017).

Clinical Application

The effects of adding dexmedetomidine to lidocaine for IVRA included faster sensory block onset, prolonged sensory blockade, and prolonged duration of postoperative analgesia compared to lidocaine alone (Bhaumik et al., 2016; Hamawy & Bestarous, 2019; Modir et al., 2017; Nilekani et al., 2016; Subramanya et al., 2017). Motor blockade onset times were also shorter, and the duration of motor blockade was longer with the use of dexmedetomidine and lidocaine than with lidocaine alone (Bhaumik et al., 2016; Nilekani et al., 2016). Dexmedetomidine also reduced the incidence of intraoperative tourniquet pain associated with IVRA (G. et al., 2020; Nilekani et al., 2016). This effect is especially promising, as tourniquet pain is often cited as the most limiting factor of IVRA (Nagelhout & Elisha, 2018). Generally, a weight-based dose between 0.5-1 mcg/kg added to lidocaine has been utilized in the literature with these positive outcomes.

Though adjunct dexmedetomidine exhibited these promising results, the NSAID ketorolac at a dose of 30 mg added to 3 mg/kg 0.5% lidocaine also proved to be effective at prolonging postoperative analgesia (Modir et al., 2017). Postoperative visual analog scale (VAS) scores were consistently lower with the use of both dexmedetomidine and ketorolac, but ketorolac was associated with lower VAS scores beyond 45 minutes post-tourniquet deflation (Modir et al., 2017). Additionally, 8 mg of lornoxicam, an NSAID not available in the United States, is more efficacious than lidocaine alone at decreasing onset and increasing duration of sensory blockade (Hamawy & Bestarous, 2019). Comparatively, dexamethasone at a dose of 8 mg did not improve any of these block characteristics or decrease pain postoperatively when combined with lidocaine (Hamawy & Bestarous, 2019). These results suggest that although

dexmedetomidine has desirable effects as an adjunct to IVRA, other medications such as ketorolac or lornoxicam contain desirable properties as well.

Adverse Effects

Traditional intravenous administration of dexmedetomidine predictably produces bradycardia, hypotension, and sedation (Subramanya et al., 2017). With tourniquet deflation using an IVRA technique, a large amount of previously isolated medication is introduced systemically. Relative to the known hemodynamic side effects of dexmedetomidine, heart rate and blood pressure are important considerations of its overall safety and efficacy for use in IVRA. Although some studies report no significant difference in blood pressure and heart rate (Bhaumik et al., 2016; Modir et al., 2017; Nilekani et al., 2016), other studies noted significant reductions in these metrics when dexmedetomidine was used (Hamawy & Bestarous, 2019; Subramanya et al., 2017). One study reported that no treatment was necessary for hypotension or bradycardia as the patients remained clinically stable (Hamawy & Bestarous, 2019). However, bradycardia associated with dexmedetomidine use was responsive to intravenous atropine (Subramanya et al., 2017). Whether patients who displayed bradycardia had a truly unstable hemodynamic status (concurrent hypotension, altered mental status, etc.) or solely met the treatment guidelines of the trial was not expounded upon (Subramanya et al., 2017).

Another effect of utilizing dexmedetomidine is the potential for sedation which may be a desirable or undesirable outcome, depending on immediate postoperative goals. Sedation scores have been reported to be slightly higher for two hours after tourniquet deflation. Unfortunately, the clinical significance is lacking in these cases (Subramanya et al., 2017). Alternatively, similar sedation scores have been reported with the use of dexmedetomidine when compared to lidocaine alone (Nilekani et al., 2016). The sedation produced by dexmedetomidine is dose-

dependent, resembles natural sleep, leaves patients readily arousable, and does not lead to respiratory depression (Nagelhout & Elisha, 2018). The cardiovascular effects produced by dexmedetomidine are also dose dependent (Nagelhout & Elisha, 2018). This suggests that using a smaller dose (0.5 mcg/kg) may exert less of an effect on hemodynamic variables as well as sedation levels, while still providing desirable effects related to the surgical and postsurgical neuronal blockade.

Peripheral Nerve Blockade

Peripheral nerve blockade, generally used in conjunction with general anesthesia, is often used to provide ongoing pain relief in the postoperative period (Nagelhout & Elisha, 2018). Longer-acting local anesthetics are often employed for this reason, but there is a limitation to the duration that these local anesthetics will provide postoperative pain relief. Adjunct medications, including dexmedetomidine, are being utilized in regional anesthesia as they have been shown to prolong block duration and subsequently, the duration of postoperative analgesia (Lotfy et al., 2020).

