A Randomized Controlled Study of Intrathecal Clonidine with Hyperbaric Bupivacaine Administered as a Mixture, and Sequentially in Caesarean Section, Government General Hospital, Nizamabad

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ABSTRACT

BACKGROUND

Spinal anaesthesia with hyperbaric bupivacaine and adjuvants such as clonidine is now the preferred technique for spinal anaesthesia. In this study, we aimed to compare the block characteristics, intraoperative haemodynamics and postoperative pain relief in Caesarean section under subarachnoid block (SAB), following administration of hyperbaric bupivacaine and clonidine as a mixture in a single syringe and sequentially in two syringes.

METHODS

The research population consisted of 128 term parturient women undergoing elective caesarean section under spinal anaesthesia in the age group of 20 - 30 years. By using computer generated random numbers, they were allocated to one of the two classes of evenly sized groups (64 each). This is a forward-looking, comparative analysis using an inclusive protocol framework for similarly sized classes. Group A received intrathecal 2 mL of 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of clonidine (30 µg) as a mixture from the same syringe and Group B received intrathecal 2 mL of 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of clonidine (30 µg) (bupivacaine followed clonidine) sequentially from two syringes.

RESULTS

At baseline and in all subsequent measurements ($p>0.05$), the mean of arterial pressure, respiratory rate, and partial oxygen concentration were similar between the two groups. None of the cases in any group experienced nausea, vomiting and respiratory depression.

CONCLUSIONS

Sequential clonidine administration reduces the time needed for maximum sensory and motor block accomplishment and substantially prolongs the overall analgesic duration. We found that sequential procedure did not raise the degree of sedation and occurrence of hypotension or bradycardia as compared with drug administration as a mixture.

KEYWORDS

Clonidine, Hyperbaric Bupivacaine, Spinal Anaesthesia, Randomized Controlled

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BACKGROUND

Spinal anaesthesia is currently the chosen procedure and is the gold standard for caesarean section, due to its simplicity and efficacy, as well as the speed at which it will develop sufficient rates of analgesia.[1,2] Several intrathecal drugs such as opioids (morphine, creatine, sufentanil, buprenorphine) and non-opioids such as α2 adrenergic agonists (clonidine, dexmedetomidine), benzodiazepines (midazolam), ketamine, etc., have been attempted to extend analgesia following surgery.[3] Many side effects such as pruritus, nausea, vomiting, urinary retention and unpredictable respiratory depression are associated with opioids administered intrathecally as adjuncts to prolong postoperative analgesia. This led to further studies into non-opioid analgesics with less severe side effects such as neostigmine, ketamine, midazolam, steroids and clonidine.[4,5]

Also, when a long-acting local anaesthetic such as bupivacaine alone is used, the length of spinal anaesthesia might become shorter and the postoperative time involves higher doses of analgesics. High doses of intrathecal bupivacaine are also associated with extreme hypotension.[6,7] Clonidine, a selective partial agonist for alpha 2 adrenoreceptors, is an alternative to widely used opioids, and is known to improve local anaesthetic sensory and motor block.[8,9] The application of clonidine to intrathecal bupivacaine offers efficient and sustained analgesia with decreased supplementary analgesic requirements.[10,11]

Adjuvants are usually combined in a single syringe with local anaesthetics (LA), before administering the drugs intrathecally. The mixture of both drugs affects the composition of all drugs, thereby impacting the distribution of both drugs in the cerebrospinal fluid. If we administer local anaesthetics (LA) and adjuvants separately, this can minimize the effect of density changes and hence their actions as well. Studies have already shown that the effect of intrathecally adding opioids such as morphine to hyperbaric bupivacaine as a mixture and sequentially demonstrated a significant difference in the duration of analgesia.[12,13]

Density is known to influence the spread of LA, but there was no extensive study on the effect of adjuvant solution density on its movement in the CSF. We hypothesized, therefore, that if we administer LA and the adjuvants separately, it could minimize the effect of density changes and hence also their actions.

