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COMPARATIVE STUDY OF DIFFERENT DOSES OF CLONIDINE AS AN ADJUVANT WITH ISOBARIC LEVOBUPIVACAINE FOR SPINAL ANESTHESIA: A LITERATURE REVIEW

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Abstract: The need to find the lowest possible effective dose of clonidine to avoid its known side effects such as hypotension, bradycardia and sedation motivated us to design the present study. We compared different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia in patients undergoing cesarean section in order to find the lowest possible effective dose. Spinal anesthesia is a safe, reliable and inexpensive technique, with the advantage of providing surgical anesthesia and prolonged postoperative pain relief, in addition to attenuating autonomic, somatic and endocrine responses to surgical stimulation.
Keywords: Clonidine; levobupivacaine; spinal anesthesia; surgical anesthesia; anesthesiology

INTRODUCTION

Spinal anesthesia is a safe, reliable and inexpensive technique, with the advantage of providing surgical anesthesia and prolonged postoperative pain relief, in addition to attenuating autonomic, somatic and endocrine responses to surgical stimulation (MILLER et al. 2014). In fact, nerve blocks have been used in several surgeries in the adult population as the main anesthetic technique and to improve analgesia and reduce the demand for analgesics after surgery. With the increasing use of real-time imaging (ultrasound) in operating rooms, the complications of the procedure of performing nerve blocks have dramatically decreased, while the accuracy of perineural drug deposition has increased as the spread of local anesthetics under the eye is observed. ultrasound guidance. This is even more significant for pediatric patients, as they have always been considered to be at higher risk of procedural complications such as pneumothorax, nerve injury, and arterial injury while performing a supraclavicular brachial plexus block (YANG et al. 2010).

Local anesthetics alone may not provide sufficient duration or quality of postoperative analgesia.

Addition of adjuvants has been found to provide remarkably prolonged analgesia, but may be associated with certain adverse effects (SWAIN et al. 2017; MARHOFER et al. 2019). In this context, many adjuvants were added to local anesthetics, such as clonidine, dexmedetomidine, dexamethasone and fentanyl. An additive of particular interest that consistently prolongs the duration of local anesthetics is clonidine. However, at clinically studied doses of 1 μg.kg −1 and 2 μg.kg −1, the use of clonidine is associated with bradycardia, sedation and hypotension as side effects (YANG et al. 2010; WAJEKAR et al. 2016). To date, there is a paucity of studies evaluating the effect of different doses of clonidine on supraclavicular brachial plexus block in children, and there are no studies evaluating the effect of using a lower dose of 0.5 μg.kg −1 on blockade. brachial plexus block features using bupivacaine as a local anesthetic. Thus, we decided to investigate whether clonidine at a dose of 0.5 μg.kg −1 when added to bupivacaine for supraclavicular block would effectively prolong the duration of postoperative analgesia (MARHOFER et al. 2019).

For decades, lidocaine was the local anesthetic of choice for spinal anesthesia. However, its use has been limited due to the short duration of action and its implication in transient neurological symptoms and cauda equina syndrome after intrathecal injection (YANG et al. 2010). Until recently, 0.5% hyperbaric bupivacaine was the only drug used for spinal anesthesia in India after discontinuation of lidocaine. Levobupivacaine does not provide prolonged duration of postoperative analgesia; therefore, clonidine is used in combination, which has been shown to prolong postoperative analgesia,

but has produced significant perioperative hypotension and bradycardia still known. Thus, the present study was performed comparing clonidine doses comparing 15 μg and 30 μg of intrathecal clonidine together with 3 mL of 0.5% isobaric levobupivacaine.

MATERIAL AND METHODS

A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); base; Web of Science, Google Scholar. Conference abstracts/articles have been deleted from Embase. No other limits have been applied. All retrieved records were organized using Endnote citation management software version 20. For the removal of duplicates, a review software and literature review citation screening software was used.

