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ORIGINAL ARTICLE

Effect of adding intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine for elective cesarean section

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ABSTRACT

Background & Aims: Cesarean section performed under subarachnoid block is often accompanied by visceral pain. Hence, various adjuvants have been tried to address this problem and to provide prolonged postoperative analgesia. Highly selective α2-agonist dexmedetomidine is increasingly used as an intrathecal adjuvant.

The study was designed to evaluate dexmedetomidine 5 µg as adjuvant to intrathecal hyperbaric 0.5% bupivacaine 9 mg in cesarean sections with respect to block characteristics, sedation and neonatal APGAR scores.

Settings and Design: A prospective, randomized, double blinded, controlled study

Methodology: 60 parturients undergoing elective lower segment cesarean section were assigned to 2 groups (n=30) to receive either 0.5% hyperbaric bupivacaine 9 mg with dexmedetomidine 5 µg (Group D) or 0.5% hyperbaric bupivacaine 9 mg with saline (Group C). Block characteristics, hemodynamic parameters, sedation scores and neonatal APGAR scores were recorded. Data obtained were compiled and analyzed with appropriate tests. A p-value of < 0.05 was considered significant.

Results: Onset of sensory and motor block were significantly faster in Group D (45 and 43 sec) compared to Group C (68 and 67 sec). Time for two segment sensory regression, duration of sensory and motor block was significantly prolonged in Group D compared to Group C (140 vs 44, 364 vs 126 and 341 vs 113 min). Time for first analgesic request was significantly prolonged in Group D compared to Group C (420 and 69 min). There was no significant difference in hemodynamic parameters, sedation and neonatal APGAR scores between the groups.

Conclusions: The addition of 5 µg dexmedetomidine as an intrathecal adjuvant to bupivacaine for cesarean section hastens and prolongs sensory and motor block and provides better perioperative analgesia without significant maternal and neonatal adverse effects.

Key-words: Cesarean section; Intrathecal; Dexmedetomidine; Hyperbaric bupivacaine; Spinal anesthesia

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INTRODUCTION

Subarachnoid block with 0.5% hyperbaric bupivacaine is the most commonly used anesthetic technique for lower segment cesarean section (LSCS).[1] Blockade to T4 dermatome is necessary to perform cesarean delivery without maternal discomfort.[2] This high level is commonly associated with hypotension and attendant decreased utero-placental perfusion. Reducing the volume of local anesthetic agent to

avoid hypotension carries a risk of limited duration of action and hence lack of postoperative analgesia.[3] When only local anesthetic is used, postoperative opioid analgesic requirement is higher.[4]

α2 adrenergic receptor agonists due to their sedative, analgesic, perioperative sympatholytic and hemodynamic stabilizing properties may be useful as adjuvants to intrathecal local anesthetics. Intrathecal clonidine used in elective cesarean deliveries is shown to have anti-hyperalgesic and analgesic effects.[5] Dexmedetomidine, a highly selective α2 adrenergic receptor agonist is being safely used as an adjuvant for subarachnoid block in urological, orthopedic and lower abdominal surgical procedures.[6] But, its use with intrathecal local anesthetic agents for cesarean delivery has not been extensively studied. Hence, the present trial was conducted to study the efficacy of addition of dexmedetomidine to intrathecal hyperbaric bupivacaine for elective LSCS.

METHODOLOGY

After institutional ethical committee approval, this prospective study was conducted in 60 parturients between ages of 18 to 35 years and a height of 150-170 cm with ASA physical status II undergoing elective LSCS under subarachnoid block in a tertiary care obstetric hospital attached to a medical college in south India.

Subjects with pre-existing medical and obstetric co morbidities, bleeding diatheses, local infection, raised intracranial pressure, known hypersensitivity to study drugs, patient refusal for spinal technique and emergency LSCS were excluded from the study.

Based on our pilot study, taking a difference in the duration of sensory and motor block of 30 min between the two groups as clinically significant, to have an 80% power in the present study with a simple stratified two sample t-based 95% confidence interval ($\alpha = 0.05$), 26 parturients were to be recruited in each arm of the study. For adequate sampling size with dropout compensation, 60 subjects were recruited for the study and randomly divided into two groups with 30 parturients ($n = 30$) in each group by shuffled sealed envelope method to receive either 0.5% hyperbaric bupivacaine 9 mg (1.8 ml) with dexmedetomidine 5 μg (0.2 ml) (Group D) or 0.5% hyperbaric bupivacaine 9 mg (1.8 ml) with 0.9% NaCl solution 0.2 ml (Group C).

