Literature Review

A Comprehensive Review of the Use of α 2 Agonists in Spinal Anesthetics

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Background: Spinal Anesthesia was the first regional anesthetic technique to be performed. It was performed by Dr. August Bier, known for the Bier block, and his colleagues on August 16, 1898. Dr. Bier opted for, what he referred to at the time as "cocainization of the spinal cord" by introducing 15 mg of cocaine intrathecally prior to the operation. The surgery was largely uneventful and painless. The patient only experienced some vomiting and a headache postoperatively. Dr. Bier's use of neuraxial anesthesia aimed to directly inject local anesthetics in and around the central nervous system (CNS) for more direct control of pain and anesthesia.

Local anesthetics were an important discovery in anesthesiology. However, since the advent of local anesthetics and spinal anesthesia as an alternative technique to general anesthesia, much has been learned about both the benefits and adverse effects of local anesthetics. It was quickly learned that use of local anesthetics would be limited by their potential for life-threatening toxic effects. For this reason, there was a push towards development of novel local anesthetics that had a larger therapeutic window with less likelihood of serious side effects. In addition to developing newer local anesthetics, the idea of adding adjuvants provided an opportunity to potentially limit the life-threatening events. These adjuvants would include medications such as epinephrine and alpha-2 agonists, such as clonidine and dexmedetomidine. Other adjuvants include opioids, glucocorticoids, and mineralocorticoids.

Objectives: In this review, we will delve further into the indications, contraindications, uses, mechanisms, and future of spinal anesthesia and its adjuvants.

Study Design: A literature review of recent publications in the field of alpha 2 agonists used in spinal anesthetics was carried out from 2015 to present day. Consensus opinions were formulated in various areas.

Setting: This literature review was carried out at various medical universities throughout the nation and Europe.

Limitations: As research has only just begun in this field data is limited at this time.

Conclusions: The use of spinal anesthesia provides a reliable dermatome blockade to facilitate many different surgical procedures. The combination of local anesthetics with opioid medications within the subarachnoid space has been the standard of care. Adjuvant medications like alpha 2 agonists may play a significant role in prolonging spinal blockade as well as limiting cardiovascular complications such as hypotension and bradycardia. The use of alpha 2 agonists instead of opioid medications intrathecally decreases pruritus and delayed respiratory depression. Animal models have demonstrated the synergistic effects of utilizing alpha 2 agonists with opioids in the subarachnoid space. The addition of clonidine to fentanyl and local anesthetic demonstrated a shorter time to neural blockade, but no significant change in duration of the spinal. Interestingly alpha 2 agonists with local anesthetics showed increase block duration compared to opioid with local anesthetics. Further human trials need to be undertaken to analyze the effectiveness of alpha 2 agonists in the intrathecal space, but preliminary data does indicate it is an exemplary alternative to opioids.

Key words: alpha 2 agonist, spinal anesthetics, obstetrics

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Spinal Anesthesia was the first regional anesthetic technique to be performed (1). It was performed by Dr. August Bier, known for the Bier block, and his colleagues on August 16, 1898. Dr. Bier opted for what he referred to at the time as "cocainization of the spinal cord" by introducing 15 mg of cocaine intrathecally prior to the operation. The surgery was largely uneventful and painless. The patient only experienced some vomiting and a headache postoperatively. Dr. Bier's use of neuraxial anesthesia aimed to directly inject local anesthetics in and around the central nervous system for more direct control of pain and anesthesia.

Local anesthetics were an important discovery in anesthesiology. However, since the advent of local anesthetics and spinal anesthesia as an alternative technique to general anesthesia, much has been learned about both the benefits and adverse effects of local anesthetics. It was quickly learned that use of local anesthetics would be limited by their potential for life-threatening toxic effects (2). For this reason, there was a push toward development of novel local anesthetics that had a larger therapeutic window with less likelihood of serious side effects. In addition to developing newer local anesthetics, the idea of adding adjuvants provided an opportunity to potentially limit the life-threatening events (3). These adjuvants would include medications such as epinephrine and α-2 agonists, such as clonidine and dexmedetomidine as well as other adjuvants include opioids, glucocorticoids, and mineralocorticoids (3).