The search strategy was designed to capture comparing intrathecal clonidine doses along with levobupivacaine. The searches were supplemented by manual searching and retrieval of any additional articles that met the eligibility criteria that were cited in our reference lists.

RESULTS

We observed that patients receiving the highest dose of clonidine (1 μg.kg −1) had significantly longer duration of analgesia, albeit with prolonged motor block and higher sedation scores compared to the group receiving 0.5 μg clonidine.kg −1 clonidine. Our review is comparable to the study by Yadava et al. with the duration of analgesia with the LC-15 clonidine group (315 min compared to the control group of 204 min) which was statistically highly significant (YADAVA et al. 2013). In the above study by Yadava et al., the local anesthetic agent used was 15 mg bupivacaine, but in our included reviews, 15 mg levobupivacaine was used.

Thakur et al. also found a statistically significant difference between the clonidine 15 mg group (223 min) and the control group (140 min) in terms of duration of analgesia (THAKUR et al. 2013). Compared to our study, the duration of analgesia in both groups was shorter, and this is due to the lower dose of bupivacaine (11 mg) used compared to our study (levobupivacaine 15 mg).

The additive effect of clonidine in the local anesthetic in upper limb surgery has been widely studied in the adult population (SINGELYN et al. 1996). In the adult population, a dose range of 30–300 μg it was used during several studies (SINGELYN et al. 1996; EL SAIED et al. 2000; HUTSCHALA et al. 2004; PÖPPING et al. 2009). Although a dose of up to 150 μg has been found to be safe and associated with minimal side effects, there is always a concern about associated hemodynamic complications (PÖPPING et al. 2009). Singelyn et al. reported that a minimal dose of 0.5 μg.kg −1 was required to produce any significant prolongation of local anesthetic block (SINGELYN et al. 1996). Further increasing the clonidine dose to 1.5 μg.kg −1 did not result in a significant benefit over that already obtained with 0.5 μg.kg −1 (SINGELYN et al. 1996).

Clonidine has been shown to be a valuable adjunct to peripheral nerve blocks when used as an additive to local anesthesia. The beneficial effect of clonidine was reported for all local anesthetics tested in a meta-analysis by Pöpping et al. concluded that the addition of clonidine to long-acting or intermediate-acting local anesthetics prolonged the duration of analgesia, along with increasing the duration of motor block (PÖPPING et al. 2009). The clonidine dose in this study ranged from 30 μg to 300 μg and side effects (hypotension and sedation) were observed with the dose above 150 μg in adult patients (PÖPPING et al. 2009).

There are few studies on the dose of clonidine that can be safely used as an adjunct to local anesthesia in supraclavicular brachial plexus block in the pediatric population. Pediatric patients are considered vulnerable to a higher rate of anesthesia-related complications, and clonidine has been associated with adverse effects such as bradycardia, hypotension and sedation, we decided to investigate whether a lower dose of 0.5 μg.kg −1 could provide post-operative analgesia. -operative compared to the commonly reported dose of 1 μg.kg −1.

There appeared to be a dose-dependent increase in the duration of motor block as well as the duration of analgesia. This may be due to the increase in potassium conductance by clonidine which blocks the conduction of A and C nerve fibers. In 2000, El Saied et al. added 150 μg of clonidine to ropivacaine for axillary block in adult patients undergoing surgery. Similar to our study, they observed an increase in analgesia duration to 828 min, whereas in the group that did not receive clonidine, analgesia lasted only 587 min (EL SAIED et al. 2000), Hutschala et al. performed a similar study using 2 μg.kg −1 clonidine (HUTSCHALA et al. 2004). They also found prolonged duration of analgesia in volunteers who received clonidine in addition to bupivacaine for brachial plexus block, but unlike our study, this study was done in adult patients. Similar findings were also reported in earlier studies by Singelyn et al., Bernard and Macaire, Iskandar et al., Iohom et al. and Duma et al (SINGELYN et al. 1996; BERNARD et al. 1999. The prolonged duration of analgesia is a benefit for surgical patients. The same cannot be said for the motor block. In addition to a delay in the recognition of a In severe nerve injury, prolonged motor block can be harmful in outpatient surgeries, as delay in mobilization is equivalent to delay in rehabilitation. Thus, considering that the difference in mean duration of analgesia was clinically irrelevant, the lesser motor block could be considered an advantage of the lowest dose of clonidine.

