A comparative study of intrathecal clonidine VS dexmedetomidine in caesarean patients

Selvakumar Rajasekaran1,*  Suresh Murugaih2, Asha Anandan3, Ayshvarya Ramalingam4

1Professor & HOD, 2Associate Professor, 3,4Senior Resident, Dept. of Anaesthesia, K.A.P. Viswanatham Government Medical College, Tiruchirappalli, Tamil Nadu, India

*Corresponding Author:
Email: drsurela@yahoo.com

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Abstract
Introduction: Spinal anaesthesia is the most commonly employed technique for Caesarean section. Many drugs such as opioids as intrathecal additives such have been widely studied found to be associated with respiratory depression, pruritis, etc. Upcoming studies on alpha-2 agonists as intrathecal additives have been found promising and will replace opioids soon. Knowledge on the efficacy of the individual α2 agonists over one another is lacking. So the aim of the study is to compare the spinal additive effect of dexmedetomidine and clonidine in pregnant patients for caesarean section.

Materials and Methods: Ninety patients belonging to ASA group I and II of age group of 20 – 40 years were included in the study. Patients with PIH, Diabetes, Body weight above 100kg, Height less than 145 cm, Post spinal surgeries, spinal deformity, and known history of Coagulopathy and allergic to study drugs, documented IUGR, intrauterine anomaly and patients those who are not willing for spinal anaesthesia were excluded from the study. They were randomly allocated into three groups of 30 patients each, Group D where the patients received dexmedetomidine 5µg with bupivacaine 10mg, Group C where the patients received clonidine 15µg with bupivacaine 10mg and Group B where the patient received bupivacaine 10mg with 0.9% saline 0.5ml. The duration of the sensory and the motor blockade, two segment regression times, duration of the postoperative analgesia, sedation and neonatal wellbeing with maternal hemodynamic changes were studied.

Results: Demographic characteristics and hemodynamic parameters were comparable between the three groups. The onset and maximal sensory block was faster in Dxm and clonidine groups (162±41.40;166±37.57) than control group (254.67±28.73) which was statistically significant. The two segment regression time was significantly shorter in control group (67.53±5.94) than Dxm and clonidine group (103.47±8.08;108±6.90). Dxm and clonidine group showed shorter time (3.40±0.84; 3.13±0.50) to reach Bromage grade 3 motor block than control group (4.52±1.78). The maximum sedation score recorded in both Dxm and clonidine group was 2. The time of onset (minutes) of sedation between Dxm and clonidine groups which was (8.9±2.85;7.43±2.27) were statistically insignificant.

Conclusion: Addition of intrathecal clonidine 15µg/ dexmedetomidine 5µg to 10mg of bupivacaine in LSCS patients increase the duration of motor and sensory blockade, with little changes in maternal hemodynamics without any changes in neonatal outcome.

Keywords: Caesarean section, Clonidine, Dexmedetomidine, Spinal anaesthesia.

Introduction
Spinal anaesthesia is the most commonly used technique for caesarean section as it is very economical and safe to administer. In spinal anaesthesia, lignocaine and bupivacaine are commonly used which give good anesthesia and analgesia during intraoperative period but short lived analgesia in the postoperative period. In postoperative period adequate pain relief is important as it ensures early mobilization and less incidence of urinary retention thus decreases the hospital stay. In order to prolong the analgesia during postoperative period, intrathecal additives like adrenaline, morphine, buprenorphine, ketamine, and fentanyl are used. Opioids are commonly used as spinal adjuncts to ensure good postoperative analgesia, but the complications associated with opioids usage such as respiratory depression are well known. The α2 agonists are gaining popularity in anesthesia as an adjunct in regional anesthesia, premedication in general anesthesia and in ICU sedation.

Clonidine is a partial α2 agonist used intrathecally with well established efficacy and safety. It prolongs the duration of motor and sensory spinal blockade when used along with local anesthetics. Dexmedetomidine(Dxm) is a highly selective another α2 adrenoreceptor agonist and has been approved by Food and Drug Administration (FDA) as an intravenous sedative and co analgesic drug. Its α1/ α2 selectivity is eight times higher than clonidine.

So far the existing studies have compared either clonidine or dexmedetomidine with that of the opioids, but studies to compare the effect of these two α2 agonists as spinal additive are lacking. So we decided to compare the spinal additive effect of dexmedetomidine and clonidine in pregnant patients for caesarean section. We also used a control group with only bupivacaine.