Thus, in present study we aimed to compare block characteristics, intra operative haemodynamics and post-operative pain relief in parturients undergoing Caesarean section under subarachnoid block (SAB), after administering hyperbaric bupivacaine (HB) and clonidine as a mixture in single syringe and sequentially in two syringes.

METHODS

After acceptance by the institutional ethics committee and written informed consent, the study was conducted in the Department of anaesthesiology, Government general hospital, Nizamabad. The duration of Study was from September 2017 to November 2018, the research group consisted of 128 representative women aged 20 to 30 years undergoing elective caesarean section under spinal anaesthesia. By using computer generated random numbers, they were allocated to one of the two evenly sized groups (64 each). This was a forward looking, comparative analysis using an inclusive protocol framework for similarly sized classes. Group A received intrathecally 2 mL of 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of clonidine (30 µg) as a mixture from the same syringe and Group B received intrathecally 2 mL of 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of clonidine (30 µg) sequentially from two syringes (bupivacaine followed clonidine).

Patients with multiple pregnancies, Pregnancy induced hypertension, Placenta previa, acute fetal distress, body weight >80 Kg, refused informed consent, any contraindication for spinal anaesthesia, allergy to local anaesthetics, ASA status more than 2, Gross spinal deformity or prior lumbar spinal surgery were excluded from study. Inclusion Criteria were parturient women with ASA grade I or II, Parturient women with term gestation, parturient women between the ages of 20 years to 30 years, parturient women who were willing to give written informed consent.

Clearance from pre anaesthetic check-up (PAC) clinic was taken for all patients before they were taken for C-section. Patients were kept nil by mouth for 6 hours after clearing out of PAC. Routine studies such as haemoglobin level, blood grouping and typing, urinalysis, blood sugar, blood urea, serum creatinine, HIV and HBS Ag etc. were performed and all mothers were tested under standard haematological and urological conditions.

Upon arrival in the operating room, 18-gauge cannula was used to secure intravenous line and an injection of Ringer's lactate was begun. Patients were monitored during the perioperative time and heart rate (HR), non-invasive measures of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), continuous electrocardiographic (ECG) monitoring, and oxygen saturation (SPO_2) were recorded. Study medication was prepared by a person who was not involved in patient care or monitoring to ensure the anaesthesiologist was blinded for the medication given. Both findings were noted by a single reviewer, who was blinded to the prescribed medications. The patients and anaesthesiologist studied were oblivious to the medication used by the research.

Under strict aseptic conditions, with patient in sitting position, intrathecal block was given at L3-L4 or L4-L5 intervertebral space with 27G spinal needle. Once the drug was given, patients were made to lie in the supine position. All the necessary equipment and drugs required for administration of general anaesthesia and resuscitation were kept ready to manage procedural failure and any complications. The following parameters were recorded: (1) the onset of sensory block was measured bilaterally by impairment of the sense of the pin prick along the mid-clavicular axis. Dermatomal level was tested every 2 minutes

after SAB until four consecutive readings had stabilized the level. The period had been noted from intrathecal injection to the highest sensory level (maximum block height). In addition, sensory level was checked every 30 min before regression was noted from peak to T4 and T6 dermatomes. (2) motor blockade: every 5 minutes before skin incision, the degree of motor block was measured with the modified Bromage scale. (Bromage 0: patients can move hip, knee & ankle; Bromage I patients cannot move hip, but can move knee & ankle; Bromage ii: patient cannot move hip & knee but can move ankle; Bromage iii: patient cannot move hip, knee & ankle). (3) haemodynamics: Heart rate & blood pressure was noted directly after injection and then for every 3 minutes for the first 30 minutes, then every 10 minutes afterwards during the procedure and every hour before full recovery from block. The record of anaesthesia was maintained and the heart rate, blood pressure was noted. Any drop in heart rate below 60 beats / min was considered bradycardia and was treated with Atropine 0.6 mg. Likewise any decrease in systolic blood pressure of more than 20 percent of the baseline was considered as Hypotension which was treated with quick crystalloid infusion and 6 mg bolus of ephedrine iv if hypotension continues. (4) sedation: Sedation was assessed with Adjusted Sedation Scale of Ramsey. Postoperatively, pain, sensory level and motor block were assessed every 30 minutes for the first 2 hours, every hourly for the next 6 hours and at 12 and 24 hours after arrival in the recovery room. (5) digital analog scale measured pain level, every hourly first for 2 hours, every 2 hours for the next 8 hours, and then every 4 hours till 24 hrs. Inj. tramadol 2 mg / Kg iv (max 100 mg) was administered as a relief analgesic when the VAS level was above or equal to 4 (VAS ranking: 0 = no pain and 10 = the worst pain imaginable).