A very important side effect of clonidine is sedation. During our study, we did not notice significant postoperative sedation in any group. Between the two groups, the level of sedation was almost the same when assessed postoperatively. All patients were comfortable and arousable to oral commands when first assessed at 5 min and were fully awake at 10 min. This can also be due to the use of "non-opioid anesthesia" and sevoflurane, which is washed out of the blood quickly. Deeper levels of clonidine sedation only occur consistently at high doses that were not used in our study. [1] In our study, most patients had an RSS of 1-3, which is a desirable level of sedation, and none of the children were deeply sedated (RSS > 4). Therefore, at the doses used in our study, dangerous levels of sedation or respiratory depression are unlikely.

We would like to reiterate that clonidine at a dose of 0.5 and 1 μg kg −1 did not lead to any significant hemodynamic changes in our study, except for one episode of hypotension at a dose of 1 μg.kg −1 when administered perineurally and, therefore, both doses can be considered a safe adjunct to be added to local anesthetics when performing brachial plexus blocks in pediatric patients. This may be due to the lower doses of clonidine used, which were also deposited around the brachial plexus. Similar findings have also been reported by El Saied et al., Singelyn et al., Bernard and Macaire, and Murphy et al. (SINGELYN et al. 1996). However, our study was insufficient to detect any hemodynamic differences and, therefore, the use of a lower dose can be considered safer, minimally compromising the duration of postoperative analgesia.

STRENGTHS AND LIMITATIONS

The main strength of the study lies in the lack of literature on the efficacy and safety of various doses of clonidine as an adjunct to brachial plexus block in this patient population. Considering that brachial plexus block is a commonly used block for upper limb surgery in children and clonidine is a commonly used adjuvant, this study would add valuable evidence to the literature. A limitation of our study was that, although the type of surgery was similar in both groups by statistics, there would be subtle differences in the surgical procedure and the level of postoperative pain for each individual case. In addition, we did not compare WBFPS scores or total rescue analgesic consumption in the first 24 h, which would be further evidence of the analgesic efficacy of the drugs used in the study. Nonetheless,

Clonidine 1 μg.kg −1 when added as an adjunct to bupivacaine for pediatric supraclavicular brachial plexus block prolongs the duration of analgesia and motor block to a greater degree compared to the 0.5 μg.kg −1 dose. However, this was at the expense of increasing the duration of motor block and sedation. Considering the clinical equivalence of the effect, a lower dose of clonidine would be preferable to avoid the undesirable effects that may be associated with the higher dose of clonidine.

Furthermore, the limitation of the study is that we did not compare it with higher doses of clonidine in relation to sensory and motor characteristics and also to the profile of adverse effects, as studies are lacking in the literature.

DISCUSSION

We observed that patients receiving the highest dose of clonidine (1 μg.kg −1) had significantly longer duration of analgesia, albeit with prolonged motor block and higher sedation scores compared to the group receiving 0.5 μg clonidine.kg −1 clonidine. There were no significant hemodynamic changes or other adverse effects in either group.

Spinal anesthesia is a safe, reliable and low-cost technique for infraumbilical surgeries, with the advantage of providing surgical anesthesia and prolonged postoperative pain relief. It also attenuates the autonomic, somatic and endocrine responses to the surgical stimulus (MILLER et al. 2014). Until recently, 0.5% hyperbaric bupivacaine was the only drug used for spinal anesthesia after lidocaine discontinuation. Bupivacaine is available as a racemic mixture of its enantiomers, dextrobupivacaine and levobupivacaine. The D-enantiomer was found to be the cause of cardiotoxicity and levobupivacaine (S-1-butyl-2-piperidylform-2',6'-xylidide hydrochloride), the pure S (-) enantiomer, does not have the cardiotoxicity. Levobupivacaine has pharmacodynamic properties similar to racemic bupivacaine, but a documented reduction of central nervous system and cardiovascular toxicity. Traditionally, the dose of levobupivacaine used for spinal anesthesia is 15 mg. Levobupivacaine was introduced in India in 2012 and is available in 0.5% isobaric 4 mL ampoules for intrathecal use. It is known that a single injection of levobupivacaine will not produce a prolonged duration of postoperative analgesia. Thus, it will be necessary to add a drug that can prolong the analgesic effect of levobupivacaine.