Materials and Methods
After getting approval from institutional Ethical committee, 90 patients were selected randomly into three groups. Those aged between 20-40 years, with ASA...
physical status of I-II, coming with singleton pregnancy scheduled for elective caesarean delivery were included in the study. Patient refusal, those with comorbidities such as PIH, Diabetes, belonging to ASA III, IV, with body weight >100kg and height <145cm, with spinal deformities, coagulation abnormalities and history of allergy to the study drugs, and those patients with IUGR, intrauterine anomaly, PROM were excluded from the study.

Patients were assigned into three groups randomly by computer based random allocation numbers.

Table 1: Drug solutions used in the three groups

| Groups    | Volume | Drugs                                                                 |
|-----------|--------|------------------------------------------------------------------------|
| Group D   | 2.5ml  | Dexmedetomidine 5μg + Normal Saline(NS) (0.5ml) + Bupivacaine 10mg (2ml) |
| Group C   | 2.5ml  | Clonidine 15μg + NS (0.5ml) + Bupivacaine 10mg (2ml)                    |
| Group B   | 2.5ml  | NS (0.5ml) + Bupivacaine 10mg (2ml)                                     |

The study drug solution was prepared by the second author who was not involved in the study. Both anesthetist and patient were blinded to the study drug.

In preoperative room area, all parturient were assessed with clinical history and examination and then baseline NIBP and pulse rate were recorded. No premedication was administered preoperatively. Preloading was done with lactated ringer’s solution of 20ml /kg started 15minutes before the induction of spinal anaesthesia. Intraoperative standard anaesthesia monitoring consists of pulse rate, ECG, NIBP, SPO2. Under strict aseptic precaution, spinal anaesthesia was performed in right lateral position at L2-3/L3-4 level through midline approach. Spinal needle used was Quincke 23G/25G. Immediately after spinal injection patient was turned to supine position and O2 (4-6L/min) was given through face mask.

The time of administration of spinal anaesthesia was taken as zero minute. The sensory block was tested by alcohol soaked cotton in midaxillary line bilaterally which was tested every 30 seconds till it reaches its maximum level. The motor blockade was assessed every minute by Modified Bromage scale. The time from intrathecal injection to two dermatome sensory regression, sensory regression to S2 dermatome and motor block regression to modified Bromage 0 was recorded.

Table 2: Modified Bromage scale

| Bromage scale | Description                                                                 |
|---------------|-----------------------------------------------------------------------------|
| 0             | Patient is able to move hip, knee, and ankle.                                |
| 1             | Patient unable to move the hip but able to move the knee and ankle.         |
| 2             | Patient is unable to move hip and knee but able to move ankle.              |
| 3             | Patient is unable to move hip and knee and ankle.                          |

Sedation score was assessed by Ramsay Sedation Score. The sedation score was assessed every 5 minutes during intraoperative period till reaches the maximum level. In postoperative period it was assessed in every 30 minutes till the patient was fully awake.

Table 3: Ramsay Sedation Score

| Ramsay Sedation Scale | Description                                      |
|-----------------------|--------------------------------------------------|
| Grade 0               | Awake, conscious, no sedation, to slightly restless |
| Grade 1               | Calm and compose                                 |
| Grade 2               | Awake on verbal command                          |
| Grade 3               | Awake on gentle tactile stimulation               |
| Grade 4               | Awake on vigorous shaking                        |
| Grade 5               | Unarousable                                      |

Postoperative pain was assessed by visual analog score using word scale. First analgesic requirement time is defined as from the time of spinal injection to the time at when the patient requires analgesia. The rescue analgesic used was inj.Tramadol 100mg i.m.
Preoperative hemodynamics was considered as base line values. Intraoperative hemodynamics was calculated from the time of spinal injection to shifting to the immediate recovery room. Post-operative parameters were recorded from immediate recovery room to first analgesic requirement period in the postoperative ward.

Intraoperative and post-operative complications like nausea, vomiting, pruritis, hypotension and respiratory depression were recorded. Hypotension is defined as 20% decrease in systolic blood pressure or systolic blood pressure of <100 mmHg. Hypotension can be treated with left uterine tilt, increasing the fluid infusion and inj. Ephedrine 6 mg i.e. bolus. Bradycardia is defined as the pulse rate of <60 bpm, which can be treated with inj. Atropine 0.3-0.6 mg IV. Respiratory depression (RR<8 or spo2 <95%) can be treated with O2 supplementation.

The observed data were analyzed by SPSS version 21.0 software. Continuous variables were compared with one way ANOVA. The comparison was done with using chi-Square or Benforroni test as appropriate value reported at the 95% confidence interval. P value <0.005 was considered as statistically significant.

