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The Effect Of Clonidine On Hyperbaric Bupivacaine And Opioid In Cesarean Section Women Under Spinal Anesthesia

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Abstract

Pain is undoubtedly one of the most undesirable outcomes associated with cesarean section in parturients. The most effective post-cesarean section pain relief option should prioritize maternal, fetal, and neonatal safety, with minimal to no medication transfer to the fetus and neonate. In obstetric anesthesia, neuraxial approaches, with the inclusion of adjuncts like clonidine for pain management may provide some additional benefits. Consequently, obstetric anesthesia practitioners have increasingly used intrathecal clonidine to alleviate post-cesarean section pain. This manuscript examines whether intrathecal clonidine, when combined with hyperbaric bupivacaine and/or opioids (fentanyl and/or preservative-free morphine), has a sustained analgesic effect in parturients following cesarean delivery under spinal anesthesia. A literature review of relevant articles was conducted. Results of the literature review suggested that the addition of intrathecal clonidine to bupivacaine reduced the 24-hour morphine consumption and prolonged the subarachnoid block duration in cesarean section patients.

Keywords: clonidine, neuraxial anesthesia, post-operative pain, cesarean section.

The Effect of Clonidine on Hyperbaric Bupivacaine and Opioid in Cesarean Section Women under Spinal Anesthesia

Adequate postoperative pain management is crucial to the recovery of parturients submitting themselves to cesarean section. Allen et al. (2018) asserted that a pregnant woman's primary concern and fear during and after cesarean delivery is pain. Although there is an increasing body of research evaluating how best to manage the pain of cesarean delivery, there is no benchmark criteria. However, neuraxial adjuncts like clonidine have gained traction in the obstetric anesthesia world to prolong analgesia during elective cesarean (Pandya, 2010).

Most obstetric anesthesia providers would agree that optimal pain management cannot be ignored in parturients undergoing cesarean section, as most parturients lack the awareness of post-cesarean section pain-relieving methods (Alshahrani, 2019). Carvalho and Butwick (2017) argued strongly that suboptimal pain management in parturients undergoing cesarean section leads to increased opioid consumption and delayed maternal recovery. They suggest employing a multimodal pain management technique is the best method for managing post-cesarean section pain. In this regard, researchers continue to investigate several options to improve pain relief for women undergoing cesarean delivery.

Talwar and Chopra (2014) and other investigators conducted studies to examine the prolonged analgesic outcome of adding clonidine to a bupivacaine plus fentanyl mixture or bupivacaine alone for spinal anesthesia during gynecological surgeries. Opponents of intraspinal clonidine are concerned about its efficacy and safety as a means of providing parturients with a better pain experience during and after cesarean delivery. Nonetheless, advocates of adjuvant neuraxial clonidine therapy believe that this pharmacological intervention is one of the best practices for managing labor and cesarean section pain. Wong (2009) concluded that intrathecal

analgesia is the most successful means of pain relief for the parturient and the only practice which provides cesarean section pain relief without posing any untoward risk to the mother and the fetus including maternal and fetal sedation.

The Pharmacology of Neuraxial Clonidine

Clonidine was first discovered in 1962 as a nasal decongestant (Whizar-Lugo et al., 2014). For many decades, clonidine has been used to treat hypertension, alcohol, opioid, and benzodiazepine withdrawal, and to induce sedation (Giovannitti et al., 2015). Clonidine is an imidazole compound (Nguyen el al., 2017). It is the first discovered member of the alpha adrenoreceptor agonists with a principal selectivity for alpha-2 over alpha-1 receptor agonism. Clonidine's sedative and analgesia properties have gained popularity in anesthesiology as it is used in addition to local anesthetics and opioids to induce and prolong analgesia during regional anesthesia techniques (Nguyen et al., 2017).

Mechanism of Action of clonidine

Nguyen et al. (2017) corroborated the primary site of action of clonidine is the brainstem. Clonidine activates alpha-2 adrenoreceptors in the brain activating gamma-aminobutyric acid (GABA). This results in reduced sympathetic nervous system activity, which is exhibited primarily as a reduction in blood pressure and heart rate. The activation of each adrenoreceptor produces different effects. The stimulation of alpha-2a adrenoreceptors by clonidine produces sedation, analgesia, and sympatholytic effects. Clonidine produces its anti-shivering and vasoconstriction mechanisms by the stimulation of alpha-2b adrenoreceptor subtypes (Nguyen et al., 2017).