Objectives

In this review, we will delve further into the indications, contraindications, uses, mechanisms, and future of spinal anesthesia and its adjuvants.

Contraindications

Contraindications to spinal and epidural anesthesia must be taken very seriously as they can result in permanent physical harm and death. Absolute contraindications to any neuraxial anesthesia include patient refusal, elevated intracranial pressure, intracranial mass, and infection at the site of the procedure because it can have an elevated risk of meningitis (1).

Relative contraindications are to be taken just as seriously; the provider is to clinically assess the risks and benefits of proceeding with a neuraxial anesthetic. These relative contraindications are preexisting neurological disease, such as multiple sclerosis, those at risk for hypotension, thrombocytopenia, mitral stenosis, aortic stenosis, and left ventricular outflow obstruction (4). Hypotension is a risk factor for patients who are dehydrated, hypovolemic, greater than 50 years old, going for emergency surgery, obese, have a history of chronic alcohol use, and/or chronic hypertensives (4). Thrombocytopenia and other coagulopathies may have an increased risk of developing an epidural hematoma (4). There is no definitive platelet count that is used for spinal anesthesia. It is left up to the provider to assess the patient's situation and make a clinical judgment based on the clinical presentation of the patient.

Complications

Common complications of neuraxial anesthesia include post dural puncture headache, nausea, vomiting, hypotension, total spinal anesthesia or high spinal, neurological injury, spinal hematoma, arachnoiditis, transient neurological syndrome mostly with lidocaine, and low-frequency hearing loss (1). These complications most often occur from epidural or spinal hematomas, which in general occur very infrequently (1:150,000 and 1:200,000 respectively) (1). These must be explained to the patient prior to the procedure.

Clinical Significance

The advent of neuraxial anesthesia has presented many benefits for patients who are either in the perioperative period or require pain management. It has offered an alternative for patients who cannot tolerate general anesthesia. Mothers undergoing cesarean delivery can undergo surgery solely under spinal anesthesia and are able to immediately establish mother and newborn bonding (5). Neuraxial anesthesia can also be a great adjunct to general anesthesia, reducing the need for opioids and other systemic anesthetics. This can enhance the recovery period of patients and help them participate in physical therapy sooner and achieve earlier recovery of bowel functions (5).

Current Common Practice

As discussed, spinal anesthesia has uses in many different patient scenarios. It has offered an alternative method that can be the sole anesthetic or an adjunct to other forms of anesthesia. The latter approach is an important multimodal approach to pain management which can help reduce or even eliminate the need for systemic medications, such as opioids, given their known adverse side effects (4). Spinal anesthesia and epidural anesthesia, referred to as a combined

spinal-epidural can be used with an epidural catheter to provide access for redosing as needed for patients undergoing more lengthy procedures (4). Different methods of delivery are available and each depends on the safety and needs of the patient.

Advancements continue to be made regarding neuraxial anesthesia. These developments include spinal therapeutics using agents that are yet to be studied in depth, such as cholinesterase inhibition and adenosine agonists (5). Other more innovative approaches include intrathecal targeting methodologies, including gene-based approaches that utilize viral vectors, plasmids, and interfering RNAs, which will require further large randomized clinical trials before they can be considered for wide clinical use (5). Spinal anesthesia and neuraxial anesthesia have proven to be important milestones in anesthetic care for patients. Neuraxial anesthesia continues to evolve and grow with new experimental methods and techniques.

Opioids: Pharmacodynamics & Pharmacokinetics

Spinal anesthesia involves the injection of local anesthetics into the intrathecal or subarachnoid space. Opioids are utilized as adjuncts to local anesthetics to produce a better quality block or prolonged postoperative analgesia. Opioids can also be injected intrathecally in procedures that involve general anesthesia for both intraoperative and postoperative pain control. Intrathecal delivery of opioids produces analgesia with little to no effect on light touch or proprioception (6). The advantages of combining opioids, specifically fentanyl, with local anesthetics includes improved quality of analgesia, prolonged duration of anesthesia, and reduced postoperative period analgesic use in patients undergoing appendectomy (7). Diamorphine is an effective commonly used opioid additive utilized in the United States and United Kingdom in spinal anesthetics (7). Additionally, sufentanil combined with intrathecal lidocaine (15 mg) versus lidocaine alone (50 mg) provided excellent intraoperative anesthesia with reduced time to ambulation following outpatient rectal surgery (8).