All the parameters were reported and statistically analysed according to the preformed.

Statistical Analysis

The quantitative figures were represented as their mean ± SD. It represented categorical and nominal data in percentage. The t-test was used to analyze quantitative data, or Mann Whitney test analyzed non-parametric data and evaluated categorical data using chi-square testing. The p-value limit was set at <0.05. All the analysis was conducted using version 2.1 of the SPSS software.

RESULTS

A demographic detail is comparable for both groups in terms of age, weight, height, length of the surgery. The median age of cases in category A and B was 23.7 years and 23.46 years respectively (p=0.95), and the anthropometric parameters in both groups demonstrated no statistically meaningful variations (p>0.05).

As per the ASA classification, ASA category I (Group A & B; 50 (78.10%)) and II [Group A & B; 14 (21.90%)] was comparable between the groups and there was no statistically meaningful difference (p=1.0).

Variables	Group-A (N=64)	Group-B (N=64)	P-Value
Onset of Sensory Block (sec)	64.16 ± 4.56	62.33 ± 3.61	0.09
Time for max. Sensory Block (min)	4.33 ± 0.08	3.46 ± 0.25	<0.01
Time for 2 segment regression (min)	85.16 ± 4.56	90.83 ± 7.77	<0.01
Duration of Analgesia (mins)	296.7± 9.87	325.10 ± 9.67	<0.01

Table 1. Mean Comparison of Sensory Block Parameters between Study Groups

* p-value is result of t-test and chi-squared and Mann Whitney test analysed categorical variables, respectively