Clinical Application

The utility of an adjunct in peripheral regional anesthesia is often to shorten onset or prolong duration of sensory blockade. In three separate studies using dexmedetomidine for PNB, onset to sensory blockade onset was shorter, and duration of sensory blockade was prolonged, however the same was true for motor blockade onset and duration (Abu Elyazed & Mogahed, 2018; Lotfy et al., 2020; Tripathi et al., 2016). The authors of these studies failed to discuss whether this prolonged duration of motor blockade led to any negative outcomes or sequelae. Prolonged duration of motor blockade is not always desirable as patients may need to participate

in postoperative physical therapy (Kukreja et al., 2019). Thus, before using dexmedetomidine for peripheral regional anesthesia, it is prudent to assess a patient's postoperative course holistically.

Dexmedetomidine dosing is inconsistent throughout the literature. Some trials utilized weight-based dosing, which was usually 1 mcg/kg dexmedetomidine with local anesthetic (Manzoor et al., 2018; Tripathi et al., 2016). Alternatively, other trials utilized a predetermined standard dose mixed with local anesthetic for all participants, usually between 40-100 mcg. The variability of dosing regimens could be explained by the need for standardized research methods for each trial, but specific rationale is lacking. Dexmedetomidine metabolism in the liver is highly dependent on hepatic blood flow and cardiac output, as well as body size. Because of this, bodyweight is a factor in the overall metabolism of dexmedetomidine. The package inserts for two brands of commercially available dexmedetomidine specifically outline weight-based dosing, though this dosing method is specified for intravenous sedation (Weerink et al., 2017). Alternatively, as reported by Marhofer & Brummett (2016), a standard dose of 100 mcg for PNB may be the most efficacious dose for reducing side effects while maintaining desirable block characteristics. More research is warranted regarding the most effective dose of dexmedetomidine for use in peripheral regional anesthesia.

Adverse Effects

Multiple studies outline the adverse effects of additive dexmedetomidine for peripheral nerve or fascial plane blockade. Blood pressure and heart rate data are most commonly reported, aligning with the known effects of dexmedetomidine administration. Decreased blood pressure and bradycardia can lead to hemodynamic instability, but these outcomes are not necessarily clinically relevant. In one study, dexmedetomidine led to increased incidence of hypotension and bradycardia, which was either managed with intravenous fluids, ephedrine boluses, or atropine

0.5 mg (Abu Elyazed & Mogahed, 2018). Unfortunately, there was no discussion of the extent to which these rescue interventions were required for patients who experienced hypotension or bradycardia (Abu Elyazed & Mogahed, 2018). Additionally, hypotension and bradycardia treatment criteria were well-defined, but the specific patient baseline data was not (Abu Elyazed & Mogahed, 2018). If a patient who received dexmedetomidine exhibited hypertension initially or had a resting heart rate near 50 bpm at baseline, treatment may have been based not necessarily on hemodynamic instability but instead on trial criteria. In another study, the authors found no significant difference in mean blood pressure when dexmedetomidine was compared to bupivacaine alone (Elmaddawy & Mazy, 2018). However, a significantly decreased heart rate was noted between 60-105 minutes after block placement in patients who received dexmedetomidine (Elmaddawy & Mazy, 2018). Unfortunately, this study fails to outline whether treatment was administered (Elmaddawy & Mazy, 2018). In three other studies, heart rate, blood pressure, or both were decreased after the administration of dexmedetomidine, but treatment was not required for any of these trial participants (Lotfy et al., 2020; Manzoor et al., 2018; Tripathi et al., 2016).

Evidence suggests that dexmedetomidine can alter hemodynamic metrics, but not always with clinical significance. In either case, a thorough preoperative exam coupled with the understood, predictable and treatable side effects of dexmedetomidine enables providers to choose the safest and most appropriate anesthetic plan for a patient. Additionally, as regional anesthesia is often coupled with general anesthesia, requirements for general anesthesia may be lower when utilizing dexmedetomidine, as sensory and motor blockade onset are significantly faster and prolonged.

Postoperative Analgesia

Consideration not only for utilization of regional anesthesia but also for the utilization of additives including dexmedetomidine is the potential reduction in postoperative analgesic requirements. Studies of various PNB techniques utilizing dexmedetomidine additive consistently show a reduction in the amount of analgesia required within the first 24-hours (Elmaddawy & Mazy, 2018; Manzoor et al., 2018), as well as a reduction in the total analgesic requirements postoperatively (Abu Elyazed & Mogahed, 2018; Lotfy et al., 2020). There is also evidence that showed patient requests for rescue analgesia postoperatively were significantly prolonged compared to control groups (Elmaddawy & Mazy, 2018; Lotfy et al., 2020; Manzoor et al., 2018). Patients also tended to have greater satisfaction with the quality of blockade when dexmedetomidine was utilized (Abu Elyazed & Mogahed, 2018; Manzoor et al., 2018).