Opioids bind to opioid receptors (μ, κ, and δ) which are found both at presynaptic and postsynaptic sites throughout various organ systems. In particular, opioid receptors are located in the central nervous system including the brain stem, thalamus, cortex and substantia gelatinosa (lamina II) of the dorsal horn of the spinal cord (9). Most of the clinically relevant effects of opioids are mediated by μ receptors, including analgesia, respiratory depression, pruritus, sedation, euphoria, and constipation (10). After binding to the μ opioid receptor, a G-protein-linked signal transduction pathway is activated which leads to inhibition of adenylate cyclase, antagonist activity at voltage gated calcium channels, and agonist activity at potassium channels. The net result is hyperpolarization of the membrane, inhibition of neurotransmitter release (acetylcholine, dopamine, norepinephrine, and substance P), subsequent dampening of second order neuron excitation, and analgesia produced by way of inhibited ascending nociceptive signals (9-11).

The diffusion distance for opioids from the site of intrathecal administration to μ receptors within the dorsal horn of the spinal cord is extremely short (12). As such, the mechanism by which intrathecal opioids produce analgesia is at least in part a spinal mechanism. However, the degree to which supraspinal analgesia, as well as side effects, occur is mediated by diffusion into the plasma for lipophilic opioids and rostral spread for hydrophilic opioids (13). Thus, the pharmacokinetics of intrathecal opioids follows a multicompartment model. The most clinically relevant aspect of intrathecal opioids is the degree of lipophilicity (14). Fentanyl is highly lipophilic and is characterized by a fast onset of action (10-20 minutes) and short duration of action (approximately one hour). Morphine is highly hydrophilic and is characterized by a slow onset of action (approximately one hour) and long duration of action (up to 24 hours) (15). Moreover, the lipophilicity of an opioid accounts for its lack of spinal selectively.

Lipophilic opioids have a greater affinity for white matter, which is largely composed of myelin and has a lipid content of approximately 80%, whereas hydrophobic opioids have a greater affinity for gray matter (12,13). Sufentanil, which has an even greater degree of lipophilicity than fentanyl (sufentanil octanol/water distribution coefficient of 1,727 compared to 816 for fentanyl) rapidly diffuses through white matter and into nonneuronal tissues, including plasma (16). This redistribution accounts for both short duration as well as the capacity to reach the brainstem and cause dose-dependent systemic issues, such as respiratory depression. Intrathecal morphine is more spinal selective with greater bioavailability, however due to its prolonged duration within the cerebrospinal fluid can spread rostrally, creating a more widespread analgesic effect as well as systemic effects (12). Additionally, there are marked differences in how hydrophilic character influences potency when comparing systemic versus intrathecal administration.

The dose potency of systemic administration increases as hydrophobic character increases. However, with intrathecal administration of opioids, dose potency decreases as hydrophobic character increases (12). More specifically, sufentanil is approximately 1,000 times more potent than morphine when administered intravenously. Compared to intrathecal administration, sufentanil is only 10 times more potent than morphine (13).

Opioid metabolism primarily takes place in the liver via a phase one cytochrome P450 (CYP) pathway, phase 2 conjugation, or a combination of both phase one and phase 2. The metabolism of synthetic opioids differs, with alfentanil and fentanyl predominantly metabolized by CYP450 3A 3/4 (17,18). Sufentanil is metabolized by a combination of N-dealkylation/O methylation/aromatic hydroxylation (19). Morphine undergoes hepatic glucuronidation to the inactive morphine-3-glucuronide. After metabolism by the liver to hydrophilic end products, opioids are excreted in the urine (20). Remifentanil is metabolized by widely distributed plasma esterases which leads to rapid clearance and a short duration of action (21).