Pharmacokinetics and Pharmacodynamics

The accepted routes of clonidine administration in clinical literature are intravenous, oral, neuraxial, and transdermal. Clonidine is a lipophilic drug that is highly absorbable. When given epidurally, clonidine circulates via epidural veins into the blood where it produces its pharmacological effect. Oral clonidine is quickly absorbed reaching effective blood levels in approximately one and one-half hour (Nguyen et al., 2017). Half of the drug is degraded in the liver into inactive metabolites and the other half is excreted unchanged by the kidneys. The elimination half-life for intrathecal clonidine is one to one-half hours. This is notably shorter than its intravenous route of approximately twenty-three hours (Fernandes, 2018).

The removal of clonidine from the human body after its administration is dependent upon the individual age and comorbidities. Nguyen et al., (2017) asserted that clonidine's removal will reach eight times that of the adult after a child's first birth date.

Anesthetic Considerations of Clonidine

Nguyen et al. (2017) acknowledged that intrathecal clonidine reduces sympathetic nerve activity. It also regulates A-delta and C-fibers of the nervous system. These events produced sedative and analgesic effects. Clonidine can also cause a decrease in the flow of blood and oxygen to the brain (Nguyen et al., 2017). Clonidine manifests its cardiovascular effect by modulating alpha-2 adrenoreceptors located in the medulla oblongata motor center. This event results in a decrease in sympathetic nerve activity, which leads to a surge in vagal nerve stimulation. The resultant effect is seen as reducing the heart rate and blood pressure, causing peripheral vasodilatation, decreasing cardiac output and systemic vascular resistance without affecting cardiac contractility (Nguyen et al., 2017).

Clonidine does not induce respiratory depression or potentiate respiratory depression caused by opioids. In fact, it can be used to reverse muscle stiffness caused by opioids (Fernandes, 2018). Clonidine does not affect respiratory rate, partial pressure of arterial carbon dioxide ($PaCO_2$) or oxygen saturation pressure (SpO_2) (Nguyen et al., 2017). As an alpha-2 adrenergic drug, clonidine blocks the release of vasopressin and its action on the kidneys. Through this mechanism, clonidine induces diuresis and exerts its natriuretic effects without opioid-induced urinary retention (Fernandes, 2018). Clonidine also reduces renal vascular resistance, plasma catecholamine concentrations, and plasma renin activity (Nguyen et al, 2017). As a potent sympatholytic drug, clonidine reduces the release of norepinephrine, epinephrine, corticotropin, and hydrocortisone. Clonidine also acts directly on the cells of the pancreas. This causes the pancreas to secrete less insulin, which leads to higher blood sugar levels. However, this hyperglycemic effect is not clinically significant (Fernandes, 2018).

Adverse Effects of Clonidine

Clonidine has been reported as a relatively safe drug in animal studies. However, Nguyen et al. (2017) reported adverse effects in humans such as sleepiness, xerostomia, slow heart rate, postural hypotension, erectile dysfunction, and sedation. When clonidine is stopped abruptly, a hypertensive crisis could ensue. The authors did not document any adverse effects of clonidine on reasoning or intellectual abilities. Although a safe drug profile for clonidine has been proposed in some patient populations, including those with reduced blood volume and heart rate, research has failed to conclude whether these adverse effects are absolute or relative contraindications.

Use of Clonidine in Anesthesia

Anesthesia providers administer clonidine via oral, intravenous, intradermal, and intrathecal routes. Oral clonidine in the preoperative area is used to reduce salivation and induce sedation without severe changes in blood pressure. Typical dosing is 2 to 4 micrograms per kilogram of body weight. When clonidine is administered by oral or intravenous routes, studies have shown that it reduces postoperative analgesic use and prolongs pain control in the first 24 hours (Fernandes, 2018). Clonidine also reduces the MAC requirements for volatile anesthetics (Nguyen et al., 2017).

Neuraxial use of Clonidine in Anesthesia

According to Fernandes (2018), clonidine produced prolonged quality of analgesia, and the quality of motor blockade at a dose of 2 to 4 micrograms per kilogram body weight when given by the epidural route. Similarly, clinicians have used clonidine in a continuous patient-controlled epidural infusion at a dose of 30 micrograms per hour without untoward side effects such as low blood pressure and fetal and maternal bradycardia. Clonidine also extends analgesia without hemodynamic instability in children when used for epidural sacral blocks. In chronic pain management, Fernandes reported that clonidine at a dose of 10-50 micrograms per hour effectively treats chronic neoplastic pain in patients unresponsive to opioids. In addition, 1-2 microgram per kilogram body weight of intrathecal clonidine has the most pronounced effect on the duration of analgesia. The addition of clonidine to opioids and local anesthetics lengthens subarachnoid block time without inducing side effects associated with opioids, such as urinary retention and respiratory depression.

