Intrathecal Clonidine with Hyperbaric Bupivacaine Administered as Mixture and Sequentially in Caesarean Section - A Randomised Controlled Study

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ABSTRACT

BACKGROUND
Spinal anaesthesia with hyperbaric bupivacaine and adjuvants like clonidine and fentanyl is commonly used technique for Lower Segment Caesarean Section (LSCS). The common practice is to add these adjuvants to hyperbaric bupivacaine in a single syringe prior to the intrathecal injection. Mixing of drugs may alter the density and baricity of anaesthetic solution and alter the spread of drug in cerebrospinal fluid (CSF). In this study we aimed to evaluate the effect of addition of clonidine to hyperbaric bupivacaine on block characteristics, intraoperative haemodynamics, postoperative analgesia and neonatal well-being after being administered intrathecally with two different techniques i.e. sequentially and as a mixture.

METHODS
60 full term parturients with singleton pregnancy scheduled to undergo elective lower segment caesarean section under spinal anaesthesia were involved in this single blind prospective randomised controlled study. Patients were divided into two groups based on the method of intrathecal administration of the drug. Group M (n=30) received mixture of clonidine (75 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally. Group S (n=30) received clonidine (75 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes intrathecally. The total volume of drug administered was constant at 2.5 ml in each group.

RESULTS
The patients in Group S had faster onset of sensory block (1.19± 0.27 min v/s. 1.47± 0.283 min p=0.0002) and motor block (1.19±0.295 v/s. 1.58 ± 0.246 min p<0.0001) than in Group M. The duration of sensory block (472 ± 20.2 min v/s. 349±26.3 p<0.0001) and motor block (289 ± 17.4 v/s. 187 ± 17.6 p<0.0001) was also found to be significantly longer in Group S. The total duration of effective analgesia was significantly longer in Group S than Group M (474±19.3 min v/s. 350 ±26.6 min p<0.0001). There were no significant maternal side effects and neonatal outcomes were not affected in any groups.

CONCLUSIONS
Intrathecal administration of hyperbaric bupivacaine and clonidine in sequential manner significantly results in superior block characteristics than administration of the drugs in the form of mixture.

KEYWORDS
Spinal Anaesthesia, Bupivacaine, Clonidine
Spinal anaesthesia is a safe, reliable and inexpensive technique with the advantage of providing surgical anaesthesia and prolonged post-operative pain relief by using various adjuvant drugs along with local anaesthetic agents. It blunts operative pain, autonomic, somatic and endocrine response, providing a fast onset and effective sensory and motor blockade. Spinal anaesthesia has been widely used for Lower Segment Caesarean Section (LSCS) deliveries because of greater maternal safety, foetal benefits, higher parental satisfaction and consumer demand. Various analgesic additives to local anaesthetics (LA) can improve the quality of analgesia both intraoperatively and postoperatively.2

Clonidine, a selective partial agonist for α-2 adrenoreceptors, is being extensively used as an alternative to neuraxial opioids for control of pain as well to increase the duration sensory and motor block of local anaesthetics.3,4 Intrathecal clonidine is free of at least some of the opioid related side effects. Mixing of hyperbaric bupivacaine and clonidine changes the density of both the drugs. Density is major contributing factor to the spread of LA solution in CSF.5

This study was designed to test whether injecting hyperbaric bupivacaine and clonidine into the intrathecal space as a mixture and sequentially using separate syringes, affects block characteristics, post-operative pain relief and foetal outcome in parturients.

Methods

After approval by institutional ethics committee, 60 full term parturients with singleton pregnancy of ASA II physical status, aged between 18-40 years scheduled to undergo elective LSCS under spinal anaesthesia were involved in this single blind prospective randomised controlled trial. Patient’s with ASA III/IV physical status, those allergic to LA and clonidine, those who refused spinal anaesthesia, bleeding disorder, patients on anticoagulants, infection at the site of injection, spinal and vertebral column anomalies, had maternal or neonatal complications, were excluded from the study.