Epidural Anesthesia

Central neuraxial blockade using epidural anesthesia can be used for a wide range of procedures and operations (Nagelhout & Elisha, 2018). Epidural anesthesia also allows for greater control over the degree of sensory and motor blockade when compared to spinal anesthesia (Nagelhout & Elisha, 2018). However, epidural anesthesia is reliant on the process of diffusion of the medication into the subarachnoid space and for this reason takes significantly longer to achieve analgesia and anesthesia (Nagelhout & Elisha, 2018). Epidural anesthesia utilizes local anesthetics primarily, but the addition of adjuncts is common (Kiran et al., 2018). The addition of opioids to epidural anesthesia carries the risk of pruritis and respiratory depression (Kiran et al., 2018). Utilizations of other effective adjuncts, including dexmedetomidine, has been shown to reduce the total local anesthetic dose and associated side effects (Kiran et al., 2018).

Clinical Application

Dexmedetomidine as an adjunct to epidural anesthesia has been utilized as both a single-shot dose with a subsequent local anesthetic infusion or as part of a combined local anesthetic-dexmedetomidine continuous infusion. This allows for the evaluation of each technique regarding block onset, duration, as well as post-operative pain and analgesia requirements. Dosing with epidural dexmedetomidine is variable in the reviewed literature. Single-shot doses ranged from 10-50 mcg combined with bupivacaine or ropivacaine, with rescue doses reported at a dose of 5 mcg dexmedetomidine combined with local anesthetic (Bharti et al., 2018; Kiran et al., 2018; Srinivas Rao et al., 2016). Alternatively, there are other reports of weight-based dosing regimens of 0.5-1 mcg/kg (Sekhar et al., 2019; Shaikh & Mahesh, 2016). With either method of dosing, the onset of sensory and motor blockade was significantly faster and prolonged when dexmedetomidine was used compared to fentanyl or clonidine. Postoperative time to rescue analgesia was also longer, and pain rating scores were lower with the use of dexmedetomidine (Kiran et al., 2018; Shaikh & Mahesh, 2016). Whether added to ropivacaine or bupivacaine, dexmedetomidine consistently shortened onset and prolonged the duration of sensory blockade, but there was a greater prolongation when used with bupivacaine (Srinivas Rao et al., 2016). This prolonged sensory blockade effect coincided with a prolonged motor blockade duration and must be weighed against the risk of immobility.

Care must be taken to avoid prolonged motor blockade for surgeries of shorter duration and required postoperative physical therapy. Ropivacaine with dexmedetomidine carries less cardiotoxic risk, includes a more stable hemodynamic profile, and allowed for earlier ambulation which may be more appropriate for same-day surgeries (Srinivas Rao et al., 2016). When compared to fentanyl with ropivacaine, dexmedetomidine was associated with prolonged sensory

and motor blockade. The downside to these effects was the incidence of hypotension, which was significant in patients who received dexmedetomidine, but it was treatable with intravenous fluids and vasopressors. The use of fentanyl was associated with a higher incidence of pruritis, which was also treatable with the use of histamine antagonists like diphenhydramine (Kiran et al., 2018; Nagelhout & Elisha, 2018).

Continuous epidural infusions of local anesthetic and dexmedetomidine have also been reported in the literature. Infusions of 0.1% bupivacaine with 0.5 mcg/ml dexmedetomidine at 6 ml/hour were effective in reducing morphine consumption, delaying time to first analgesic request, and decreasing overall pain intensity in the first 48 hours after gastrectomy, Whipple's procedure, pancreatectomy, or partial hepatectomy (Hetta et al., 2018). This effect was seen without clinically significant alterations in hemodynamic variables (Hetta et al., 2018). Additionally, 8 ml/hour infusions of 0.08% ropivacaine with 0.5 mcg/ml dexmedetomidine in parturients for labor analgesia was shown to decrease the incidence of postpartum urinary retention and was associated with higher blood pressures and arterial oxygen saturation compared to similar infusions of ropivacaine with 0.5 mcg/ml of sufentanil (Cheng et al., 2019).

Dexmedetomidine as an epidural adjunct has the potential to cause hemodynamic alterations in heart rate and blood pressure. These effects are often predictable and responsive to treatment. There is no apparent trend in the incidence or extent of hemodynamic alterations based on the dose of dexmedetomidine alone and central neuraxial local anesthetics can also affect hemodynamic metrics. The effects of adjunct dexmedetomidine can help to reduce the necessary dose of local anesthetics, however, which can reduce the overall side effects of sympathectomy associated with epidural anesthesia (Kiran et al., 2018).

Spinal Anesthesia

Spinal anesthesia can be used for any type of procedure that epidural anesthesia can be used for, with the caveat that a single-shot spinal technique is limited by the duration of the medications injected. While an epidural catheter allows for re-dosing for ongoing anesthesia and analgesia, single-shot spinal anesthesia does not (Miller et al., 2015). Thus, the utility of adjunct medications to prolong the duration of spinal anesthesia can have profound impacts on postoperative analgesia.