Fernandes also reported several studies demonstrating the benefits of intrathecal clonidine in obstetrics, including its long-term effects on sensory and motor block, and reduction

of postoperative opioid consumption. Although the synergistic mechanism between clonidine and opioids is unknown, Whizar-Lugo et al. (2014) asserted that when combined intrathecally with opioids, clonidine enhances the effect of opioids and local anesthetic to prolong postoperative analgesia. Khezri et al. (2014) have documented that clonidine modulates its pain relief by activating alpha-2 adrenoreceptors receptors in the spinal cord. Activation of neurons in the sympathetic nervous system decreases pain transmission by inhibiting the transmission of neurons. By these mechanisms, clonidine produces pain relief via a non-opioid pathway. Khezri et al. maintained that clonidine is lipophilic and very potent when given neuraxially compared to systemically, where it may produce adverse effects in pregnant women, such as sedation. However, clonidine does not potentiate opioid-induced respiratory depression when given by the neuraxial route (Schug et al., 2006).

According to Schug et al. (2006), clonidine produces hypotension and bradycardia at a greater rate when it is given intrathecally comparative to when it is given by other routes. These effects are more pronounced in patients with a history of hypertension. Schug et al. also noticed that these dose-related hemodynamic changes are more pronounced when clonidine is given by intrathecal than the epidural route. Advocates for use of intrathecal clonidine argued that when administered intrathecally, it does not cross the placenta barrier into fetal circulation. Hence, clonidine does not have any effects on the fetus or Apgar score (Khezri et al., 2014).

Method

Database search of Cochrane Library, PubMed, EBSCOhost, Google Scholar, and Embase was conducted using search terms: “clonidine and neuraxial anesthesia,” “spinal anesthesia,” “post-operative pain” and “cesarean section.” The generated articles were reviewed for their quality and relevance. In determining the quality of evidence used, the Center for

Evidence-based Medicine's (CEBM) 2016 quality of evidence guidelines was used. Literature reviewed prioritized systematic reviews or meta-analysis of cross-sectional studies and randomized controlled trials. The author of this manuscript independently reviewed the articles according to the following criteria: The importance of the study to the explored question and the level of evidence. The primary outcome was the first need for pain medication out of total pain medication consumed by subjects with 24 hours immediately after surgery. In addition, the secondary results, such as the time it took for the sensory and motor blocks to set in and their total duration, were included.

Synthesis of Results

Khezri et al. (2014) compared the outcome of adding clonidine to 10 mg of preservative free hyperbaric bupivacaine to bupivacaine with 25 micrograms of fentanyl solution in a randomized controlled trial among 90 American Society of Anesthesiologist (ASA) physical status I-II pregnant women ages 18 to 45 for elective cesarean delivery under subarachnoid block. The investigators excluded subjects with kidney diseases, hepatic disorders, cardiovascular diseases, any allergy to bupivacaine, fentanyl, or clonidine, and opioid-dependent patients. The investigators randomized the study participants into three groups of 30 subjects each and blinded the study by using an equal number of drug syringes labeled A, B, and C. The content of the drugs in the syringes was not known to the anesthesia providers who administered the treatments.

The researchers administered preservative-free bupivacaine-fentanyl mixture in the ratio of 10 mg to 75 micrograms respectively to one group, while the other group received preservative-free bupivacaine-fentanyl mixture in the ratio of 10 mg to 25 micrograms. Subjects in the control group received a distilled water mixture. All treatments were administered

intrathecally. The investigators concluded that adding 75 micrograms of clonidine to bupivacaine in a subarachnoid block for cesarean delivery prolonged the time it took for the subjects to demand a breakthrough pain compared to when fentanyl alone was used. The researchers also reported a decreased pain medication consumption in the first twenty-four hours post-cesarean delivery in the clonidine group compared to the non-clonidine group.