After written informed consent patients were allocated into two groups using sealed envelope technique. Group M (n=30) received mixture of clonidine (75 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally. Group S (n=30) received clonidine (75 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes intrathecally. The total volume of drug administered was constant at 2.5 ml in each group. The patients were kept nil by mouth overnight and premedicated with Inj. Glycopyrrolate (0.004 mg/Kg) I.M. half an hour before sending to operation theatre. In the operation theatre monitors for heart rate, non-invasive blood pressure, electrocardiography and oxygen saturation (SpO2) was connected and baseline parameters were recorded. After establishing 18G venous cannula, patients were pre-loaded with 15 ml/Kg of lactated Ringer’s (RL) solution 15-20 min before spinal block. Under all aseptic precautions subarachnoid block was administered with 25G Quincke spinal needle through mid-line approach in sitting position. Intrathecal drug was injected in L3-L4 interspace over 30 sec (including the time for change of syringe in sequential administration). After the block was performed, the patients were made supine with 15°-20° left displacement of uterus until birth of baby by keeping a wedge under the right pelvis. Fluid therapy was maintained with RL solution 10 mL/Kg/h. An experienced anesthesiologist who was unaware of the given drug, evaluated the block characteristics and other physiological parameters. Hemodynamic parameters such as heart rate, systolic and diastolic blood pressure were monitored every 5 minutes till completion of the surgery. Any episode of bradycardia or hypotension was noted. Hypotension (decrease in systolic blood pressure <20% of baseline) was treated with rapid fluid infusion of 200 ml RL and bolus of 6 mg Inj. Ephedrine. Bradycardia was treated with tibrated dose of Inj. Atropine 10 mcg/Kg I.V.

Sensory block was assessed by loss of pin prick along midclavicular line bilaterally. Maximum block height i.e time from intrathecal injection to highest sensory level was noted. Level was tested every 30 min till regression from highest level to T10 dermatome was noted. Degree of motor block was assessed by modified Bromage Scale as- Bromage 0: no motor block. Bromage 1: Inability to raise extended leg, just able to flex knees, able to move feet. Bromage 2: Inability to raise extended leg and move knees; able to move feet. Bromage 3: Complete motor block of the lower limb.

Onset of motor block was measured as time elapsed between the intrathecal injection to a point where modified Bromage score is 1. Time to achieve complete motor block was measured as time elapsed between intrathecal injection to a point where modified Bromage score is 3. Duration of motor block was measured as time elapsed between injection of drug till Bromage score is back to 0. Respiration was monitored and respiratory depression was defined as SpO2 <92% and was treated with O2 at 4 lit/min. Duration of effective analgesia (i.e. time from intrathecal injection till any episode of pain where VAS>3) is noted and rescue analgesia in terms of Inj. Diclofenac Sodium 75 mg was given.

Any complications like nausea, vomiting, bradycardia, hypotension were noted and treated accordingly. APGAR score of the baby was monitored at 1 min and 10 min after delivery. Sedation score was assessed every 30 minutes until 2 hours postoperatively by Ramsay sedation score (RSS). Postoperatively any incidence of bradycardia, hypotension, nausea/vomiting, prolonged sedation were observed and managed accordingly. The parturients were also interviewed for post-dural puncture headache (PDPH), backache, and examined for any neurological deficit.
Power analysis suggested that a sample size of 30 patients/group was required to achieve a power of 80% and a level of significance of 0.05 to be able to detect a difference between the groups, based on the assumption that an increase in the mean duration of analgesia by 60 min in sequential group. Data analysis was carried out with the help of Microsoft® Excel and SPSS® software version 19. Data was represented as Mean ± standard deviation for continuous data and frequency (percentage %) or median (range) for non-parametric data. The two groups S and M were mutually exclusive i.e. patients in S are not part of M and vice versa hence we have used Unpaired or Students t-test to compare parameters with continuous data. In situations of categorical data Chi square test has been used (eg sex distribution and respiratory depression). For clinical scores such as APGAR score and RSS comparison, Mann Whitney U test has been used. p <0.05 was considered significant and p <0.01 was considered highly significant.

RESULTS

Demographic data in terms of age, weight, height, duration of surgery were comparable in both the groups. (Table 1).

The onset of sensory block in Group S is significantly faster than in Group M (1.19±0.27 min v/s. 1.47 ±0.283 min, p= 0.0002). The onset of motor block in Group S is also quicker than in Group M (p< 0.0001). Time to achieve the highest level of block (T4) is significantly lower in Group S (3.28 min) than in Group M (4.53 min) (p<0.0001).

Duration of sensory block was longer in Group S (472±20.2 min) as compared to Group M (349±26.3 min) (p<0.0001). Motor block also lasted longer in Group S (289 ±17.4 min) than in Group M (187±17.6 min) (p<0.0001). The duration of effective analgesia was longer in Group S (474±19.3 min) than Group M (350±26.6) (p<0.0001). Also complete motor blockade occurred significantly faster in Group S (4.56±0.31 min) compared to Group M (5.75± 0.5 min) (p<0.0001). (Table 2)

Hemodynamic parameters showed that there is significant fall in heart rate at 2 min and 4 min from administration of drug in both groups (p<0.05) but no patient had significant bradycardia. The rise in heart rate was observed at 16-20 min during baby delivery followed by decrease in heart rate once again to baseline value. The lowest values of the HR were seen after 45 minutes of administration of the drug in both groups. (Figure 1)

