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Clonidine, Fentanyl and Bupurenorphine as an Adjuvant Agent to Bupivacaine in LSCS Cases

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Abstract

Context: Various additives are mixed with local anaesthetic agents to increase the quality of block in spinal anesthesia. We want to compare quality at low doses and effective adjuvant among them. *Aims:* Comparing the efficacy of lowest possible doses of clonidine, fentanyl and buprenorphine with minimal side effects by evaluating onset and duration of sensory and motor block, when added as adjuvants to bupivacaine in patients posted for caesarean section under spinal anaesthesia. *Settings and Design:* Prospective randomized and comparative study of 60 ASA I and II patients undergoing LSCS under spinal anaesthesia. *Methods and Material*: Patients were randomly allotted into 3 groups(n=20). Group BC received 1.8ml of 0.5% injection hyperbaric bupivacaine with 30 µg (0.2ml) of Clonidine. Group BF received 1.8ml of 0.5% injection hyperbaric bupivacaine with 20µg (0.2ml) of fentanyl. Group BB received 1.8ml of 0.5% injection hyperbaric bupivacaine with 60µg (0.2ml) of buprenorphine. *Statistical Analysis Used:* For categorical data chi-square test and continuous data was compared using ANNOVA test. *Results:* The onset of motor blockade was faster in Clonidine group. The duration of block and post-operative analgesia were prolonged in BC when compared to BB and BF ($P < 0.001$). No significant difference noted in the onset time of sensory block. Clonidine 30µg is optimal low dose for LSCS cases without causing much hemodynamic variation and sedation. *Conclusions:* Intrathecal Clonidin 30µg is an effective spinal adjuvant when compared to 20µg fentanyl or buprenorphine 60µg in LSCS patients with better haemodynamic stability, no sedation with nil side effects.

Keywords: Fentanyl; Buprenorphine; Clonidine; LSCS; Subarachnoid Block.

Introduction

Subarachnoid block is the preferred procedure for elective LSCS. Due to limited duration of action of local anesthetics, opioids were commonly added to prolong post-operative analgesia but nausea, vomiting, urinary retention and delayed respiratory depression are the undesirable effects of narcotics as additives. Due to the above reason other drugs have been tried as adjuvants. Clonidine, a selective partial α_2 -adrenergic agonist, is being extensively studied as an adjuvant to intrathecal local anaesthetics and has proven to be a potent analgesic free of opioid-related side effects [1]. It increases both sensory and motor blockade of local anesthetics [2] . Intrathecal

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clonidine has been used as an adjuvant to local anaesthetics in various surgical procedures without any clinically significant side effects [3,4]. Many studies have been conducted on a wide range of doses of clonidine from 15ug to high doses of 150ug [3,4,5,6]. This study was conducted to compare the effectualness of lowest possible doses of clonidine, fentanyl and buprenorphine with minimal side effects by evaluating quality of sensory and motor blockade when added as adjuvants to bupivacaine in patients posted for caesarean section under spinal anaesthesia.

Materials and Methods

Following ethical committee approval, patients were explained regarding the study. Written, informed consent was taken from all patients.

60 patients of ASA I and II undergoing elective LSCS were considered for the study. This is a prospective, randomized and double blinded study.

Exclusion Criteria

Patient's refusal, drug allergy, coagulopathy, cardiac problems, raised intra ocular pressure, bronchial asthma or any contra indications to spinal anaesthesia, placenta previa, abruption placenta, pre-eclampsia and eclampsia.

60 women of age 20-30 yrs with ASA status I and II who were posted for elective LSCS, were randomly allocated in three groups.

Group BC received (1.8ml of 0.5% injection hyper baric Bupivacaine with 30µg (0.2ml) a total volume of 2ml.

Group BF received (1.8ml of 0.5% injection hyper basic Bupivacaine with 20µg (0.2ml) a total volume of 2ml.

Group BB received (1.8ml of 0.5% injection hyperbaric Bupivacaine with 60µg of buprenorphine (0.2ml) a total volume of 2ml.

In Operation theatre pulse rate, blood pressure, respiratory rate were recorded before and during spinal anaesthesia. Pre operatively 6hrs fasting was confirmed. Using 18G intravenous cannula was inserted and patient was pre-loaded with Ringer Lactate solution 15ml/kg minimum of 500ml and premedicated with Inj.Ranitidine 50mg IV and Inj. Metoclopramide 10mg IV before proceeding with the subarachnoid block.

Under all aseptic conditions with the patient in left lateral position, subarachnoid block was performed and after free flow of CSF drug solution was injected with 25G spinal needle in L_3 – L4spaces with midline approach. Immediately the patient was turned supine and a lumbar-pelvic wedge positioned under the right posterior-superior iliac crest for 15 degree left uterine tilt to prevent the aortocaval compression causing hypotension.