Clinical Application

Dosing of intrathecal dexmedetomidine ranges from 3-16 mcg in the literature, but most commonly was 5 mcg (Jandial et al., 2018; Liu et al., 2019; Sharma et al., 2020; Sudhakar et al., 2017). The use of intrathecal dexmedetomidine was associated with a 24% reduction in the subarachnoid bupivacaine dose for cesarean section patients, as well as reduced postoperative opioid consumption (Liu et al., 2019).

The use of intrathecal adjunct dexmedetomidine was not associated with a faster time to onset of sensory or motor blockade but the duration of sensory and motor blockade was significantly prolonged with its use. In patients who received intrathecal anesthesia with bupivacaine (0.5%, 2.5ml), sensory blockade mean duration was prolonged with the use of dexmedetomidine compared to control, calcitonin, and fentanyl (Jandial et al., 2018). Additionally, the average time to regression of motor blockade was prolonged with dexmedetomidine (Jandial et al., 2018). Postoperatively, the time to rescue analgesia was prolonged in patients who received adjunct dexmedetomidine (Jandial et al., 2018; Liu et al., 2019). Intrathecal dexmedetomidine was also associated with less shivering in the setting of

cesarean section and did not increase the risk of postoperative nausea and vomiting, hypotension, or bradycardia (Miao et al., 2018).

Subarachnoid use of dexmedetomidine can exert desirable effects when coupled with local anesthetics. The prolonged duration of this technique with dexmedetomidine may be useful for longer surgical procedures of the lower extremities, even procedures that are traditionally done with general anesthesia. The clinical significance of prolonged motor blockade is not discussed in the reviewed literature but should be weighed against the benefits of using dexmedetomidine as an adjunct clinically. Dexmedetomidine lowers the ED95 of bupivacaine, thus a lower dose of bupivacaine with dexmedetomidine may prove to exert less of an effect on motor blockade. This should be further explored in future research.

Intrathecal administration of dexmedetomidine has also been compared to intravenous infusion of dexmedetomidine as a supplement to intrathecal anesthesia. Intrathecal dexmedetomidine in a dose as small as 3 mcg with 2.5 ml of 0.5% bupivacaine was associated with prolonged duration of analgesia, decreased 24-hour analgesic requirements, and lower pain scores postoperatively compared to intravenous dexmedetomidine (Sharma et al., 2020). The use of intrathecal dexmedetomidine was associated with a more stable hemodynamic profile than that of intravenous dexmedetomidine, even at a relatively low dose of 0.25 mcg/kg/hour following subarachnoid block with 0.5% bupivacaine (Sudhakar et al., 2017). The use of intrathecal dexmedetomidine was not associated with increased levels of sedation compared to intravenous dexmedetomidine (Sharma et al., 2020).

Conclusion

Regional anesthesia is a mainstay in the field of anesthesia and thus, anesthesia providers must remain competent to keep up with this ever-changing discipline. The details of providing

regional anesthesia to patients are often in the hands of the anesthesia provider. A clinical dilemma that often arises is the choice of whether to add an adjunct medication to regional anesthesia and subsequently, which adjunct to add. A plethora of research exists in this realm, yet no adjunct medication holds a clear advantage over the rest. There are certain clinical aspects to each adjunct that are often useful, and when utilized appropriately, can provide desirable effects. These desirable effects might include decreased time to onset of surgical blockade, increased duration of sensory blockade, little to no effect on motor blockade duration, or decreased pain and opioid consumption postoperatively. However, the benefits of adjunct medication must be weighed against the risks and side effects associated with their use.

Dexmedetomidine is an appropriate adjunct medication in the literature, exhibiting desirable effects in regional anesthesia. These effects generally include decreased time to onset of blockade, increased duration of blockade, and decreased non-opioid and opioid consumption postoperatively. Amidst an opioid epidemic, the latter effect is particularly desirable, especially as patients are becoming acutely aware that opioid medications can lead to chemical dependency, which is a particularly undesirable outcome. Although dexmedetomidine has been shown to provide certain desirable effects, the adverse side effects it can produce must be taken into account. Most commonly these side effects include hypotension, bradycardia, and increased level of sedation or drowsiness. This side effect profile is certainly predictable and easily treatable but must be weighed in the overall risk of the procedure.

More research is certainly necessary, as dexmedetomidine use in regional anesthesia techniques is fairly novel. Because dexmedetomidine has been shown to significantly improve certain block characteristics, local anesthetic dose reduction strategies may be helpful, especially when considering neuronal damage attributable to local anesthetics. Additionally, the dosing of

dexmedetomidine is variable throughout the literature and future research could focus on optimal doses for use in regional and neuraxial anesthesia.

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