Opioid Side Effects

Opioids administered in the intrathecal or epidural compartments, while limited to the perioperative setting, are not without their own risks. Side effects are dose-dependent, and include nausea, urinary retention, respiratory depression, delirium, sexual dysfunction, ocular dysfunction, cardiac dysrhythmia, neurotoxicity, and anaphylaxis (22).

Respiratory depression

Respiratory depression is a well-established side effect of spinal anesthesia, split into early (< 2 hours) and delayed presentations (> 2 hours) (23). Early respiratory depression is generally associated with lipophilic opioids, while delayed respiratory depression is associated with hydrophilic morphine. There are multiple risk factors that increase a patient's risk of spinal anesthesia-related respiratory depression, most notably sleep apnea (23). Although previously thought to be of greater risk, more recent data suggest that the risk of respiratory depression with use of neuraxial morphine versus intravenous morphine when dose-adjusted is similar (23). Of note, epidural morphine carries the added risk of entering the subdural and intrathecal compartments, increasing the risk of oversedation and the need for airway support and reversal agents (23).

Delirium

The elderly, as defined as ≥ 65 years old, are particularly susceptible to developing postoperative delirium. One of the major contributing factors of the development of postoperative delirium is the optimization of postoperative pain control. It was previously thought that intrathecal opioids would result in a larger risk of the development of postoperative delirium; however, studies show no significant differences in the incidence of postoperative delirium when comparing intravenous morphine to intravenous morphine administered in conjunction with intrathecal preoperative morphine (24).

α *2 Agonists*

In order to prolong anesthetic blockages and decrease postoperative pain, α agonists can be added to anesthetic agents (25-27). Adrenaline and phenylephrine were traditionally used in these settings, but recently clonidine, an α 2 agonist, has emerged as similarly effective to prolong anesthesia and attenuate pain in neuraxial analgesia. Stimulation of α 2 reduces sympathetic stimulation and improves vagal tone. Specifically, in the setting of pain management, α 2 stimulation leads to activation of dorsal horn receptors in the spinal cord, resulting in potassium and calcium channel blockage (28). This ultimately inhibits nociceptive receptors and substance P, producing the majority of the resulting analgesic effect.

α 2 agonists can be used in a neuraxial setting and have proven efficacious in various animal pain models. Specifically, dexmedetomidine, clonidine, and xylazine are α 2 agonists used in humans and animals, though clonidine is the only α 2 agonist currently FDA approved for epidural analgesia in humans (29). The use of α 2 agonists is limited by their central sympatholytic effects. Similar to opioids, sedation is a significant side effect that limits the use of α 2 agonists. It is theorized that separating the analgesic effects from sedation is possible if future drugs target certain subclasses of α 2 receptors, specifically α 2A and α 2C (29).

Dexmedetomidine

Dexmedetomidine has emerged recently as a potential alternative to clonidine as an off-label intrathecal pain medication, as it has an 8-times greater affinity for α 2 receptors, specifically the α 2A and α 2C receptors, when compared to clonidine (30). Studies have shown a 10-fold increase in α 2 receptor affinity by dexmedetomidine compared to clonidine (30). Dex-

medetomidine is the D-enantiomer of medetomidine, an extremely potent and full agonist of the α 2 receptor (31). Though this implies more potent sedation when compared to clonidine, dexmedetomidine-based sedation puts a patient in a physiologic sleep-wake state that makes them easily rousable, thus minimizing respiratory depression (31). Additionally, dexmedetomidine is reversible upon administration of an α 2 antagonist, atipamezole, making it a more favorable option over other α 2 agonists (30). Side effects are limited to ones of hemodynamic instability, but given dexmedetomidine's ability to dampen the stress response, hemodynamic changes during surgical procedures are minimal (31). There is concern that the analgesic effects of dexmedetomidine are inadequate to withstand heat or electrical stimuli. In a trial comparing dexmedetomidine against remifentanil, dexmedetomidine was less analgesic than remifentanil (31). Current US Food and Drug Administration-approved application of dexmedetomidine is limited to intravenous sedation in a patient for less than 24 hours, but there is evidence for its efficacious use beyond 24 hours and via different routes of administration (30). More research is required to determine if there is a significant opioid-sparing effect in the use of dexmedetomidine.