Khezri et al. (2014) controlled confounding variables that might affect the study's outcome as follows: Each patient received 5-7 mL/kg of intravenous lactated ringers before the subarachnoid block. This was done to decrease the hypotension produced by sympathectomy. A Quincke needle was used aseptically to enter the L4-L5 space through a midline approach for each treatment while all patients were in a seated position. This study's primary outcomes evaluated the time for the subjects to demand a breakthrough pain medication and the total consumption of pain medication twenty-four hours post-cesarean delivery. The effect of the treatment on both sensory and motor block duration was measured as well as the effects on the fetus and the mother such as non-reassuring fetal heart tone measured by tocometry, maternal hypotension, and sedation. The investigators used the verbal rating scale (VRS) where zero is no pain and 10 is the worst pain reported by the subjects to assess post-cesarean delivery pain (Khezri et al.2014). Although the time to onset of motor block was not significantly different among clonidine and fentanyl group in the study by Khezri et al., the duration of motor and sensory block was significantly longer in the clonidine group compared with the fentanyl group ($p<0.001$). When compared to the placebo (211 minutes) and fentanyl (192 minutes) groups, the clonidine group had a longer duration of anesthesia (275 minutes).

To further investigate the benefits of subarachnoid clonidine, Allen et al. (2018) performed a meta-analysis review of 394 randomized control trials in which they analyzed 18 of

the articles for the effect of intraoperative neuraxial clonidine on postoperative analgesia in cesarean delivery under spinal anesthesia. Subjects in 12 to 14 of the studies reviewed received 30 to 800 micrograms of subarachnoid clonidine in addition to a bupivacaine fentanyl mixture.

Unlike Khezri et al. (2014), Allen et al. analyzed articles based on the intravenous (IV) morphine consumption twenty-four hours after cesarean delivery under spinal anesthesia, and the time to demand pain medication post cesarean delivery. The authors also reviewed the use of additional pain medication during the cesarean delivery and the reported post-cesarean delivery pain by the subjects. Allen et al. explained that when their evaluation was constrained to studies where clonidine was given by the subarachnoid means, the twenty-four-hour morphine intake was reduced by 4.3 mg. Sixteen studies also reported a prolonged time to participants first demanded of pain medication after cesarean section under spinal in which clonidine was added to the bupivacaine mixture. Overall, the researchers concluded after their examination of eighteen studies that neuraxial clonidine added to a bupivacaine/fentanyl mixture extended the time it took for cesarean delivery parturients to demand pain medication after cesarean delivery by an average of 135 minutes. In addition to this, when clonidine was added to morphine intrathecally, it enhanced the time it took the cesarean delivery women to request pain medication by 126 minutes when compared to the control group. (Allen et al. 2018).

In a comparative research, Owen et al., (2000) also evaluated the impact of intrathecal clonidine on a bupivacaine plus fentanyl mixture for labor pain. Their study randomized forty-five parturients to receive intrathecal doses of different dextrose-containing solutions for combined spinal-epidural technique. The medications were injected into specific lumbar interspaces and their outcomes were measured. The investigators measured the subject's baseline verbal pain scores on a 10-point scale where zero means no pain and ten means the worst pain.

The investigators established that intrathecal clonidine does not significantly affect pain scores in the first one hour but significantly prolongs analgesia by 165 minutes when added to fentanyl and bupivacaine versus 90 minutes when only fentanyl and bupivacaine is used.

The researchers also systematically assessed levels of both sensory and motor block, and the side effects of the medications administered. This research indirectly determined the outcome of clonidine on bupivacaine and opioids in cesarean section patients, and demonstrated that when given by the intrathecal route, clonidine does have a prolonged analgesic effect regardless of the population in which it is used.

In another review, Crespo et al. (2017) analyzed 12 out of 201 articles for the consequence of subarachnoid clonidine in parturients undergoing cesarean delivery. The authors searched databases for research that used clonidine as an adjunct to neuraxial anesthesia in cesarean delivery. Crespo et al. determined that clonidine lengthens sensory block by 128 minutes and motor block by 44 minutes. In addition, the investigators reported that intrathecal clonidine did not produce any fetal and maternal untoward outcomes. Crespo et al. documented that neonatal Apgar scores at one or five minutes were not affected.

Contrary to Crespo et al., Ghosh et al. (2020) conducted a double-blinded study in which they randomized 90 elective cesarean delivery parturients into three groups and reported a much different result in favor of morphine. The subjects reported significantly more pain when clonidine was used intrathecally than morphine on a postoperative visual analog scale (VAS) scale. The time required for the subjects to demand additional pain medication was longer in the morphine group compared to the clonidine group. The total dose of additional pain medication administered in the subjects who received morphine was less in the 24 hours post-cesarean

delivery. This effect was attributed to the intrathecal clonidine added to the administered treatment.