Sample size was calculated using priori power analysis. We did a pilot study in which the average difference in the duration of sensory blockade between dexmedetomidine and clonidine groups was 78 minutes with a standard deviation of 5.2. Using these variables and assuming a confidence level of 95% and power of 0.8 and alpha error of 0.2, we calculated 26 patients for each groups and calculating for the dropouts and mishaps we arrived to use a sample size of 30 for each groups.

Results

Demographic data regarding age, weight and height was compared among the three groups. Base line mean pulse rate and MAP was similar in three groups. During Intraoperative period mean pulse rate recorded showed no significant difference among three groups. Three groups were showed reduction in pulse rate but more with Dexmedetomidine and clonidine group (82.75±8.09 & 87.18±14.86) than control group (86.36±3.31). But postoperative mean pulse rate was significantly lower in both Dexmedetomidine and clonidine groups (79.27±3.97; 78.33±3.95) than control group (86.45±0.94). Mean BP changes during intraoperative period was insignificant among the three groups but the reduction more in dexmedetomidine and clonidine group (80±6.05 & 78.32±5.88) than control group (80.93±4.26). But in the postoperative period, MAP was significantly lower in dexmedetomidine and clonidine groups (86.70±5.27; 81.14±3.79) when compared to control group (87.88±3.36). Both (dexmedetomidine) Dxm and clonidine produces fall in pulse rate and blood pressure but with clonidine the fall in pulse rate and blood pressure was slightly more than Dxm group. But both drugs did not produce any significant hypotension or bradycardia which warranted treatment.

The onset and maximal sensory block was faster in Dxm and clonidine groups (162±41.40;166±37.57) than control group(254.67±28.73) which was statistically significant. But between Dxm and clonidine group it was statistically insignificant (P>0.05). The two segment regression time was significantly shorter in control group (67.53±5.94) than Dxm and clonidine group(103.47±8.08;108±6.90). Clonidine group showed slightly longer time than Dxm group but statistically insignificant (P>0.05). Time to reach S2 level was estimated at the time taken for the return of full skin sensation which was significantly longer in Dxm and clonidine group (304±22.53;294.67±28.73) than the control group (214±17.14). Dxm group shows clinically significant longer time than clonidine group but it was statistically insignificant (P>0.05). First analgesic requirement time was significantly prolonged in Dxm and clonidine group (231±17.08; 316±16.93) than control group (102.23±7.40). Clonidine group shows clinically longer time than Dxm group but it was statistically insignificant (P>0.05)

All patients involved in the study achieved Bromage grade 3 motor blockade. However Dxm and clonidine group showed shorter time (3.40±0.84; 3.13±0.50) to reach Bromage grade 3 motor block than control group (4.52±1.78). Both Dxm and clonidine groups were almost similar in character in this regard. Motor recovery time was longer in Dxm and clonidine groups than control group.

The maximum sedation score recorded in both Dxm and clonidine group was 2. The time of onset (minutes) of sedation between Dxm and clonidine groups which was (8.9±2.85;7.43±2.27) were statistically insignificant (P>0.05). No sedation recorded in control group.

The neonatal assessment was recorded among the three groups as 1st and 5th minute Apgar score. There is no significant difference (Apgar> 7) among the study groups (P>0.05)

Hypotension was mild to moderate among the three groups but it was less in Dxm and clonidine groups 7 (23%); 8 (26.6%) when compare to that of control group (33%). No event of bradycardia was recorded in the groups. Nausea and vomiting were more in number in
control group 6 (20%) than study group 4(13%) each. No pruritis and dryness of mouth was recorded among the three groups.

**Table 5: Patient demographic data**

| Variables     | Dxm(n=30)       | Clonidine(n=30) | Cont(n=30)       |
|---------------|-----------------|-----------------|-----------------|
| Age(years)    | 23.73±3.35      | 24±1.43         | 23.9±1.42       |
| Weight(kg)    | 57.7±1.82       | 59.13±4.60      | 57.97±5.44      |
| Height(cm)    | 154.6±4.09      | 155.87±2.78     | 153.9±2.72      |