All patients received supplementation of O_2 (4L/min) via Hudson's mask.

Monitoring

Intraoperatively pulse rate, respiratory rate, blood pressure and oxygen saturation monitoring were recorded every 2mins for first 20min, then every 10mins for remaining intra operative period. In post-operative period vitals were monitored every 30mins until patient complained of pain. Occurrence of side effects likepruritus, nausea, vomiting, shivering were noted.

Sensory Block Assessment

Sensory block is assessed by pinprick method using hypodermic needle. The onset of analgesia was defined as time period between injection of drug into subarachnoid space to loss of pinprick at T12. Time taken for achieving highest level of sensory blockade(T4) is assessed by pinprick in midclavicular line every minute till the level is stable for 2 sequent tests. Similarly time for sensory regression (from T4 to L1) is noted.

Motor Block Assessment

The time from administration of drug in subarachnoid space till the inability of the patient to move hip, knee and feet was defined as onset of motor blockade. The extend of motor blockade was assessed by using Bromage scale(Table 1). Duration of motor

Table 1: Bromage Scale

Grade	Definition
Grade 0	No motor block
Grade 1	Inability to raise extended leg; able to move Knees and feet
Grade 2	inability to flex knee
Grade 3	unable to move Hip, Knee and Feet

Table 2: The Wilson Sedation Score

Score 1	Fully awake and oriented
Score 2	Drowsy
Score 3	Eyes closed but arousable to command
Score 4	Eyes closed but arousable to mild physical stimulation (earlobe tug)
Score 5	Eyes closed but un arousable to mild physical stimulation

Table 3: Demographic profile of three groups with mean SD value

Variable	Group BF	Group BB	Group BC
Number of patients	20	20	20
Age	25 ± 3.1	26 ± 1.25	25 ± 2.15
Weight(kg)	58 ± 4.1	57 ±4.5	57 ± 3.5
Height (inches)	63 ± 1.1	63 ± 1.35	64 ± 1.2
Intra thecal injection to delivery time(min)	15 ± 1.25	16 ± 1.75	15 ± 4.55
Surgical time (min)	47 ± 3.6	47 ± 6.6	46 ± 6.75

Table 4: Characteristics of sensory and motor block

Variable	Group BF	Group BB	Group BC
Highest sensory level	T_4	T_4	T_4
Time taken for highest sensory levels (mins)	7.96 ± 1.1	7.95 ± 1.25	7.71 ± 2.1
Time for sensory regression to L_1 from highest sensory level (mins)`	134 ± 41	220 ± 54	284 ± 67
Onset of grade III motor block (mins)	3.46 ± 4.5	4.76 ± 5.1	2.46 ± 3.1
Duration of motor block (min)	144.5 ± 8.21	210 ± 63	244.5 ± 82.1
Duration of analgesia (min)	180.85	284 ± 15.33	343.14 ± 6.76

blockade was considered from time of injection to complete recovery from block Bromage grade 0.

Baby condition was evaluated by applying neonatal APGAR score at 1 minute and 5 minute.

Wilson sedation Score (Table 2) was used for assessing intraoperative sedation.

The Wilson Sedation Score

Patients were evaluated for pain postoperatively with Visual analogue scale (VAS). For VAS less than 4 no analgesics were pescribed. From 5 to 44mm oral analgesics in the form of tablet diclofenac was suggested and for cases more than 45mm intravenous tramadol 50mg was given slowly.

Statistical Analysis

As our study has categorical independent variable more than 2 values, chi square test and one-way ANOVA were used for data analysis.P value less than 0.05 was considered to be significant.

Results

There was no statistical difference among the groups with respect to demographic parameters like age, weight and height .There is also no difference among the three groups in intrathecal injection to delivery time and surgical time as shown in Table 3.

Table 4, describes the effects of the three adjuvants on the different parameters of the block .

There was no difference statistically among the three groups in time required for the onset of sensory analgesia, although Clonidine group had fastest onset. The highest level of the block T4, was comparable in all the three groups. The mean time required to reach the peak level is lowest in clonidine group, fentanyl group intermediately and buprenorphine group taking longest time to attain peak level($p< 0.001$). The onset time of motor block is fastest in BC group. Duration of sensory and motor block and duration of analgesia were longest in clonidine group being statistically significant .

The duration of post-operative analgesia was 343.14 ± 6.76 mins in clonidine group, 284 ± 15.33mins in buprenorphine group and about 180mins in fentanyl group.

