

COMPARISON OF INTRATHECAL CLONIDINE AND HYPERBARIC BUPIVACAINE ADMINISTERED AS PREMIXED FORM OR SEQUENTIALLY FOR CEASAREAN SECTION- A RANDOMIZED CONTROLLED STUDY

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ABSTRACT

BACKGROUND: Spinal anesthesia is the technique of choice for lower segment caesarean section (LSCS) as general anesthesia has several limitations in parturients. Administration of clonidine premixed with local anesthetic was found to be less effective than when administered in a sequential manner. This study has been designed to compare the impact of low dose clonidine as adjuvant to 0.5% Bupivacaine for spinal anesthesia in a premixed form versus sequentially administered form. Various other factors like intraoperative hemodynamic fluctuations, motor effects, duration of postoperative analgesia and possible side effects are studied.

MATERIALS AND METHODS: The study group comprised of 60 term-parturient women posted for elective LSCS. This is a prospective, comparative study between equal sized groups using an open protocol design. Group A received 2ml 0.5% hyperbaric Bupivacaine + 30µg of clonidine as a mixture intrathecally and Group B received 2ml 0.5% Bupivacaine followed by 30 µg of clonidine in sequential manner.

RESULTS: Addition of clonidine either in premixed form or sequential form with hyperbaric bupivacaine intrathecally prolonged the duration of analgesia. Prolongation was significantly extended in the sequential group, thereby reducing postoperative analgesic requirements. The time to two segment regression and motor regression was significantly prolonged by the sequential addition of clonidine. There was a significant difference in the onset of motor blockade with sequential clonidine.

CONCLUSIONS: Sequential technique hastens the onset of complete sensory and motor block, enhances the duration of sensory and motor block also, the postoperative analgesia without much hemodynamic adverse effects.

KEY-WORDS: Intrathecal Clonidine, Bupivacaine, postoperative analgesia. drreddymadhavi@gmail.com

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INTRODUCTION

Neuraxial anesthesia is now the preferred technique for lower segment caesarean sections. Even when a long acting local

anesthetic like bupivacaine is used, the duration of postoperative analgesia is not adequate ending up in the early analgesic intervention. Even when a long acting local anesthetic like bupivacaine is used, the

duration of spinal anesthesia is shorter and higher doses of analgesics are required in the postoperative period. Several intrathecal additives were tried to prolong analgesia after surgery. Adding clonidine to intrathecal bupivacaine provides effective and prolonged analgesia with reduced requirement for supplemental analgesics.^{1,2} Therefore, achieving a subarachnoid block that provides high quality postoperative analgesia is a choice. Opioids administered intrathecally as adjuncts to ensure prolonged postoperative analgesia are associated with many side effects such as pruritus, nausea, vomiting, urinary retention and unpredictable respiratory depression. This prompted further research towards non-opioid analgesics with lesser serious side effects such as neostigmine, ketamine, midazolam, steroids and clonidine.

The effect of adding opioids like morphine to hyperbaric bupivacaine intrathecally as a mixture and sequentially showed significant difference in the duration of analgesia. Premixing them reduces the spread of morphine intrathecally and hence the duration of analgesia. Clonidine is an α_2 adrenergic agonist. Addition of clonidine to intrathecal bupivacaine provides effective and prolonged analgesia with a decreased requirement for supplemental analgesics. Our study aims to evaluate and compare the effect of premixed clonidine and hyperbaric bupivacaine to that of sequentially administered form for spinal anesthesia in elective cesarean section. The parameters compared in the study were: Onset and duration of sensory block, onset and duration of motor block, intraoperative hemodynamic changes, post-operative analgesia and side effects.

MATERIALS AND METHODS

The study group comprised of 60 term parturient women with ASA Grade I between the age groups of 20-30yrs, admitted in a maternity hospital attached to Osmania General Hospital were scheduled to undergo elective caesarean section under spinal anaesthesia. This is a prospective, comparative study between equal sized groups using an open protocol design. Group A received 2ml of 0.5% hyperbaric Bupivacaine (10mg) + 30 μ g of clonidine as a mixture intrathecally and Group B received 2ml of 0.5% hyperbaric Bupivacaine followed by 30 μ g of clonidine in a sequential manner. Patient refusal, multiple pregnancy, pregnancy induced hypertension, gross spine abnormalities and coagulation abnormalities were considered as exclusion criteria.