Comparison of α 2 Agonists Versus Opioids as Local Anesthetic Adjuncts

Local anesthetic adjuncts function to prolong the duration of anesthetic effects, potentiate the quality of the anesthetic, shorten onset time of anesthetic agents, and decrease the required dose of anesthetic agent needed to achieve analgesia. Adjuvants are successfully applied when they achieve the aforementioned effects while mitigating unwanted side effects such as pruritis, shivering, bradycardia, hypotension, decreased respiratory drive, and postoperative nausea and vomiting. Opioids (fentanyl, morphine, and sufentanil) and α 2 agonists (dexmedetomidine and clonidine) are commonly used as anesthetic adjuvants in neuraxial and peripheral nerve blocks. To compare the effectiveness of α 2 agonists (clonidine and dexmedetomidine) versus opioids as local anesthetic adjuncts, their effect on anesthetic agents' time to onset of action, duration of action, degree of postoperative analgesia, and side effect profiles will be reviewed.

In a meta-analysis by Sun et al (32), comparing the effect of fentanyl versus dexmedetomidine as adjuvants in adult patients receiving spinal anesthesia for either lower abdominal or lower limb surgery, it was found that the groups receiving either bupivacaine-based or ropivacaine-based spinal anesthesia with dexmedetomidine as an adjuvant reported prolonged duration of sensory block, a longer pain-free period, and less postoperative analgesic requirements. Of note, the incidence of pruritis was significantly increased in patients receiving fentanyl when compared to the dexmedetomidine group; there was not a statistically significant difference in the incidence of hypotension and bradycardia between the 2 groups (32). Other commonly encountered side effects of opioid adjuvants are nausea, vomiting, shivering, and respiratory depression, which the meta-analysis revealed no statistical significance between the fentanyl and dexmedetomidine groups (32).

Paramasivan et al (33) conducted a meta-analysis comprising 24 studies with a total of 1,460 patients that assessed the effect of intrathecal dexmedetomidine on postoperative pain via postoperative pain scores. Their study showed that at 6 and 12 hours postoperative, there were no statistically significant differences in pain scores between the dexmedetomidine and placebo groups; however, at 24 hours postoperative the group that received dexmedetomidine intrathecally reported a mean Visual Analog Scale (VAS) score of one fewer point out of a maximum of 10 points (95% CI -1.9 to 0.20, P = 0.02) (33). This has significant implications because longer postoperative pain control will consequently decrease the need to attenuate pain with the use of opioids during the recovery period. The loss of pinprick sensation at the T10 dermatome was used to assess time to sensory blockade while a Bromage Scale score of 3 was used to assess onset of motor blockade. Patients in the dexmedetomidine group reported a faster onset of sensory and motor blockade. The significantly longer duration of sensory and motor blockades, which were assessed by regression of the sensory blockade to the S1 levels, and a Bromage score of 0 respectively, shows that dexmedetomidine enhances the effect of the anesthetic drugs when used as an adjuvant for neuraxial blocks (33).

Similarly, clonidine as an adjuvant for intrathecal anesthesia with bupivacaine has been studied to investigate the effect of 50 μg of clonidine on the duration of sensory and motor spinal block, as well as the risk of adverse events. In a study conducted by Singh et al (34), comprising 100 patients undergoing lower abdominal surgery, patients received either bupivacaine (0.5%, 3 mL) with normal saline (0.33 mL) or bupivacaine (0.5%, 3 mL) with 50 μg clonidine (0.33 mL).