Nausea and vomiting were seen in 4 patients in fentanyl group and 6 patients in buprenorphine group as compared to none in Group BC. Shivering was observed in 3 patients in fentanyl group and 4 patients in buprenorphine group. Mild pruritus was observed in 6 patients in BB and 3 patients in BF and

none in BC group. Hypotension was observed in 4 patients in BF, 5 patients in BB and 8 patients in BC. Injection Ephedrine was used in 5 patients in BC, 3 patients in BB, 2 patients in BF group and in rest of them fluid replacement was sufficient in correcting

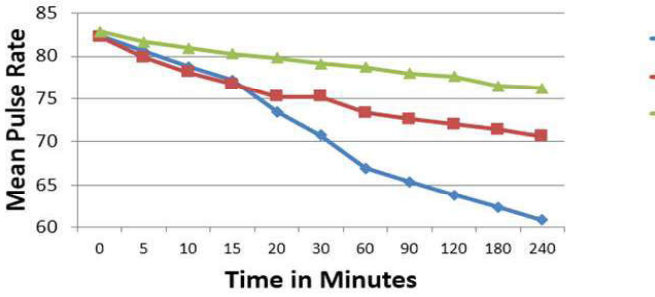

Fig. 1: Variations in Pulse Rate

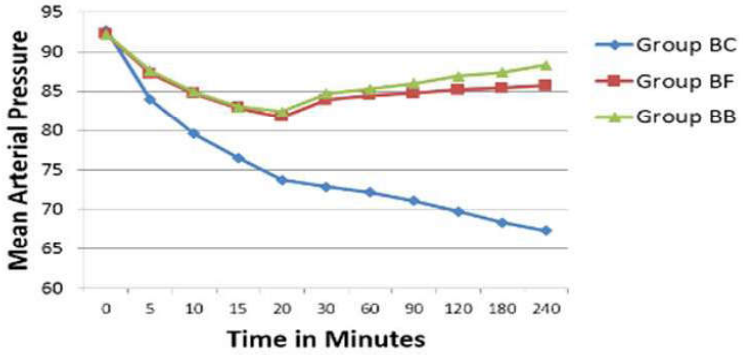

Fig. 2: Variation in mean Arterial Pressure

hypotension. In BC group heart rate was between 60 to 65 bpm , where as in BF and BB group it was above 70 bpm. Injection atropine was not required in any patients. None of the patients had sedation.

Discussion

The search for safer regional procedure with reduction of LA dose by addition of adjuvants seems to be endless. The results of our present study have established that at low doses, clonidine as an adjuvant produced better anesthetic and analgesic effects with minimal side effects when compared to fentanyl and buprenorphine when added to bupivacaine for LSCS cases. Shah Bhavini Bhushan et al [7] conducted a study on different doses of clonidine 0f 15 µg, 30µg, and 60µg and concluded that 3 groups were comparable with respect to onset, peak sensory level, motor block and overall hemodynamic stability, but they have observed dose dependent variability in duration of analgesia and sedation .Similar findings were observed in the randomized trials conducted by Elia N et al [8]. So we have opted 30µg of clonidine in our study, as it has minimal sedation.

Reuben et al [9] used different doses (5, 10, 20, 40, 50µg) of fentanyl in their study and found that even at low doses of 20µg of fentanyl in combination of 0.5 % of bupivacaine gave good amount of analgesia. So, we have used 25µg of fentanyl in our study.

Buprenorphine is an agonist - antagonist opioid with high affinity to both µ and kappa opiate receptors. We choosed 75 ug because at higher intrathecal doses itis associated with significant side effects like nausea, vomiting and pruritus as stated by KorulaS et al[10] in their comparative study of intrathecal and epidural buprenorphine using combined spinal-epidural technique for caesarean section, where they have used 150ug of intrathecal drug.

60 patients of ASA I and II patients posted for elective caesarean section were randomized into 3 equal groups Group BC Clonidine, Group BF Fentanyl, and Group BB Buprenorphine. Patients in all 3 groups were comparable regarding age, weight, height and duration of surgery.

Effect on Sensory and Motor Blockade

In the present study the mean time of onset of sensory blockade and peak level of analgesia were similar in all 3 groups. The addition of adjuvant did not alter the onset of sensory blockade or height of blockade, as supported by Singh et al [11] and Strebel et al [12]. They found that addition of fentanyl to hyperbaric bupivacaine and Clonidine to isobaric bupivacaine in their studies respectively did not alter the onset of sensory block and maximum level of block.