Data were collected in pretested performa meeting the objectives of the study. Preoperative assessment was done for each patient and written informed consent was taken. All parturients were premedicated on the night before surgery with tablet ranitidine 150 mg, and kept nil per os after that. All patients were transported to OT in left lateral position where they were preloaded with Ringer's lactate 500 ml half an hour before anesthesia. All patients received preoperative aspiration prophylaxis with inj ranitidine 50 mg IV and inj metoclopramide 10 mg IV. Routine ASA monitoring was established.

The study drugs were prepared by the senior anesthesiologist who was not involved in further observations of the parturients. Under aseptic precautions, with patients in right lateral position, lumbar puncture (midline approach) was performed at the level of L3-L4 using 26 G Quincke spinal needles and study drug was injected by the principal investigator after confirmation of clear and free flow of cerebrospinal fluid. Sensory blockade was tested using pinprick method with a blunt 27G hypodermic needle every 15 sec till the onset of sensory blockade and thereafter at 2 min intervals till the maximum level of sensory blockade was achieved and subsequently at every 5 min during first 30 min, then at every 15 min up to 120 min, and thereafter at 30 min intervals until complete recovery. For the purpose of the present study, loss of pin prick sensation at T10 level was defined as the onset of sensory blockade. Time taken for maximum sensory blockade was defined as the time from the completion of the injection of the study drug to the maximum sensory blockade attained. Duration of sensory blockade was the time taken from the time of injection till the subject felt sensation at S1. Duration of pain relief was defined as the time from spinal injection to the first request for analgesics (VAS > 5). Inj diclofenac 75 mg IM was used as rescue analgesic with a maximum dose of 150 mg in 24 h.

Quality of motor blockade was assessed by modified Bromage scale.7 Time for two segments sensory regression time, total duration of sensory and motor blockade and total duration of analgesia were noted. Hemodynamic parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), respiratory parameters like respiratory rate (RR) and SpO_2, sedation score using Ramsay sedation score (RSS) were recorded every 2 min up to 10 min, every 5 min till 40 min, then every 10 min till the end of surgery. Any reduction of SBP more than 20% below baseline or fall in SBP less than 90 mmHg was considered as hypotension 3 mg IV increments if necessary. Neonatal APGAR scores were assessed by attending pediatrician at 1st and 5th min. Postoperative pain was assessed at 30 min, hourly

for the next 6 h, and 2 hourly till 24 h using visual analogue scale (0–10) and time to rescue analgesic request were recorded. Subjects were also monitored for occurrence of adverse events after spinal injection like nausea, vomiting, desaturation, hypotension, bradycardia (requiring inj atropine), excessive sedation and others, if any.

Statistical analysis:

All the data were entered in Microsoft Excel and analysed using Statistical Package for Social Science (SPSS) version 22.0. Descriptive statistical methods were used to summarize the data. Student's t-test and Chi square test were used for continuous and categorical variables respectively. $p < 0.05$ was considered significant.

RESULTS

The parturients in both groups were comparable with respect to demographic characteristics. All the parturients completed the study (Table 1).

Table 1: Demographic characteristics

Variable	Group D	Group C	p-value
Mean Age (y)	24.6 ± 2.9	25.2 ± 3.8	0.45
Mean Weight (kg)	59.7 ± 6.3	59.8 ± 5.6	0.95
Mean Height (cm)	155.9 ± 4.4	156.3 ± 4.5	0.73
Mean BMI (kg/m^2)	24.6 ± 2	24.4 ± 2.9	0.82

Table 2: Comparative block characteristics in two groups

Block Characteristics	Group D	Group C	p-value
Time for onset of analgesia (sec)	45 ±11.3	68 ± 11.3	< 0.001
Maximum sensory level	T 5.6 ± 1.2	T5.7 ± 1.4	0.77
Time to peak sensory level (min)	3.98 ± 1.8	4.98 ± 1.6	0.023
Time for two segment sensory regression (min)	140 ± 12.3	44.15 ± 6.5	< 0.001
Time taken for sensory regression to S1 (min)	364 ± 48.2	126.3 ±12.4	< 0.001
Duration of analgesia (min)	420.3 ± 74.6	68.9 ± 11.1	< 0.001
Time for onset of motor block (sec)	42.8 ± 15.6	67 ± 15.8	< 0.001
Time for maximum motor block (min)	3.8 ± 0.8	7.7 ± 2.8	< 0.001
Duration of motor block (min)	341 ± 39.9	113.2 ± 11.6	< 0.001

Sensory and motor blockade characteristics are shown in Table 2.