There was a statistically significant increase in the mean duration of sensory blockade, mean duration of motor blockade, and the duration of postoperative analgesia in the clonidine group. The duration of sensory blockade in the clonidine group was 280.80 ± 66.88 minutes versus 183.60 ± 77.06 minutes in the control group as measured by return of perception of a cold ice pack. The duration of motor blockade in the clonidine group 295.20 ± 81.17 minutes versus 190.80 ± 86.94 minutes in the control group as measured by the modified Bromage Score. The duration of postoperative analgesia in the clonidine group was 551.06 ± 133.64 minutes versus 254.80 ± 84.19 minutes in the control group as obtained by the11-point VAS. Another significant finding from this study was that there was no statistically significant increase in the risk of adverse hemodynamic events in patients who received clonidine with bupivacaine intrathecally, deeming it a safe adjuvant to prolong anesthetic effects (34).

The use of local anesthetics to deliver spinal anesthesia in parturient women prior to undergoing cesarean delivery can possibly yield adverse effects of hypotension, shivering, pruritis, nausea, and vomiting for the mother, and acidosis in neonates due to the increased dose requirement needed to achieve analgesia. The addition of an adjuvant that enhances analgesia and allows for a decrease in the required dose of anesthetic is essential in lowering the risk of adverse effects in patients receiving intrathecal anesthesia for cesarean delivery. Increased doses of local anesthetics to prolong anesthetic time without the use of an adjuvant can result in decreased circulation and compromise the central nervous system and cause cardiotoxicity (35). Intrathecal dexmedetomidine as an adjuvant to intrathecal local anesthetic is favorable as it results in prolonged duration of sensory blockade and motor block, thus requiring lowered doses of local anesthetics (35,36).

A review by Shen et al (36), assessing 10 trials with a total of 970 patients receiving lumbar spinal anesthesia preoperatively, with a range of 2.5 to 7.5 μg dexmedetomidine as the adjuvant for cesarean deliveries, revealed that intrathecal dexmedetomidine markedly reduced the onset time of sensory block (standardized mean difference (SMD), -1.50, 95% CI -2.15 to 0.85, I^2: 92%), reduced the onset of motor block (SMD -0.77, 95% CI -1.50 to 0.49, I^2: 60%) prolonged sensory block duration time (SMD, 2.02, 95% CI 1.29 to 2.74, I^2:93%), and prolonged motor block duration time (SMD 1.90, 95% CI 1.07 to 2.74, I^2: 94%)(5).

The incidence of postoperative shivering is significant in patients who receive spinal anesthesia. A notable outcome of the studies included in the meta-analyses conducted by Sun et al (35) and Shen et al (36) was the reduced incidence of shivering in patients who received dexmedetomidine as an adjuvant versus placebo, which was defined as no use as an adjuvant. The proposed mechanism for reduced shivering with dexmedetomidine is due to its direct effect on α 2 adrenergic receptors in the hypothalamus and its effect on decreasing the perioperative stress-induced sympathetic response. Dexmedetomidine also did not increase the risk of maternal hypotension and bradycardia (relative risk, 0.88; 95% CI, 0.71 to 1.08; P = 0.22; I^2 = 22%) (36).

Another concern of using intrathecal dexmedetomidine as an adjuvant is the risk of adverse effects to the fetus. Potential risks to the fetus include decreased respiratory drive, hypotension, bradycardia, and sedation, all of which could result in decreased Apgar scores and fetal acidosis. The short-term outcome of using dexmedetomidine on neonates was assessed via the use of Apgar scores and umbilical blood pH in studies in which low-dose dexmedetomidine adjuvant, defined as ≤ 25μg, was used intrathecally. Neonates exposed to intrathecal anesthesia with dexmedetomidine versus a placebo adjuvant showed no statistically significant difference in Apgar scores or blood pH between the 2 groups, thus indicating that dexmedetomidine use did not have adverse effects on neonates (35,36).