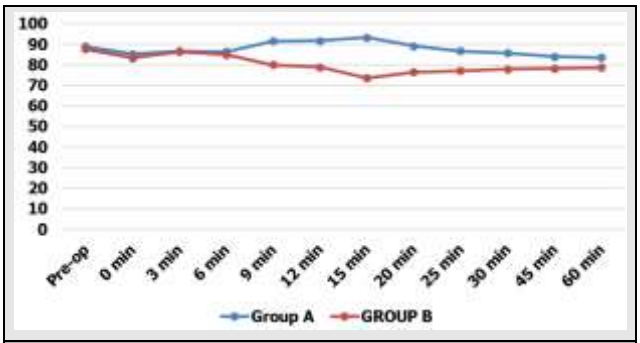

Figure 1. Mean Heart Rate Comparison between Study Groups

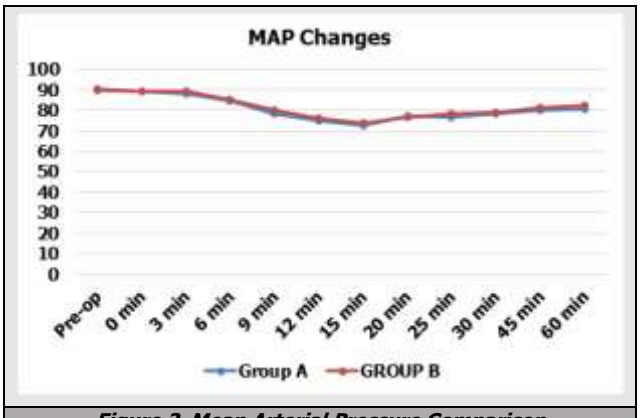

Figure 2. Mean Arterial Pressure Comparison between Study Groups

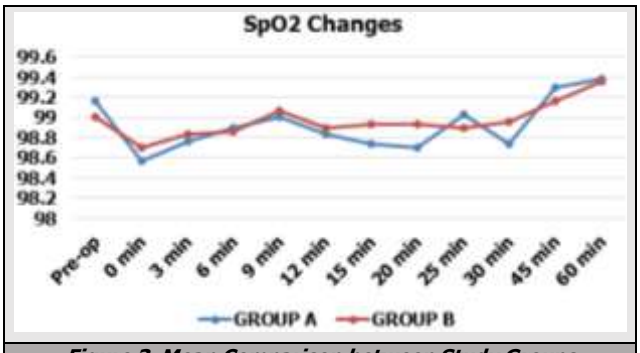

Figure 3. Mean Comparison between Study Groups as per Oxygen Saturation

Adverse Effects	Group-A (N=64)	Group-B (N=64)	Total	P-Value
Bradycardia	1(1.6%)	4(6.3%)	5(3.9%)	0.36
Hypotension	19(29.70%)	18(28.10%)	37(28.90%)	1.00
Nausea/ Vomiting	2(3.10%)	5(7.8%)	7(5.5%)	0.44
Resp. Depression	0(0.0%)	0(0.0%)	0(0.0%)	NA

Table 2. Distribution of Cases as per Incidence of Adverse Events

* p-value is result of t-test and chi-squared and Mann Whitney test analysed categorical variables, respectively

The mean onset of the sensory block in group B (62.33 vs. 64.16 sec.; p=0.09) was comparatively quicker, but the discrepancy was statistically insignificant. Time for maximal sensory block was slightly shorter in group B (3.46 min vs. 4.33 min; p<0.01), although time was substantially longer for 2 level regression (90.83 vs. 85.16 min) and overall analgesic length (325.1 vs. 296.70 min) (Table 1).

T4 was the highest block point achieved in group A (90.6%) when compared with group B (93.8%) and there was no statistically meaningful discrepancy (p=1.0). Onset of Motor Block was significantly faster in group B (71.0 vs 76.32 sec; p<0.01) while duration of motor block was significantly longer (186.7 vs 182.5 min; p=0.12).

Mean heart rate was comparable between the two groups at baseline (p=0.62) (Figure-1). However, from 9th minute onwards, mean heart rate was significantly lower in group B than baseline and also when compared to group A, where the heart rate was more than baseline till 60th minute reading (p<0.01).

Mean arterial pressure was comparable between the two groups at baseline and in all subsequent readings (p> 0.05) (Figure-2).

Mean respiratory rate was comparable between the two groups at baseline and in all subsequent readings (p> 0.05). Mean oxygen saturation was comparable between the two groups, at baseline and in all subsequent readings (p> 0.05) (Figure-3).

There was no statistically significant difference in the adverse effects among the two groups (p>0.05). A total of 29.7% patients in Group A and 28.1% in group B had episodes of hypotension (vasopressors were required in 5 cases in each group (7.8%)). One patient in Group A and four patients in group B had bradycardia and they were treated with inj. Atropine 0.6 mg (Table 2). Two patients in group A had nausea, vomiting as compare to 5 in group B. None of the cases had respiratory depression in any group.

DISCUSSION

The preferred method for elective caesarean section is spinal anaesthesia as being easy to administer, economical and providing rapid anaesthesia with full muscle relaxation. This brings high efficiency, involves fewer doses of drugs, reduced neonatal agitation and less occurrence of pneumonitis aspiration. This also results in a set anaesthesia period, less block height control, postdural puncture headache and hypotension,[14-16] however. Hypotension is also considered to result in maternal morbidity; diarrhoea, vomiting and dizziness, by reducing uteroplacental blood supply, may also specifically affect the well-being of neonates.[17] The connection between the magnitude of the sympathetic block and the occurrence of hypotension has resulted in multiple attempts to reduce the dosage of local anaesthetic and also to attach opioids due to their synergistic activity with local anaesthetics on the sensory block without the sympathetic block for caesarean section.[18,19]