The mean time of onset of analgesia to T10 level was significantly faster in Group D compared to Group C ($p < 0.001$). The maximum sensory levels obtained in two groups were comparable and sufficient for the surgery (T3-T8). Peak sensory level was achieved earlier in Group D compared to Group C ($p = 0.023$). The mean time for two segment sensory regression was significantly prolonged in Group D compared to Group C ($p < 0.001$). The time taken for sensory regression of the blockade to S1 level was more in Group D compared to Group C ($p < 0.001$). Duration of analgesia was prolonged in Group D compared to Group C.

24 hours postoperative VAS scores were consistently low in Group D compared to Group C (Figure 1).

The time of onset of Bromage Grade I and IV motor block was rapid in Group D compared to Group C ($p < 0.001$). The duration of motor block was less in Group D than Group C ($p < 0.001$).

The RSS measured at various intervals in both groups were almost similar and all parturients had RSS ≤ 2. Neonatal APGAR scores at 1 and 5 min were comparable between Group D and Group C.

There were no significant alterations in the hemodynamic parameters (HR, SBP, DBP and MAP) between the two groups. Variations in HR and MAP are shown in Figures 2 and 3

There was no significant difference between Group D and C with respect to respiratory rate, oxygen saturation (SpO_2) and the incidence of bradycardia and hypotension. The mean consumption of mephentermine and atropine for treatment of hypotension and bradycardia were similar and the differences were statistically not significant.

Both the groups were observed for occurrence of possible adverse effects like nausea, vomiting, pruritus,

Table 3: Comparative frequency of adverse effects in the groups

Adverse effects	Group D n (%)	Group C n (%)	p-value
Hypotension	8 (26.7)	8 (26.7)	1
Shivering	0	1 (3.3)	.32
Bradycardia	6 (20)	6 (20)	1
Pain	0	3 (10)	0.07
Total	14 (46.7)	17 (56.7)	0.17

shivering and respiratory depression. Incidence of these adverse effects were low and not significant. (Table 3)

DISCUSSION

Neuraxial block for LSCS has become increasingly popular, as data indicating decreased maternal morbidity with regional anesthesia have accumulated.[8,9] In this era of advanced obstetric care, spinal anesthesia for LSCS continues to be the technique favoured by most anesthesiologists due to its ease and reliability, rapid onset of analgesia, motor blockade and muscle relaxation and also for having a definitive end point.10 Although various local anesthetics can be used for spinal blockade, hyperbaric bupivacaine 10 to 15 mg is frequently used to achieve an adequate (T4) block level. In our institution, considering the patients' demographic profile and as proposed by Danelli G et al[11], 9 mg 0.5% hyperbaric bupivacaine is the dose of spinal local anesthetic used in parturients of height 150-170 cm.

The cesarean sections done under spinal anesthesia are often associated with visceral pain, nausea, and vomiting.[2] Studies have reported that in cesarean sections, spinal anesthesia, using only local anesthetic (without any additive) has a short duration of effect, and is insufficient for preventing the above side effects especially during uterine manipulation and peritoneum closure, and that it leads to postoperative analgesic requirement at an earlier stage.[12] Though a long acting local anesthetic with high-potency and differential