There was a significant fall in systolic blood pressure (SBP) at 2 min and 4 min after administration of block in both groups. A temporary spike was observed between 20 to 25 minutes at the time of delivery of baby which subsided shortly. In either case the systolic blood pressure did not fall below 60 mm of Hg. A significant fall in diastolic blood pressure (DBP) was seen at 2 min, 4 min, 6 min and 8 min after intrathecal injection in both groups. A spike in diastolic blood pressure was observed between 18 to 20 minutes which subsided shortly and it maintained baseline values between 30 and 75 minutes. In either case the diastolic blood pressure did not fall below 60 mm of Hg. The results were significant at p≤0.05. (Figure 2 and 3) Intraoperative incidences of hypotension, bradycardia, respiratory depression, nausea/ vomiting, dry mouth were comparable in both groups.
In both Group S and Group M the APGAR scores for neonatal wellbeing are similar at both 1 min (p = 0.83366) and 10 mins (p=0.99202). The result is not significant (p≥0.05). The sedation was assessed by Ramsay Sedation Scale at baseline, 30 min, 60 min and 90 min. In both Group S and Group M sedation level is similar at 0 min (p = 0.99) At 30 mins (p = 0.3788). At 60 mins (p = 0.27134) and 90 mins (p = 0.378860). The results are not significant p≥0.05.

**DISCUSSION**

The advantage of awake patient, simple to perform, rapid onset of action, relatively less side effects has made spinal anesthesia the choice of many surgical procedures. It is preferable in LSCS because it avoids all complications of general anesthesia without much effect on the baby. Addition of clonidine to intrathecal bupivacaine improves the nature and duration of subarachnoid block. Activation of post-synaptic α2 receptors in substantia gelatinosa of spinal cord is presumed mechanism by which clonidine produces analgesia. These receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial lamina of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.

Patients scheduled for LSCS were chosen for the study because it is well known fact that visceral discomfort and pain is a common occurrence in caesarean section under subarachnoid block. We wished to investigate whether intrathecal administration of hyperbaric bupivacaine through two separate syringes would improve the block characteristics without increasing side effects.

Various authors have used different doses of intrathecal clonidine ranging from 15 mcg to 300 mcg along with local anesthetics. Kaabachi et al., in their study used 2 mcg/Kg of intrathecal clonidine and reported extended duration of post-operative analgesia, but with moderate side-effects. Sethi et al. used 70 mcg of clonidine and found a significant decrease in mean arterial pressure and HR in clonidine group, but no therapeutic intervention was required for either. A recent study by Singh et al used a dose of 75 mcg of intrathecal clonidine with hyperbaric bupivacaine showed increased duration of analgesia significantly without maternal side effects. Hence we selected 75 mcg of preservative free clonidine as adjuvant to hyperbaric bupivacaine.

To study the effects of baricity on the spread of drug in CSF, We calculated baricity as follows- density of CSF is 1.003 ± 0.0003 gm/ml at 37°C which is studied to have been changed during pregnancy (1.003 ± 0.00004). The density of hyperbaric bupivacaine is 1.026 and that of clonidine is 0.993. The density of the mixture of 2 mL (10 mg) of hyperbaric bupivacaine and 0.5 mL (75 mcg) clonidine was also estimated and it was found to be 1.0189. As per formula Density = Mass/ volume and Baricity= Density of substance/ Density of CSF. We calculated average baricity of both groups. Group M = 1.015, Group S= 0.99. The observations and results obtained in the study are based on the assumption that the original densities of hyperbaric bupivacaine and clonidine are lost when they are premixed in a syringe thus, they exert suboptimal actions when compared to their intrathecal administration in a sequential manner. The above assumption is supported by the work of Sachan et al in their study. It is also supported by the work of Desai et al. who studied the same effect by adding opioids to LA solution intrathecally.

We observed that onset time of sensory block in Group S is significantly faster than in Group M. Hypobaric solution in Group S (average baricity 0.99) could have led to more cephalad spread of the drug than Group M (average baricity 1.015). In a similar study conducted by Sachan et al with same 75 mcg of clonidine given sequentially and mixed with 10 mcg Hyperbaric bupivacaine, mean onset of sensory block was faster in sequential group than in mixed group which is similar to the results obtained in our study. However, their result is not significant (p>0.05).

Mean time to reach maximum block height in Group S and Group M is 3.28 and 4.53 mins p<0.0001 which is statistically significant hence time to reach maximum block height is faster in Group S than in group M This difference might have existed because of the preferential cephalad spread of clonidine when we administered it through a separate syringe, owing to its hypobaric nature which is lost when the drugs are premixed. Gecaj-Gashi A et al conducted a double blinded study to investigate the effects of addition of intrathecal clonidine to bupivacaine in 66 male patients. They found that mean time achievement of highest sensory block was significantly shorter in group BC (bupivacaine +clonidine) than in group B (Plain bupivacaine), (p=0.0000).