Routine pre-anesthetic checkup of all the parturients was done. Routine evaluation, including hemoglobin%, blood group and typing, urine examination, blood sugar, blood urea, serum creatinine, HIV and HBS Ag etc., was done. Parturients with normal hematological and urological parameters were taken up for the study. Standard pre-operative preparation consisted of overnight fasting, preoperative parenteral Ranitidine 50mg, Metoclopramide 10mg and 500ml of Ringer lactate as preload. Preoperative pulse, blood pressure, respiratory rate and oxygen saturation were recorded. The parturient was placed in the left lateral position. Under aseptic precautions subarachnoid space is identified in L₃ – L₄ intervertebral space by 25G Quinke needle. After the free flow of CSF, group A parturients received the study drug 2ml of 0.5% Hyperbaric Bupivacaine

premixed with 0.2ml(30µg) clonidine at the rate of 0.25ml/sec. Group B cases received 2ml of 0.5% hyperbaric Bupivacaine followed by 0.2ml (30µg) of clonidine with bevel directing cephalad.

The patient was placed in supine position with left uterine displacement. Oxygen with face mask (at the rate of 6 L/min) was administered till the delivery of the baby. Cardiac and respiratory parameters were monitored and assessment of level of sensory and motor blockade was recorded at regular intervals. Inj. Mephentermine (3-6mg) IV was administered when necessary to maintain the systolic blood pressure at or above 90mmHg. Blood pressure was monitored at 2 minute intervals for the first 10 min and every 5 minutes thereafter. Pulse rate and oxygen saturation were monitored with a pulse oximeter. Parturients of Group A and B are monitored for the time taken for the:

- Onset of sensory block and progression to T4/T6 dermatomal segment
- Time to achieve maximum sensory and motor block
- Duration of sensory anaesthesia (Time to two segment regression)
- Onset of motor block and mean duration of motor block
- Mean duration of analgesia.

Assessment of intensity of sensory block was done using the Visual Analogue Scale Score on a 10cm scale {Grade 0 No pain, Grade 1:1 – 2.5 (Mild Pain), Grade 2: 2.6 – 5(Moderate Pain), Grade 3: 5.1 – 7.5 (Severe Pain), Grade 4: 7.6 – 10 (Worst possible pain)}. Assessment of the motor blockade was done according to the Modified Bromage scale. Grade 0- No block (full flexion of knee and ankle possible), Grade I: Partial block (able to

flex ankle normally with impaired knee flexion), Grade 2: Almost complete block (unable to flex knee, but still able to flex ankle), Grade 3: Complete block (unable to flex knee or ankle).

Time for complete regression of motor block was recorded. The Ramsay Sedation score was utilized to assess the level of sedation. During surgery, the incidence of shivering, nausea and vomiting were recorded by direct questioning at regular intervals and symptomatic treatment given. Baby delivery time was noted. After delivery of the shoulder Oxytocin was administered. Other side effects like hypotension (>25% fall in mean arterial pressure) and bradycardia (<50/min) were recorded during and after surgery and the patients were visited to record the time of first analgesic request, time of sensory and motor regression.

STATISTICAL ANALYSIS AND RESULTS

In our study, patients were between 20-30 years of age and the mean age was 23.7 in group A and 23.4 in B group. The mean height in A group was 162.36cms and group B was 163.33cms. The mean weight in A group and B group were similar. The difference in the mean values of the demographic parameters was not significant [$p<0.05$]. Both the groups were compared based on demographic data and ASA classification of the physical status and there was no statistically significant difference [$p<0.05$]. Observations in relation to onset of sensory blockade, onset of motor blockade, duration of motor blockade, duration of sensory anesthesia and mean duration of analgesia are tabulated and depicted in graphs.

Both the groups were having similar MAP values throughout the intraoperative and postoperative periods with $p > 0.05$ groups. There was no statistically significant difference in the adverse effects amongst the two groups. Nine patients in Group A and nine patients in group B had hypotension. None of the patients in Group A and two patients in group B had bradycardia. None of the patients in group A had nausea, vomiting, respiratory depression and dry mouth. In group B one patient had nausea and two patients had vomiting and none had respiratory depression or dry mouth.

DISCUSSION

Spinal anesthesia is the technique of choice for cesarean section either performed as an elective or an emergency procedure enabling early recognition of complications, as the patient remains conscious. Local anesthetics were administered alone for providing anesthesia for this procedure for several years. The local anesthetic dosage must be increased to prolong the duration of postoperative analgesia. However, this contributed to considerable hemodynamic adverse effects. The need to prolong postoperative analgesia led to the addition of a multitude of adjuvants to intrathecal local anaesthetics. In addition, these adjuvants should ideally minimize the discomfort of visceral manipulation, which is a possibility in cesarean section despite achieving adequate sensory level. An ideal combination of local anaesthetic and adjuvant should provide adequate intraoperative anaesthesia, good extended postoperative analgesia without prolonging the motor blockade or producing adverse hemodynamic or respiratory consequences.