Since the last decade, spinal anesthesia has been refined with the addition of adjuvants to local anesthetic agents. It has been reported that the exclusive use of local anesthetic in cesarean section undergoing spinal anesthesia does not provide sufficient anesthesia during uterine manipulation and uterine closure (HAMBER et al. 1999). Clonidine is a selective partial agonist for α-2 adrenoreceptor and

used as an adjunct to local anesthetic to prolong the duration of spinal anesthesia (KOTHARI et al. 2011). In our study, it is observed that when levobupivacaine is used with different doses of clonidine, the onset of sensory block, as well as motor block, decreases with increasing clonidine dose. The duration of sensory and motor blockade is prolonged with increasing doses of clonidine. It is also noted that the need for postoperative analgesics is early in patients in whom lower doses of clonidine were used. Similar results were observed in the study by Shah BB et al. but bupivacaine was used in this study.

The sedation score moved towards the higher site as the clonidine dose was increased. Maximum patients in group C had a sedation score of three, while in group A it was one in all patients. Study carried out by Shamad et al. 2017 also suggested that increasing clonidine dose causes more sedation, but no significant difference was found and it was also done in supraclavicular brachial plexus block.

In another study, complications such as a drop in systolic blood pressure below 80% from baseline and a drop in heart rate below 80% from baseline were more common in the group in which the highest dose of clonidine was used as an adjuvant. Our findings were also consistent with Shah BB et al 2011.

In a study by Takhur et al, it was seen that 30 mcg of clonidine was associated with more incidence of hypotension than 15 μg of clonidine. 15 mcg of clonidine added to 11 mg of hyperbaric bupivacaine provide better sensory and motor blockade for inguinal herniorrhaphy (THAKUR et al. 2013). As this study was performed in inguinal herniorrhaphy patients with hyperbaric bupivacaine, the results were not very comparable, but it was observed that with increasing clonidine dose, the incidence of hypotension increases.

It is clear in our study that levobupivacaine when used in combination with different doses of clonidine, desirable early sensory and motor blockade was found with 45 mcg of clonidine, but considering hemodynamic changes and side effects, these were significantly higher than the others. groups. With 30 mcg of clonidine, desirable sensory and motor blockade was found in a timely manner and side effects were also less. It is also verified that with 45 mcg of clonidine, the sedation score was high and it is advisable to use this dose when there is a need for sedation in this patient after weighing the risk-benefit ratio.

Thus, in this study, we observed that the addition of 30 μg of clonidine as an adjuvant to levobupivacaine produced sensory block of faster onset and prolonged duration compared to 15 μg of clonidine, without significant changes in cardiorespiratory parameters.

FINAL CONSIDERATIONS

From this study, we conclude that spinal anesthesia performed with isobaric 0.5% levobupivacaine with 30 mcg of clonidine provides better hemodynamic stability, early onset of sensory and motor block, less need for postoperative analgesia, comfortable sedation with fewer side effects neonates compared to 15 and 45 mcg of clonidine. Thus, this combination provides an effective and safe alternative to cesarean section.

The addition of 30 μg of clonidine as an adjunct to spinal block can be safely used with prolonged duration of postoperative analgesia when compared to 15 μg of clonidine. However, further comparative studies must be done with higher doses of clonidine before 30 μg of clonidine can be considered as the appropriate dose for spinal block as an adjuvant.

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