Nonetheless, Kallapur et al. (2017) conducted another double-blinded randomized controlled trial to examine the effectiveness of adding intrathecal clonidine to bupivacaine in elective cesarean delivery parturients. The authors used computer software to randomize 105 American Society of Anesthesiologist physical status I-II parturients into three equal groups. The authors added clonidine to the treatment mixture in one of the three groups and measured the time it took for the sensory and motor block to set. The investigators also measured the duration of pain relief to determine how effective intrathecal clonidine is in cesarean delivery women in prolonging the duration of analgesia. Kallapur et al. reported that the time it took for both sensory and motor block to set was faster when clonidine was added to the bupivacaine mixture versus control. The authors reported that the group of patients in whom clonidine was used in their subarachnoid block did not request any pain medication until after 480 minutes compared to the non-clonidine group of patients who requested pain medication in 180 minutes.

Kothari et al. (2011), in their assessment of the effectiveness of intrathecal clonidine as a pain management modality in cesarean delivery women, randomized 210 American Society of Anesthesiologist physical status I-II parturients at term for emergent cesarean delivery into three equal groups. The patients in one of the groups between the three received a clonidine-fentanyl-bupivacaine mixture, and the other two did not. Unlike other studies reviewed, these authors controlled confounding variables that might have affected the validity of the results by having one anesthetist assess the quality of sensory blockade, and one surgeon assess the degree of motor blockade. In addition, the frequency of sensory pain reported during the cesarean delivery was assessed as reported by the patient. The authors concluded that the post-cesarean section

pain relief was prolonged (246 minutes) with the addition of clonidine to bupivacaine compared to the non-clonidine group (146 minutes).

Li et al. (2014) also randomized 84 patients into four groups to assess the quality of analgesia when clonidine was added to a mixture of intrathecal bupivacaine treatment for elective cesarean delivery women. The authors measured outcomes, including the time it took for the block to set, the level of the block as measured by dermatomal response to pinprick, the block duration, and the duration of pain control. Despite the small sample size, the authors concluded that the time it took for both the sensory and motor block to set was faster in the population of patients that received clonidine as part of their treatment compared to the group with only bupivacaine-fentanyl. The investigators also found the duration of pain relief to be comparably higher to the bupivacaine-dexmedetomidine group when compared to the bupivacaine-clonidine group. The time for the motor block to recede was higher in the group with bupivacaine-dexmedetomidine. These findings are comparable with other studies which demonstrated that clonidine, like other alpha-2 adrenoreceptors, extends the duration of pain relief and motor blockade in cesarean delivery women under spinal anesthesia.

Contrasted to the study of Owen et al. (2000), Pandey et al. (2018) conducted another comparative double-blinded study in which they examined the outcome of adding clonidine to bupivacaine intrathecally in a dose-dependent manner among three patient groups. Pandey et al. concluded that, on average, the time it took for the sensory block to set in was longer among the patient group in which clonidine was added, much like the duration of block compared to the non-clonidine group. The authors also noticed that the length of the motor blockade was prolonged in the group that received clonidine compared to the group that did not. While this study was conducted in orthopedic lower limb surgical patients and could not be generalized to

the obstetric population, the overall mechanism of intrathecal clonidine and its effect on prolonging analgesia seem to be the same for both populations.

Much like other studies in the obstetric population in which clonidine was used to prolong analgesia, Pandey et al. (2018) concluded that the duration of motor and sensory block was longer among the group in which clonidine was added to the treatment than the group in which clonidine was not added. Pain control duration was also longer among the group of patients that received clonidine compared to those that did not receive clonidine. In a double-blinded randomized trial, Paech et al. (2004) randomized 232 healthy parturients for elective cesarean section in which subarachnoid block was performed into six groups and measured the effectiveness of intrathecal clonidine's analgesic property. The authors measured the time it took the patient to active the patient-controlled analgesia (PCA) pump and the amount of morphine that was administered post-cesarean delivery. An important finding of this research was that intrathecal clonidine prolonged the duration of analgesia. One pitfall of this study is that it causes vomiting in the cesarean delivery women post-operatively claims Paech et al.

Tuijl et al. (2006) investigated the benefits of intrathecal clonidine to bupivacaine on pain control after cesarean delivery and how much morphine women used after cesarean delivery. The researchers randomized 106 American Society of Anesthesiologist physical status I-II patients for elective cesarean section in which subarachnoid block was used as the primary anesthesia. The authors measured the amount of morphine consumed in the 24 hours after surgery and concluded that the non-clonidine-supplemented group consumed more morphine than the clonidine-supplemented group.