Clonidine being an α_2 adrenergic agonist is presumed to activate post-synaptic alpha-2 receptors in the substantia gelatinosa of the spinal cord to produce analgesia. Clonidine inhibits preganglionic sympathetic activity centrally, mainly mediated at a thoracic level, but large doses cause a biphasic response, with initial peripheral pressor effects before a decrease in arterial blood pressure toward baseline. This study has been designed to compare the impact of 'low dose' clonidine as adjuvant to 0.5% Bupivacaine for spinal anesthesia in a premixed form versus sequentially administered form.

Several authors studied the effect of addition of different doses of intrathecal clonidine ranging from 15 μ g to 300 μ g along with local anaesthetics. Marked decrease in blood pressure was observed only with intermediate doses of spinal clonidine (150 μ g) and relative hemodynamic stability is maintained after large doses (300-400 μ g). The intrathecal application of 25 μ g clonidine in combination with bupivacaine improves the duration and quality of spinal anesthesia; it also provides longer duration of postoperative analgesia, without significant side effects.⁸ Hence, in our study we selected 30 μ g of preservative free clonidine as an adjuvant for spinal anaesthesia in caesarean section. Based on previous studies a comparative study of the drugs administered as premixed or sequentially are evaluated.

The effect of adding opioids like morphine to hyperbaric bupivacaine intrathecally as a mixture and sequentially showed significant difference in the duration of analgesia. In a study, premixing of

bupivacaine and morphine reduced the spread of morphine intrathecally and hence the duration of analgesia. Similarly, it was assumed that the original densities of hyperbaric bupivacaine and clonidine would change when they are premixed in a syringe resulting in suboptimal action as opposed to their administration in a sequential manner.⁴

This hypothesis is supported by the authors who studied the effect by adding 75µg of clonidine to hyperbaric bupivacaine intrathecally as premixed form and sequentially administered form in caesarean section.³ The densities of the drugs were measured. For Hyperbaric bupivacaine and clonidine densities were 1.0260 and 0.9930, respectively. The density of the mixture of 2 ml (10 mg) of hyperbaric bupivacaine and 0.5 ml (75µg) clonidine was found to be 1.0189 in the study conducted by Prachee et al. They observed duration of analgesia was significantly longer in sequentially administered group (474.33 ± 20.79 min) than those administered in premixed form (337 ± 18.22 min). Furthermore, the time to achieve highest sensory block and complete motor block was significantly less in sequential group. Besides this, there was no evidence of major hemodynamic instability when clonidine and hyperbaric bupivacaine were administered in a sequential manner. Block characteristics improved significantly compared to the administration of the mixture of the two drugs. There were no adverse consequences in neonatal outcome as well. The result of our study is in concordance with other studies.^{3,5}

It was found that the onset of sensory block does not get any better after a specific dose

as supported by a study, who did not report any difference even after using 150 µg clonidine [7]. In our study mean time to onset of sensory block was 64.16sec in Group A and 62.33sec in Group B [$p < 0.3$]. This was not statistically significant. Whereas, there was a statistically significant difference amongst the two groups in the time to reach maximum level of sensory block [$p < 0.0001$]. The time to reach maximum sensory block height was significantly less in Group B, (sequential drugs) than in Group A (mixed drugs) in this study. This difference might have existed because of the preferential cephalad spread of clonidine when administered through separate syringe, owing to its hypobaric nature which is lost when the drugs are premixed.

In the present study, the mean time taken for two segment regression was 85.16mins in group A compared to 90.83mins and was significantly prolonged in group B compared to group A [$p = 0.001$]. In another study, there was relatively increased duration in the sequential group as compared to our study (240.67 min) probably due to the higher dosage of clonidine (75µg) and the target being “mean time to T10 segment regression” instead of 2 segment regression.³

In a similar study, there is a significant difference between groups in total duration of analgesia with Group B having a much longer duration compared to Group A [$p < 0.0001$]. Group B has a mean duration of analgesia is 325.16 mins and duration in the sequential group was still longer (337 ± 18.22 min) due to higher clonidine dosage.^{3,9} Our results are in concordance with others proving that sequential administration of bupivacaine and

clonidine significantly increases (325.16 ± 9.69 min) the mean duration of analgesia than when the agents are administered in a premixed form (295 ± 9.68 min). The mean time to onset of Bromage 2 motor block was longer in group A than group B [$p=0.0001$]. The mean duration of motor block was higher in sequential group with a statistically significant difference. In another study there was relatively increased duration in the sequential group owing to a higher dose of clonidine.⁴ In the present study, there is significant difference between both the groups with respect to intraoperative and postoperative mean heart rates with $P<0.001$. Out of 60 patients, 2 patients in sequential group developed bradycardia and treated with Atropine 0.6mg.