Various scholars have used different dosages of local anaesthetics, and the amount needed for spinal anaesthesia in the delivery of caesareans. Nagata et al.,[20] indicated that 8 mg of hyperbaric bupivacaine in cesarean section spinal anaesthesia is preferable to 10 mg in order to achieve sufficient analgesia and to prevent maternal hypotension. In the Ben David research, they intrathecally used 5 mg of isobaric bupivacaine with 25 µg of fentanyl, but a number of patients experienced brief and mild intraoperative pain which was inappropriate. Subedi et al.,[21] observed that the comparatively small dose of bupivacaine used restricted parts of the spinal block and hence the size of the sympathetic barrier, thereby increasing the safety margin of hemodynamic effects seen after spinal anaesthesia. Therefore, in our study, we were involved in testing the potency of the low-dose (7.5 mg) mixture of (0.5 percent) hyperbaric bupivacaine and 25 µg of fentanyl in spinal anaesthesia. Patients scheduled for the caesarean section were chosen for the study as abdominal nausea and pain under spinal anaesthesia are well known.[22]

In our study, we observed that the time required for the onset of sensory blockade up to T4 was statistically not significant (p less than 0.05), we observed that the mean onset time of sensory block was similar in both groups. However, onset of sensory block does not get any better after a particular dose as supported by a study done by Heo et al.,[23]

In group A the time to achieve full sensory block point was 4.33 min and in group B it was 3.46 min. Differences between two participants is statistically important (p<0.01). In this study (24), the time to achieve full sensory block height was slightly lower in Group B, (sequential drugs) than in Group A (mixed drugs). Researchers found evidence that these findings were statistically highly important difference in this analysis between two classes (p was <0.01). Consequently, it is possible that concurrent administration of local anaesthetic and adjuvant drugs would take less time to reach the maximum level of the sensory block and the gap in length to reach the maximum level of the sensory block would rely on the dose of clonidine and hyperbaric bupivacaine used.

Mean heart rate was comparable between the two groups at baseline (p=0.62). However, from 9th minute onwards, mean heart rate was significantly lower in group B than baseline and also as compared to group A, where the heart rate was more than baseline till 60th minute reading (p<0.01). However, in our study 4 patients in group B and 1 patient in group A developed bradycardia and they were treated with inj. Atropine 0.6 mg (p=0.36). From the observation that these drugs can induce bradycardia, we concluded that the maximum fall in the heart rate when compared to the baseline in sequential group and mixed group was statistically significant (P <0.001). Clonidine decreases heart rate by a presynaptic mediated inhibition of nor epinephrine release and by a direct depression of atrioventricular nodal conduction after systemic absorption.[24]

In our study, there is no significant difference between both the groups with respect to intraoperative and post-operative mean arterial pressure (p>0.05). In our study, fall from baseline MAP in both groups was 30%. A total of 29.7% patients in Group A and 28.1% in group B had episodes of hypotension. Hypotension was managed by IV fluids and vasopressors were required in 5 cases in each group (7.8%) and there was no significant difference between both the groups probably because of lower dose of clonidine in our study**.** similar studies reported that significant fall in arterial blood pressure after SAB was observed in their studies, but was statistically insignificant between the groups.[13,25]

There was no major variation in respiratory rate and oxygen saturation between the two groups (P>0.05), and no episode of respiratory failure existed in both groups. The application of intrathecal clonidine in accordance with other trials did not negatively impact the neonatal result.[10,26]

In our study, when intrathecal clonidine was provided with hyperbaric bupivacaine, none of the patients needed additional analgesics to achieve a sufficient anaesthesia for surgery. No patient reported nausea, diarrhoea, respiratory depression and dry mouth.

CONCLUSIONS

Sequential clonidine administration decreases the time needed for maximum sensory and motor block accomplishment and substantially prolongs the overall analgesic duration. Addition of clonidine to hyperbaric bupivacaine provided dense surgical anaesthesia regardless of the administration technique. We found, however, that sequential technique did not raise the degree of sedation and frequency of hypotension or bradycardia when compared with drug administration as a combination. Newborn findings were also untouched.

The drawback of our analysis was that we calculated in vitro solution densities; however, when injected into the CSF, we did not quantify the densities. Therefore, we do not intrathecally determine what really happens to the product densities. Similarly, effects of temperature of drugs when injected were not considered.

The study was approved by the Institutional Ethics Committee of Government General Hospital, Nizamabad, Telangana, India.

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