Discussion

The results of the meta-analysis by Allen et al. (2018) highlighted some important key findings. Allen et al. documented that the neuraxial administration of clonidine reduced the amount of morphine consumed in the twenty-four hours after cesarean delivery and prolonged the time it took cesarean delivery women to ask for pain medication. Despite the safety and efficacy concerns raised by the opponents of neuraxial clonidine, Allen et al. confirmed that neuraxial clonidine did not negatively affect neonatal outcomes by Apgar scores and does not affect maternal outcomes, hence, neuraxial clonidine is safe for use in the pregnant population. Even though Allen et al.'s meta-analysis is a multinational study, including the USA, one shortfall of all the studies reviewed in this manuscript is that all the included studies only investigated healthy pregnant populations and could not be generalized to AS III and IV patients with significant comorbidities. The studies also failed to outline the ideal dose of clonidine to mitigate the desired pain effect in the subjects studied. The biophysical parameters of the subjects analyzed in the study were similar, including age, weight, and age. The study participants' average weight was less than 100 kg. Is it possible to duplicate these findings in severely obese pregnant women? This is a topic that requires more investigation. To remove procedure-specific biases, the procedures were conducted in stages by the same anesthetic providers.

Despite the functional outcomes of the studies reported in this manuscript, the small sample size and the subjects' homogeneity decreased the generalizability and power of most of the studies (Polit and Beck, 2012, p. 237). However, recruiting for human subject research can be very difficult, and for this matter, these results can be accepted by the obstetric anesthesia

community. Most of the studies were focused on maternal pain relief without monitoring fetal well-being except for neonatal Apgar scores after the fetus is delivered.

Ghosh et al., (2020) and Crespo et al., (2017) reported that neuraxial clonidine increased sedation and can produce hypotension and bradycardia but as documented in all the studies reviewed, neuraxial clonidine has no adverse fetal outcomes based on APGAR score measurements at one and five minutes. Crespo et al.'s study evaluated different dose response effect of intrathecal clonidine by performing a stratified analysis and dividing the study subjects into three groups to receive low dose (15–49 micrograms), intermediate dose (50–75 micrograms), and high dose (76–150 micrograms) and suggested that the average duration of analgesia increased from 176minutes to 462 minutes when a low dose clonidine is compared to high dose. Motor block was also increased from 14minutes to 120 minutes when the dose of clonidine changed from 15-49 micrograms verses 76-150 micrograms. Despite these benefits, the small number of studies used by Crespo et al. in the meta-analysis could be a limitation and produces a type 2 error for some of its outcomes. Another limitation of Crespo et al.'s study was the exclusion of parturients less than 18 years of age which may prevent the use of these finding to the adolescent population.

Khezri et al. (2014) study concluded that the administration of intrathecal clonidine 75 micrograms with bupivacaine prolonged intraoperative anesthesia and the time to first analgesic request after cesarean delivery compared to fentanyl but caused transient hypotension and increased vasopressor requirement. Khezri et al. reported one controversial finding that clonidine at doses between 37.5 and 150 micrograms failed to cause a significant decrease in blood pressure when added to a high dose of bupivacaine (18 mg). One important finding by Khezri et al. is that intrathecal clonidine does not prevent post-operative shivering in the

parturient but when given intravenously, clonidine is effective in preventing post-operative shivering. The study did not mention the most effective dose to achieve these effects.

Conclusion

This manuscript examines the synergistic benefits of intrathecal clonidine in cesarean section. After review of the literature, the findings suggest that when clonidine is added to bupivacaine and fentanyl intrathecally, it prolongs pain relief, sensory and motor block, and decreases the 24-hour intravenous morphine consumption in pregnant women undergoing elective cesarean section. Singh et al. (2014) concluded that adding 50 micrograms of intrathecal clonidine to bupivacaine leads to increased pain relief and subarachnoid block duration. Anesthesia providers should be mindful of the hypotensive side effect and be ready to treat it.

One important implication for clonidine use reported by Crespo et al., (2017) is the significantly increased levels of sedation observed in the subjects. Crespo et al.'s analysis suggest that there is no increased risk of pruritus, post operative nausea and vomiting or hypotension, even in the cases where higher intrathecal doses of clonidine was used.

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