In our study, there was a fall in mean arterial pressure of more than 25% from the baseline in 9 patients each in both the groups. Hypotension was managed with i.v fluids and vasopressors were needed for 10% of patients. There was no significant difference between both the groups probably because of lower doses of clonidine and was comparable in both groups, suggesting that the clonidine groups did not have a higher predisposition for the development of hypotension if administered sequentially. There was no significant difference between both the groups ($P>0.05$) in respiratory rate and oxygen saturation, there was no episode of any respiratory depression in both groups. In agreement with other studies addition of intrathecal clonidine did not adversely affect the neonatal outcome in terms of APGAR scores.³

In line with our observations, it was confirmed that when intrathecal clonidine

was administered with hyperbaric bupivacaine, none of patients required supplement analgesics to obtain an adequate sensory block.^{1,5} None of the patients complained about nausea, vomiting, respiratory depression and dry mouth.

SUMMARY AND CONCLUSION

The present prospective and randomized clinical study was carried out on 60 full term parturients undergoing lower segment caesarian section, under subarachnoid block by 2ml 0.5% hyperbaric bupivacaine and 30 μ g of clonidine in premixed and sequentially administered forms. Both the groups received a total volume of 2.2ml. Patients vital parameters, sensorimotor effects, onset and duration of analgesia and adverse effects, if any, were recorded intraoperatively and postoperatively. The following conclusions were drawn -

- The time to two segment regression was significantly prolonged with the Sequential addition of intrathecal clonidine to hyperbaric bupivacaine.
- The time to motor regression was significantly prolonged with the sequential addition of clonidine.
- Addition of clonidine either in premixed form or sequential form along with hyperbaric bupivacaine intrathecally prolonged the duration of analgesia especially in sequential group and reduced postoperative analgesic requirements.
- There was no appreciable difference in the time to onset of sensory block. Sequential administration of clonidine reduces the time to achieve complete sensory and motor block.
- There was a significant difference in the onset of motor blockade with

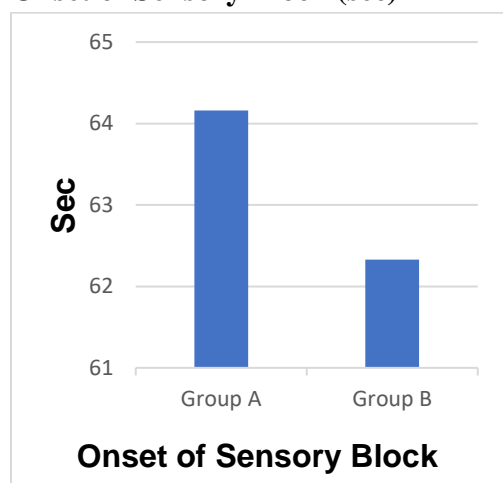
sequential addition of clonidine requiring less time than mixed form.

However, we noticed that sequential technique did not increase the level of sedation and incidence of hypotension or bradycardia as compared to the administration of drugs as a mixture. New-born outcome also remained unaffected.

The limitation of our study was that we measured the densities of solutions in vitro; but, we could not assess, measure the densities in vivo i.e., after injecting into the CSF. Hence, we could not measure drug densities after intrathecal administration. Similarly, the effects of temperature of drugs after administration were not considered. It requires having further studies of a greater number of patients for evaluation considering physiological changes in pregnancy too.

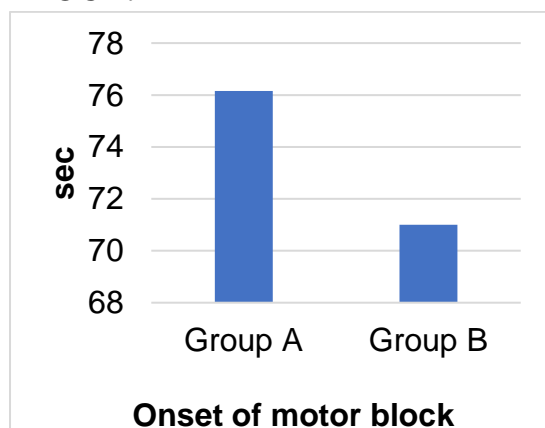
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GRAPH 1 Comparison of Mean Onset of Sensory Block (sec)**TABLE 1: Distribution of mean onset of sensory block to T4 dermatomal segment (sec)**