**Table 6: Characteristics of spinal block**

| Observations                                | Dxm group(30)  | Clonidine group(30) | Cont group(30) | F test | P value |
|---------------------------------------------|----------------|---------------------|----------------|--------|---------|
| Time to reach maximum sensory level/seconds (T4) | 162±41.40      | 166±37.57           | 254.67±28.73   | 241.08  | 0.001   |
| Time to reach Grade 3 motor block/mins      | 3.40±0.84       | 3.13±0.50           | 4.52±1.78      | 105.33  | 0.000   |
| Two segment regression time/ mins           | 103.47±8.08     | 108±6.90            | 67.53±5.94     | 298.157 | 0.000   |
| Sensory recovery time to S2/mins            | 304±22.53       | 294.67±28.73        | 214±17.14      | 135.462 | 0.000   |
| First analgesic requirement time/mins       | 231±17.08       | 316±16.93           | 102.23±7.40    | 1648.861| 0.000   |

**Table 7: Ramsay Sedation Score**

|                           | Dxm group(30)  | Clonidine group(30) | P value |
|---------------------------|----------------|---------------------|---------|
| Mean Onset Time           | 8.9±2.85       | 7.43±2.27           | 0.27    |

**Table 8: Neonatal Assessment**

| Apgar score   | Dxm group(30) | Clonidine group(30) | Cont group(30) | F test | P value |
|---------------|----------------|---------------------|----------------|--------|---------|
| 1st min Apgar | 8.07±0.45      | 7.93±0.45           | 7.97±0.18      | 6.013  | 0.104   |
| 5th min Apgar | 9.27±0.45      | 9.43±0.50           | 9.13±0.35      | 3.531  | 0.234   |

**Table 9: Adverse effects in studied groups**

| Complications    | Dxm group(30) % | Clonidine group(30) % | Cont group(30) % |
|------------------|-----------------|-----------------------|------------------|
| Hypotension      | 7 (23)          | 8 (26.6)              | 10 (33)          |
| Bradycardia      | 0               | 0                     | 0                |
| Nausea/vomiting  | 4(13)           | 4 (13)                | 6 (20)           |
| Pruritis         | 0               | 0                     | 0                |

**Table 10: Hemodynamic Changes**

| Mean Pulse /MAP   | Dxm group(30)       | Clonidine group(30)  | Cont group(30)  | F test  | P value |
|-------------------|---------------------|----------------------|-----------------|---------|---------|
| Intraop pulse     | 82.75±8.09          | 87.18±14.86          | 86.36±3.31      | 0.449   | 0.644   |
| Postop pulse      | 79.27±3.97          | 78.33±3.95           | 86.45±0.94      | 21.95   | 0.000   |
| Intraop BP        | 80.6±0.05           | 78.32±5.88           | 80.93±4.26      | 0.471   | 0.631   |
| Postop BP         | 86.70±5.27          | 81.14±3.79           | 87.88±3.36      | 8.195   | 0.001   |
Fig. 1: Mean Pulse Rate

Fig. 2: Mean Arterial Blood Pressure

Fig. 3: Complications
Discussion

Additives in regional anaesthesia extend the duration of analgesia in post-operative period. In our study we compared the spinal additive effect of dexmedetomidine and clonidine. Clonidine is used in high dose (1-2 μg/kg) intrathecally to increase the sensory and motor blockade of the local anaesthetics. This high dose clonidine improves analgesia but it is also associated with side effects like sedation, hypotension and bradycardia. In our study the low dose clonidine (15μg) along with bupivacaine 10mg (2ml) improves the onset and duration of sensory and motor blockade. It also increases the first analgesic requirement time with minimal side effects. The sensory blockade of Clonidine is by its vasoconstrictive effect. Van Tuijl et al showed peak sensory level was not dose dependent and the duration of peak sensory level was 4minutes which was similar to our study. 

De kock et al also recorded that increasing the dose of clonidine from 15 to 45μg did not increase the duration of sensory and motor blockade. Intrathecal clonidine potentiates the local anaesthetic action by cellular modification in the ventral horn of the spinal cord and thereby potentiates the motor blockade duration. Dobrydnjov et al compared 15μg and 30μg of clonidine with 6mg hyperbaric bupivacaine for inguinal hernia repair. They found that the duration of motor blockade was 155mins and 185minutes in 15μg and 30μg of clonidine groups respectively. In our study the motor blockade was (210 minutes) which was similar to that of the previous study.

α2 agonists produce sympatholysis and reduction in arterial blood pressure through direct effect on brain stem nuclei and on preganglionic sympathetic neuron level. Normally this effect is counteracted by the peripheral vasoconstrictive action. The sympatholytic effect was enhanced with local anaesthetics and produces excessive fall in blood pressure.