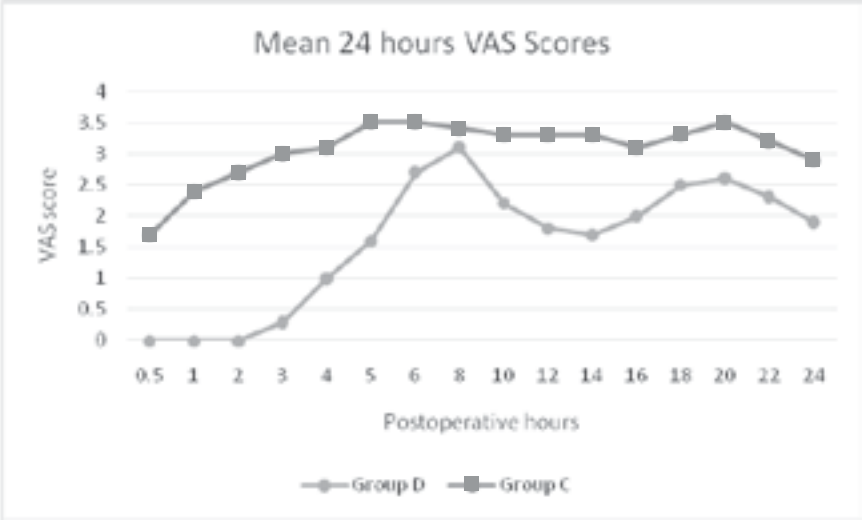

Figure 1: Mean VAS scores for 24 hours in two groups

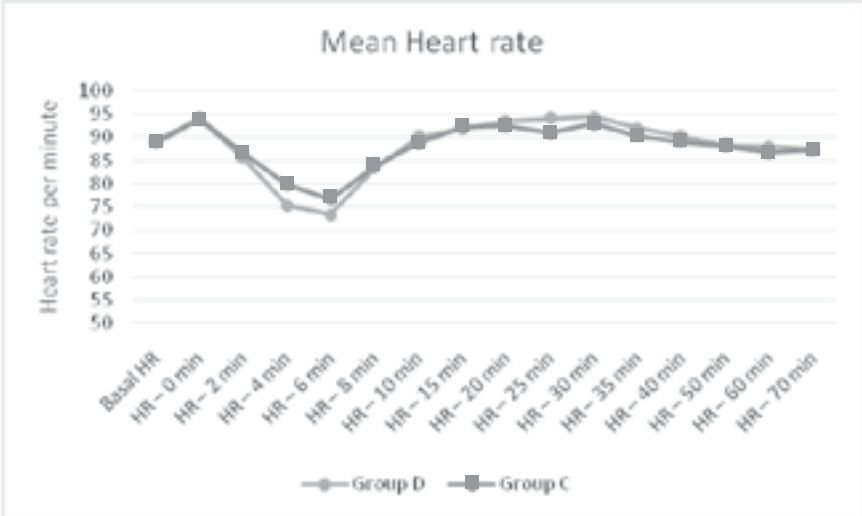

Figure 2: Comparative mean heart rates in two groups

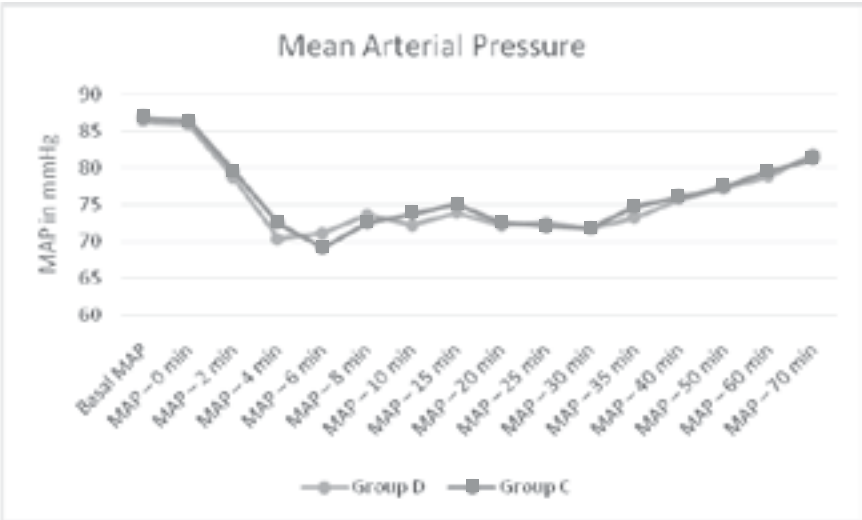

Figure 3: Comparative mean arterial pressures in two groups

sensorial-motor blockade , bupivacaine doesn't obliterate visceral pain and does not have advantage of prolonged postoperative analgesia.[13] Lipophilic opioids like fentanyl are commonly used adjuvants to overcome these shortcomings, but there are some concerns about disadvantages of opioids use in this setting. The use of non-selective α2-agonists like clonidine as intravenous adjuvants has shown to be without the side effects of opioids e.g. respiratory depression and pruritus, while providing improved perioperative analgesia and beneficial sedation. Clonidine has also been used intrathecally as an adjuvant with bupivacaine up to a dose of 1 μg/kg in various surgeries and in parturients undergoing LSCS, without significant maternal and neonatal side-effects.[14,15] But, the usual dose of clonidine (15-150μg) may be sometimes associated with bradycardia, hypotension and sedation.[4]