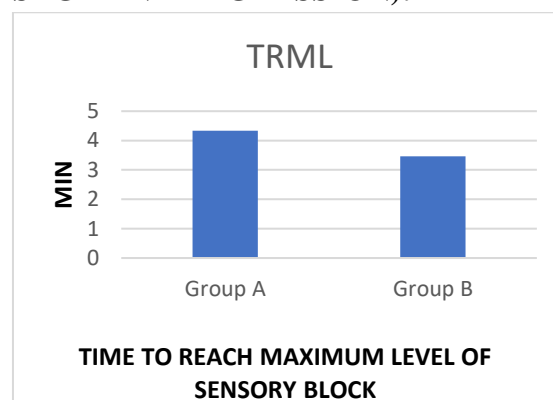
Onset of sensory block	Group A (sec)	Group B (sec)	'p' value
No. of cases	30	30	0.09
Mean	64.16	62.33	
SD	4.56	3.65	

There is no significant difference between two groups when compared in terms of onset of sensory blockade [$p < 0.05$].

GRAPH 2 ONSET OF MOTOR BLOCK:**TABLE 2: Distribution of mean onset of motor block (sec)**

Onset of motor block	Group A (sec)	Group B (sec)	'p' value
No. of cases	30	30	0.0001
Mean	76.16	71	
SD	5.20	4.43	

There is a significant difference between groups in the onset of Motor block- 76.16 vs 71 seconds [$p < 0.05$]-

GRAPH 3 DURATION OF SENSORY ANAESTHESIA (TIME TO TWO SEGMENT REGRESSION):**Table 3: Distribution of mean time to two segment regression**

Time to two segment regression	Group A (min)	Group B (min)	'p' value
No. of cases	30	30	0.001
Mean	85.16	90.83	
SD	4.45	7.77	

There is significant difference in time to reach maximum level of sensory blockade, with Group A (4.33 vs 3.46 min) requiring a much longer time compared to Group B [$p < 0.0001$]-

GRAPH 4, MEAN DURATION OF MOTOR BLOCK

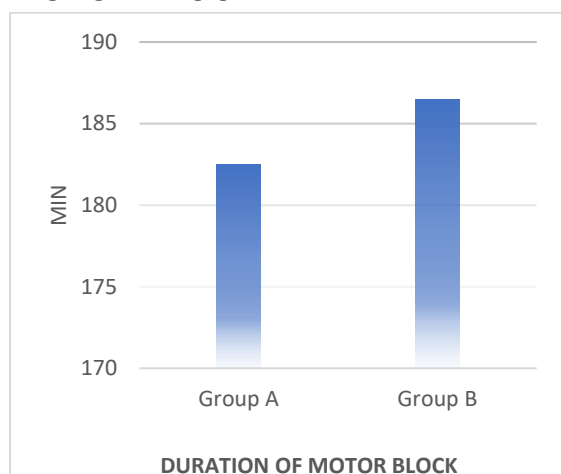


TABLE 4 Distribution of mean duration of motor block (min)

Duration of motor block (min)	Group A (min)	Group B (min)	'p' value
No. of cases	30	30	0.0126
Mean	182.5	186.5	
SD	6.012	6.03	

There is significant difference between the groups in duration of motor block, with group A (182.5 vs 186.5 min) having longer duration compared to group B [p value < 0.0126]-

GRAPH 5: Comparison of Mean Duration of Analgesia (min) between study groups

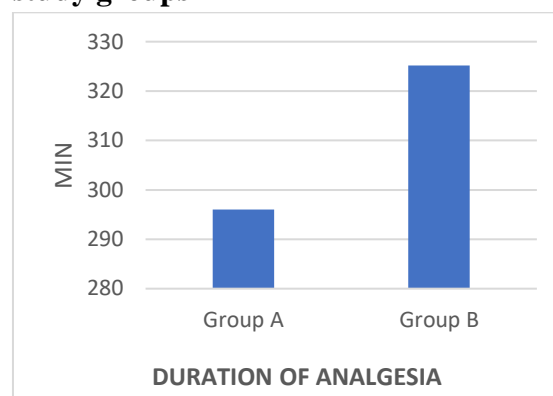


TABLE 5 Distribution of mean duration of analgesia (min)

Duration of analgesia	Group A (min)	Group B (min)	'p' value
No. of cases	30	30	<0.0001
Mean	296	325.16	
SD	9.68	9.69	

There is a significant difference between the groups in the mean duration of analgesia with Group B (325.16 VS 296 min) having a much longer duration compared to Group A [p value <0.0001]-