The clonidine group has highest sensory retrogression time to L1 of 284±67 minutes when compared to fentanyl and buprenorphine group. Similarly , time required for first rescue analgesia was also significant (p<.001) being longest in group BC 343.14±6.76 min) and lowest in group BF (180.85±7.30 min). Comparable observations

are noted in the study conducted by Krishna kumar Srinivasagam et al [13] where they have used 50 ug of clonidine, 25 μg fentanyl and 75 μg buprenorphine.

The onset and duration of motor blockade were statistically significant in all the 3 groups (p <.001). The motor block onset time of buprenorphine 4.76±5.1 mins was comparable to onset time of 4.5±2.1mins achieved with 60μg of buprenorphine in a study done by Gupta M et al [14]. Also duration of motor block (210±63 min) was on a par with duration of 205.7±63.0 minutes in this study. Intrathecal fentanyl does not prolong duration of motor blockade as demonstrated in the study conducted by Singh et al [11]. On other hand , clonidine prolonged the motor block duration as found in studies of Elia et al [8] and Jain et al [15].

Side Effects

Side effects observed were nausea, vomiting, pruritus, shivering and hypotension. No patients had respiratory depression and sedation at these low doses. Fentanyl is a synthetic opioid and is a strong agonist at μ receptors whereas .buprenorphine is a long-acting, lipid soluble, mixed agonist-antagonist opioid. Buprenorphine is a thebaine derivative with a partial agonist activity at the ì-opioid receptor. Adverse effects from neuraxially administered opioids are potentially due to the cephalad spread of opioid in the CSF or via systemic absorption from the epidural space which can lead to similar adverse effects observed following parenteral administration.

Intrathecal and hydrophilic opioids are more likely to cause adverse effects secondary to cephalad migration, while epidural and lipophilic opioids are more likely to cause central effects after systemic absorption. Most side effects are dose related and are due to opioid receptor interactions.

The incidence of nausea and vomiting associated with neuraxial opioids is reported as being between 20-50%. Nausea and vomiting following the administration of subarachnoid opioids is due to their interaction with opioid receptors of chemoreceptor trigger zone of fourth ventricle. Similar to the findings in the study conducted by Capogna et al [16], buprenorphine produces dose dependent pain free interval, but the most common side effect associated with it is nausea and vomiting. It was present in 6 patients in buprenorphine group, 4 patients in fentanyl group and none in Group BC.

Pruritus was seen in both the opioid groups and none in clonidine group. Sergio DB [17] stated that pruritus was the main side effect of use of intrathecal opioids. But pruritus was of short duration , mild in intensity and no treatment was needed for it. Agrawal A et al [18] also noted pruritus as main side effect of intrathecal opioids which is usually localized to the face, neck and thorax. The mechanism for pruritus is not fully understood but is thought to be mediated by cephalad migration of opioid which binds to opioid receptors in the trigeminal nucleus. Clonidine is a selective partial agonist for alpha-2 adrenergic receptors; the analgesic effect following its intrathecal administration is mediated spinally through the activation of postsynaptic alpha-2 receptors in substantiage-latinosa of the spinal cord [19,20]. However, higher doses of clonidine have been reported to cause important decreases in arterial pressure and marked sedation, as found in the studies conducted by Filos KS et al [21] and Pan PM et al [22]. Therefore we have selected a lower dose of 30μg of clonidine for the study.

Although MAP was lower in the BC group when compared to group BF and BB, this apparently was not considered clinically important, as the mean doses of ephedrine used did not differ between 3 groups. Furthermore, the average MAP did not decrease >20% from baseline. I. van Tuijlet al [23] also had similar findings in the study conducted by them using intrathecal clonidine. No respiratory depression was observed in any of the group. When compared to fentanyl and buprenorphine group, clonidine group has low VAS scores which was supported by the studies of Jain et al [15] and Grandhe et al [24]. Due to lower dose of clonidine sedation was not observed in our study when compared to the study conducted by Krishnakumar Srinivasagamet al [13], where they have used 50 μg of clonidine.

Key Messages

To compare onset and duration of sensory and motor block, hemodynamics along with analgesia in post-operative period in LSCS patients receiving subarachnoid block with low doses of adjuvants which includes clonidine, fentanyl and buprenorphine. 30μg clonidine was an attractive choice with good quality of block with nil adverse effects.

Conclusion

Low dose clonidine of 30μg compared to low doses of fentanyl and buprenorphine when added to

bupivacaine has better sensory and motor blockade with longer duration of post-operative analgesia with no sedation, though greater fall in blood pressure and heart rate there was hemodynamic stability.

Respiratory depression was not seen at these low doses of opioids but patients had undesirable effects like nausea, pruritus, shivering, etc. Thus 30μg of clonidine is the optimal drug for better blockade, longer duration of post-operative analgesia with no undesirable effects and sedation.

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