Mean duration of sensory block in Group S and group M is 472 and 349 min respectively which shows that duration was significantly longer in group S than in group M p<0.0001. Sachan et al also found a similar result in their study (p=0.0000). The mean onset time of motor block was found to be significantly faster in Group S (1.19 ± 0.295) than in Group M (1.58± 0.246, p<0.0001). Sachan et al also observed that the mean onset time of motor block was shorter in sequential group than in mixed group however the results were not significant (p>0.05). The difference in time achievement of complete motor block between groups was statistically significant in favour of the sequential group, Group S (4.56± 0.31 min) v/s Group M (5.75±0.5 min, p<0.0001). The study conducted by Gecaj-Gashi A et al had similar results (Group BC 8.27±1.94 vs Group B 9.69±1.55)however we got faster achievement of motor blockade which can be attributed to use of higher dose of clonidine in our study (75 mcg) as compared to that used by Geraj- Gashi (25 mcg).

The mean duration of motor blockade was found to be significantly longer in group S (289 ± 17.4 min) than in Group M (187±17.6min) p<0.0001. Sachan et al also observed similar results sequential group (292.3±15.24 min)
showing significantly longer duration than in mixed (189.5±16.31 min) (p=0.0000) group.

Similarly, the duration of effective analgesia lasted significantly longer in Group S (474 ± 19.3 min) than in Group M (350 ± 26.6 min) p<0.0001, depicting significant prolongation of analgesic effect in the group receiving drugs in a sequential fashion. We also observed that there was profound relaxation and hence very good surgeon satisfaction. Our findings are consistent with findings of Van Tulji et al who investigated effects of addition of intrathecal clonidine to hyperbaric bupivacaine in prolongation of duration of post-operative analgesia and post-operative morphine consumption after caesarean section in 106 parturients. They observed post-operative decrease in morphine consumption in the group receiving bupivacaine + clonidine.7 Our findings are also similar to the study conducted by Sanchan et al who observed that, duration of analgesia lasted significantly longer in sequential group (474.33 ± 20.79 min) than in mixed Group (337 ± 18.22 min, p=0.000).15

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.16 Haemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min, reach maximum within 1-2 h, and last approximately 6-8 h after a single injection.17 The average maximum fall in heart rate as compared to baseline in Group S is 25.94% and Group M is 19.4%. However none of the patients had bradycardia. A significant fall in SBP and DBP after intrathecal injection was observed in our study. The fall from baseline SBP and DBP in Group S was 23.01% and 23.17% and in Group M was 19.6% and 20.94%, respectively.

The APGAR scores were normal and statistically comparable in both groups in our study. Benhamou et al also concluded that addition of intrathecal clonidine did not adversely affect the neonatal outcome in terms of APGAR scores.5 Singh et al also observed there was no change in neonatal outcome after administration of intrathecal 75 mcg clonidine which is similar to our study.12 In our study, the level of sedation provided by intrathecal clonidine (RSS 2 and 3) was not only acceptable, but also beneficial owing to its anxiolytic role. The sedation scores were normal and statistically comparable in both the groups.

There was one incidence of respiratory depression in both groups where saturation fell below 95% and was treated with oxygen 4 lit/min. This was not statistically significant. We had no significant hypotension or significant bradycardia in either groups. There was one incidence of PDPH in either of the groups, hence was statistically not significant. Intrathecal clonidine in our study did not produce any pruritus. Although dryness of mouth and sedation are well known side effects of clonidine we did not notice any of these in our study. A study conducted by van Tulji et al also detected no side effects on addition of intrathecal clonidine to hyperbaric bupivacaine which is similar to our study.7

We studied block characteristics of two different methods of injection of additive clonidine i.e. Sequential versus premixed in a single syringe. Sequential group produced faster, longer sensory and motor blocks. We have observed that this can be attributed to the change in baricity. Baker et al who also concluded that increasing the baricity of intrathecal clonidine solution reduces haemodynamic side effects but decreases the duration of analgesia.16 However further studies need to be done in this direction.

CONCLUSIONS

Addition of intrathecal clonidine to hyperbaric bupivacaine provided a dense surgical anaesthesia irrespective of the technique of administration. However, sequential administration of clonidine reduces the time of onset, time to achieve complete sensory and motor block and significantly prolongs the total duration of the block and effective analgesia. It also did not increase the incidence of hypotension or bradycardia or increased the level of sedation. Neonatal outcomes remained unaffected.

REFERENCES

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