Dexmedetomidine is a highly selective α2-agonist with a selectivity ratio for the α2 receptor to α1 receptor of 1600:1, as compared with a ratio of 220:1 for clonidine.[16] It acts pre-junctional to reduce neurotransmitter release and post-junctional to cause hyperpolarization and reduction of impulse transmission. Intrathecal α2 receptor agonism in the dorsal horn of the spinal cord can produce anti nociceptive action for both somatic and visceral pain.[17] Highly selective α2 agonism of dexmedetomidine produces better hemodynamic stability and preserves baroreceptor reflex and heart rate response to pressors.[18]

Intravenous dexmedetomidine has been reported to produce favorable maternal and fetal outcome in labor analgesia and cesarean delivery.[19] No adverse effects were reported with the use of IV dexmedetomidine in a pregnant patient undergoing neurosurgery.[20] In a pregnant patient with Klippel-Feil syndrome with difficult airway, IV dexmedetomidine was successfully used to facilitate fiberoptic intubation before administration of general anesthesia without any untoward maternal and neonatal adverse effects.[21]

Ala-Kokko TI et al. working with clonidine and dexmedetomidine on isolated perfused human placenta observed that the highly lipophilic dexmedetomidine disappeared from maternal circulation earlier than clonidine but appeared in fetal circulation later than clonidine suggesting higher placental retention.[22] This may be advantageous in labor analgesia and anesthesia for cesarean delivery. As such, dexmedetomidine, by virtue of its increased α2 selectivity, limited effects on uteroplacental blood flow, and minimal placental transfer is advantageous over clonidine.

Intrathecal dexmedetomidine is an off label use. Fyneface-Ogan S. et al. using low dose bupivacaine and dexmedetomidine for single-shot intrathecal labor analgesia, observed that the combination produced prolonged analgesia without significant motor block. They reported no adverse neonatal effects.[23]

In various studies where intrathecal dexmedetomidine (dose ranging from 3 to 15 μg) was used for orthopedic, endo-urological, lower abdominal and perianal surgeries no neurological symptoms or signs have been reported on short term follow up.[8,24,25]

The concerns about demyelination caused by high doses of epidurally administered dexmedetomidine in rabbits reported by Konakci S et al. in the year 200826 have been addressed well by Zhang H et al. in 2013.[27] They studied the molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and evaluated its neurotoxicity in vivo and in vitro experimental study on mice. They observed that in addition to prolongation of analgesia, dexmedetomidine by itself may be neuroprotective and has a potential protective property on local anesthetic-induced neurotoxicity.

The optimal dose of intrathecal dexmedetomidine has not been established. Based on the effects on α2 receptors and the characteristics of neuraxial block when these two drugs are added as adjuvants, 3 μg of dexmedetomidine is claimed to be equipotent to 30 μg of clonidine intrathecally.[28] An optimal intrathecal dexmedetomidine dose necessary for sensory and motor blockade appears to be in between 2.5 μg and 10 μg, 5 μg of dexmedetomidine being the optimum.[29,30] Hence for the present study we selected 5 μg dexmedetomidine as adjuvant.

Our findings of rapid onset and delayed offset of sensory block with prolonged duration of analgesia are consistent with earlier studies. We also observed rapid onset of motor block. As most authors have defined onset of motor block as time taken to reach modified Bromage grade III block we could not compare our results with earlier studies. The mechanism of such faster onset is not well understood, but may be due to direct action of α-2 agonists on α-motor neurons in ventral horn of spinal cord and facilitation of local anesthetic action.[31] We also found significant prolongation in duration of motor block which has been reported by most authors except Li Z et al.,[32] who found no significant prolongation of motor block. The hemodynamic stability and minimal sedation with dexmedetomidine in the present study correlates with similar findings by other investigators. [30,32,33]

Neonatal assessment using APGAR scores at 1 and 5 min in both the groups in the present study were normal. Other researchers also found no significant effect of dexmedetomidine on APGAR scores and umbilical blood gas analysis. [23,30,32,33] No neuro-behavioral scoring and umbilical artery blood gas analysis were conducted in this study as they are not routinely done in our institution.

CONCLUSION

To conclude, the results of the present study indicate that 5 μg dexmedetomidine as an intrathecal adjuvant to 9 mg 0.5% hyperbaric bupivacaine for cesarean section is useful as it hastens the onset of sensory and motor block and prolongs postoperative analgesia and motor blockade, without producing significant hemodynamic changes, sedation and neonatal adverse effects.

Conflict of interest: None declared by the authors

Authors' contribution:

SMR: Conduction of the study work, data collection, preparation of manuscript

DG: Concept, review of articles, manuscript editing

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