The use of morphine as an adjuvant to intrathecal anesthesia for cesarean deliveries is widely used to provide postoperative analgesia, a shortened time to onset of sensory and motor block, as well as for prolonging the duration of action, hence it is necessary to compare how dexmedetomidine provides the same effects while maintaining a comparatively optimal side effect profile. In a study conducted by Xiaofei et al (37), intrathecal administration of 2 mL of 0.5% bupivacaine containing 100 μg morphine (n = 40) was compared to 2 mL of 0.5% bupivacaine containing 5 μg of dexmedetomidine and only 2 mL of 0.5% bupivacaine (n = 40) to determine primary outcomes of time to peak sensory block and motor block, and secondary outcomes of side effects to the parturients and neonates (37). Results showed that the group receiving dexmedetomidine and morphine had improved anesthesia effects and increased duration of anesthesia with no statistically significant difference between the 2 groups (37). The most significant outcome of this study that favors the use of dexmedetomidine

over morphine as an adjuvant is that the group receiving dexmedetomidine experienced fewer incidences of shivering, nausea, and vomiting, and entirely eliminated the presence of pruritis versus the morphine group (37). As far as the incidence of bradycardia and hypotension being a concern with the administration of dexmedetomidine, when maintained at doses of 5 μg, intrathecal dexmedetomidine has no significant effect on blood pressure or heart rate.

A meta-analysis investigating the impact of clonidine as an adjuvant for neuraxial anesthesia in women undergoing caesarean delivery across 18 studies showed that clonidine administered intrathecally decreased 24 hour morphine consumption by 3.9 mg (95% CI: -7.0 mg to -1.5 mg, I^2: 0%); this was even more significant when clonidine was administered via the epidural route, resulting in decreased morphine consumption by 18.9 mg (95% CI: -34.8 mg to -0.3 mg, I^2: 79%) when compared with placebo. The use of clonidine also resulted in an increased time to first analgesic request by 150 minutes (95% CI: 110 minutes to 190minutes, I^2: 97%) when compared with the placebo group (38). However, a key adverse impact seen with the use of clonidine as an adjuvant was the increased incidence of intraoperative hypotension, which was 49% (260/525) in the clonidine groups versus 33% (114/342) in the control group (38). Another unwanted effect seen with neuraxial clonidine was increased intraoperative sedation (odds ration 95% = 2.355, 1.016 to 5.459, I^2: 23%), which consequently delays the enhanced recovery protocols employed in current obstetric anesthesia. While prolonged sedation results in delayed onset of breastfeeding, skin-to-skin contact, and discharge from the postanesthesia care unit, the use of neuraxial clonidine had no adverse effects on the neonate umbilical artery pH or Apgar scores (38). Respiratory depression was not an adverse effect of clonidine administration in any of the studies included in the meta-analysis. However, further research is needed to investigate the effect of clonidine on postoperative sedation, intraoperative bradycardia, intraoperative and postoperative nausea and vomiting, and pruritis as the results from the studies included were inconclusive due to a wide 95% CI (38).

Comparison of α 2 Agonists Combined With Opioids as Local Anesthetic Adjuncts

Adjuvants to local anesthesia, such as opioids and alpha 2-agonists, have been shown to provide quality analgesia, both chronically as well as in the perioperative setting. While local anesthesia, such as bupivacaine, has long been considered the standard of care, various additives have been evaluated in recent literature in a quest for an ideal adjuvant to limit the amount of intrathecally administered local anesthesia (39,40). This evaluation has been primarily to ensure a higher quality of analgesia, with longer duration and minimal side effects, such as hypotension, bradycardia, pruritis, respiratory depression, nausea, vomiting, and urinary retention (40). A synergistic effect of α 2 agonists (clonidine, dexmedetomidine) with opioids (fentanyl) has been demonstrated in animal models, however, the current data are unclear on the significance of this effect. These adjuvants, alone, are known to reduce anesthetic requirements while providing dose-dependent sedation, pain relief, and anxiolysis (39,40). Their combination has recently been studied in the literature to determine an optimal option for quality analgesia with fewer side effects.

In Paech et al (41), 101 patients were split into 4 study groups; each group received a unique intrathecal injection for combined spinal/epidural analgesia during labor. These formulas were composed of bupivacaine and fentanyl plus either saline or increasing levels of clonidine. Data showed that there was no significant difference in pain scores, as measured by a 100-mm VAS, among the 4 groups from time 0 to 120 minutes. Additionally, there was no difference in the duration of analgesia among the group subsets. In this experiment, clonidine, added to a spinal opioid and local anesthetic, did not ultimately affect the quality of pain relief or the incidence or severity of side effects, such as pruritis, nausea, sedation, or patient satisfaction, while in certain animal models and clinical trials, it was shown to have synergistic effects (41).