Dobrydnjov et al observed that increasing the dosage of clonidine caused increasing changes in hemodynamics causing hypotension. He also observed that clonidine did not have any direct effect on heart rate. In our study with 15μg clonidine there was no significant hemodynamic complications observed. Only 8 out of 30 patients showed mild to moderate hypotension and there was no incidence of bradycardia. The hypotension was effectively managed with 6mg of ephedrine. Sethi et al documented that the high dose clonidine was associated significant rise in nausea and vomiting. But in our study with low dose clonidine, only 4 out of 30 patients had nausea and vomiting.

Central sedative effect is well known with α2 agonist. Nicmi et al and Aaalovschi et al documented that the sedative action is dose dependent. They observed significant sedation with 1 μg/kg dosage when used intrathecally. In our study the maximum sedation score observed was 2.

Sethi et al documented dryness of mouth is one of the side effects observed with 1 μg/kg dosage of clonidine. In our study there was no incidence of dryness mouth.

Ranju Singh et al observed that intrathecal clonidine in dosage of 50 μg or 75 μg did not produce any maternal or neonatal side effects. Another study done by nikil Kothari et al showed no neonatal side effects with 50 μg. In our study also there is no maternal and neonatal side effects (Agar score 7.73±0.45; 9.43±0.50)

Dexmedetomidine is a newer selective α2 agonist. The analgesic action is not well known. But it may exert their action through presynaptic C fibres and postsynaptic dorsal horn neurons. It potentiates local anaesthetic action through the same mechanism as that of clonidine.

S.Fyneface-Organ et al, used intrathecal low dose Dxm (2.5μg) with low dose bupivacaine for uncomplicated vaginal delivery as labor analgesic technique. They observed the extent of analgesia in post delivery period and there were no neonatal or maternal side effects. S.M .Al Ghanem et al found the duration of sensory block with intrathecal Dxm (5 and 10 μg Dxm) was dose dependent. In our study intrathecal bupivacaine with Dxm 5 μg significantly prolong the post operative analgesic period like the previous study.

In my study both the α2 agonists significantly increase the time for first analgesic requirement (D-231±17.08; C-316±16.93). Axelsson and Gupta found that intrathecal α2 agonists improved the quality of post operative analgesia by increasing the duration of 2 segment regression time and motor blockade in a dose dependent manner. In our study both the α2 agonists increased the 2 segment regression time (D-103.47±8.08; C-108±6.90) and also duration of the motor blockade (D-304±22.53;C-294.67±28.73) as compared to placebo group(67.53±5.94 and 214±17.14).

The study regarding transfer of clonidine and Dxm across the isolated human placenta showed that the transfer was faster with Dxm than clonidine. This is because of the increased lipophilicity of Dxm which leads to placental tissue retention of Dxm than clonidine. S.Fyneface-Organ et al observed no significant neonatal depression with Dxm. They used multiple parameters for neonatal assessment. We used Apgar score at 1st and 5th minute to assess the neonatal wellbeing. There was no significant neonatal depression in both the Dxm and clonidine (8.07±0.45; 9.27±0.45) compared to the control group (7.97±0.18; 9.13±0.35). Many studies have shown the safety aspect of Dxm in pediatric population as an intravenous ICU sedation. Shukry et al and Munro et al used Dxm as a sole intravenous anaesthetic agent in pediatric general anaesthesia without any side effects, where it prevented the emergence delirium from GA.

A follow up study was done by Gupta et al to rule out neurological complication following intrathecal Dxm. In that 4 weeks follow up did not notice any form
of neurological deficit. They reported that 5 μg intrathecal Dxm as compared to intrathecal fentanyl 25 μg produced better post operative analgesia and did not produce any hemodynamic adverse effect. Similarly in our study good post operative analgesia without any significant side effects were observed in Dxm group.

The most significant side effect of intrathecal α2 agonists are hypotension and bradycardia. With reduction in intrathecal dose of α2 agonists unwanted hypotension and bradycardia may be prevented. In our study we observed no bradycardia and minimal hypotension in both Dxm and clonidine groups. They were more with control group with bupivacaine (10mg).

**Conclusion**

Our study shows that addition of intrathecal clonidine 15μg/dexmedetomidine 5μg to 10mg of bupivacaine in LSCS patients increase the duration of motor and sensory blockade, with little changes in maternal hemodynamics with any changes in neonatal outcome. Both clonidine and dexmedetomidine add adequate sedation during perioperative period and also improve the quality of analgesia in the postoperative period. Comparing dexmedetomidine and clonidine the duration of post-operative analgesia was longer with clonidine.

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