Mohamed et al (42) found comparable data when comparing the use of dexmedetomidine alone to its use in combination with fentanyl as an adjunct to local anesthesia. They studied a subset of patients undergoing major abdominal surgery, and specifically looked at the safety and analgesic efficacy of these solutions. Mohamed et al used 3 groups of patients. A control group received hyperbaric bupivacaine and saline, one received bupivacaine with dexmedetomidine, and one received bupivacaine, dexmedetomidine, and fentanyl. The fentanyl group showed significant hemodynamic variability intraoperatively, specifically a drop in heart rate from 20 minutes until 120 minutes. However, postoperatively, there was no significant change among groups when looking at hemodynamics ($P < .05$). Mean

VAS scores were evaluated postoperatively to evaluate analgesia quality and duration. While the dexmedetomidine group alone and the added fentanyl group both showed significant analgesia properties as compared to the control, there was no significant difference between the 2 groups. Additionally, in the postanesthesia care unit, mean consumption of intravenous tramadol rescue analgesia was analyzed. The requirements were decreased in the dexmedetomidine (142.85 mg ± 13.04 mg) and opioid (131.25 mg ± 11.96 mg) groups compared to control (310.00 mg ± 12.08mg), but again with no significant difference (42).

Success with additives has been variable, especially when looking at side effects. Singh et al (39) studied the addition of opioids to solutions of local anesthetic and clonidine, and how this would affect motor, sensory blocks, and side effects. He found that patients who received a clonidine, fentanyl, and local anesthetic solution had a shorter time of onset of sensory block, while no significant difference was found with the duration of block. Interestingly, sedation scores were higher in patients that received just clonidine at 10 minutes, 1.5 hours, and 2.5 hours. The results of their study demonstrate that the addition of clonidine to bupivacaine and fentanyl minimizes the time of onset of sensory and motor blockade, while also providing a longer duration of block (39). While studies have varied with their data, it is evident that there is no significant advantage to giving an α 2 agonist with opioid as an adjunct to local anesthetic.

Discussion

The evolving improvements in medications and technology in recent years has provided greater overlap in the fields of anesthesiology and pain medicine. In this regard, there is an overlap among acute and chronic pain management with techniques evolving that demonstrate efficacy and safety. Enhanced efficacy has been demonstrated with recent evidence to support quicker onset and longer duration with α 2 agonists for different types of anesthesia techniques, including spinal anesthesia. There is also a role for other adjuvants in the delivery of different types of anesthesia in that they provide additive and/or synergistic effects. In chronic pain management, for example, intrathecal trials with opioids are a reliable part of the algorithm leading to intrathecal pump insertion. The use of α 2 agonists may be beneficial for an intrathecal pump trial or permanent implants. The fields of acute and chronic pain continually intertwine as adjuvants used in one specialty have been utilized in the other.

Conclusion

The use of spinal anesthesia provides a reliable dermatome blockade to facilitate many different surgical procedures. The combination of local anesthetics with opioid medications within the subarachnoid space has been the standard of care. Adjuvant medications like α 2 agonists may play a significant role in prolonging spinal blockade, as well as limiting cardiovascular complications such as hypotension and bradycardia. The use of α 2 agonists instead of opioid medications intrathecally decreases pruritus and delayed respiratory depression. Animal models have demonstrated the synergistic effects of utilizing α 2 agonists with opioids in the subarachnoid space. The addition of clonidine to fentanyl and local anesthetic demonstrated a shorter time to neural blockade, but no significant change in duration of the spinal block. Interestingly, α 2 agonists with local anesthetics showed an increased block duration compared to an opioid with local anesthetics. Further human trials need to be undertaken to analyze the effectiveness of α 2 agonists in the intrathecal space, but preliminary data does indicate it is an exemplary alternative to opioids.

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