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Randomized Controlled Trial to Evaluate the Efficacy of Intrathecal Dexmedetomidine to Low dose hyperbaric 0.5% Bupivacaine in Elective Lower Segment Caesarean Section

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ABSTRACT

Introduction: Dexmedetomidine has been safely used as an adjuvant for subarachnoid block in obstetric as well as non-obstetric surgeries and was found to be effective without adverse effects. Hence, this study was conducted to determine the efficacy of intrathecal Dexmedetomidine for elective lower segment caesarean sections with reduction of local anesthetic dose.

Objectives: This double blinded, randomized controlled study was designed to compare the effects of addition of Dexmedetomidine on 1) Sensory and motor block 2) Maternal hemodynamics 3) Post-operative analgesia and 4) Neonatal outcome.

Methods: Eighty parturients were enrolled in study and randomized into two groups as of 40 each and named as Group D and Group B. Group D received 0.5% Hyperbaric Bupivacaine 9mg (1.8ml) + Dexmedetomidine 5μg (0.2ml of 25 μg per ml) and for Group B received 0.5% Hyperbaric Bupivacaine 10mg (2ml) . Characteristics of block, maternal hemodynamics and neonatal outcome were recorded. P value <0.05 was considered as significant.

Results: Sensory onset was rapid in D group as compared to B group (3.7 $\pm$ 1.1vs 4.5$\pm$1.2) and motor onset was also rapid in D group (3.8$\pm$2.0 vs 4.9 $\pm$1.9) with 95% CI. Duration of analgesia was also significantly high in Group D (230.5$\pm$40.5 vs 145.1$\pm$28.5). No adverse maternal and fetal outcomes were reported.

Conclusion: Intrathecal Dexmedetomidine with low dose bupivacaine for cesarean section hastens the sensory as well as motor onset without adversely affecting mother and neonate.

KEYWORDS: Intrathecal Dexmedetomidine, Cesarean section, Low dose Bupivacaine.

INTRODUCTION

Cesarean section is one of the most commonly performed surgical procedures. Spinal anesthesia with 0.5% hyperbaric bupivacaine is extensively used for lower segment caesarean section. Moreover, surgery on the uterus performed under subarachnoid block is often accompanied by visceral pain. To accomplish surgery without maternal discomfort, sensory blockade to the T4 dermatome is necessary to perform caesarean delivery. It is commonly associated with hypotension and decreased utero-placental perfusion. [1] Reducing the volume of local anaesthetic agent can decrease incidence of hypotension, but it carries a risk of inadequate analgesia and limited post-operative analgesia. [1] Hence, various adjuvants have been used with local anesthetics in subarachnoid block to avoid intra-operative visceral and somatic pain and to provide prolonged post-operative analgesia. Dexmedetomidine and clonidine are α2 adrenergic receptor agonists and have been studied as an adjuvants to intrathecal local anesthetics due to their sedative, analgesic, perioperative sympatholytic and hemodynamics stabilizing properties. [2–4] Dexmedetomidine has got relatively high ratio of α2/α1 activity (1620:1) compared to clonidine thus it is a highly selective α2 adrenergic receptor agonist with a (220:1). Dexmedetomidine has been safely used as an adjuvant for subarachnoid block in urological, orthopedic and lower abdominal surgical procedures. [5–8]

Dexmedetomidine as an adjuvant to local anaesthetic agent for caesarean delivery has been recently studied with promising results. Following intrathecal administration of Dexmedetomidine as an adjuvant with hyperbaric bupivacaine for uncomplicated caesarean deliveries, quality of spinal anesthesia was found to be good with no adverse effects on mothers and neonates. [5, 6, 9] Dexmedetomidine to has been used for ICU sedation in neonates and infants. [10] Hence, study the efficacy of addition of Dexmedetomidine to intrathecal hyperbaric bupivacaine for elective lower segment caesarean sections with reduction

of local anesthetic dose, in improving quality of sensory and motor blockade without maternal and fetal side-effects needs to be assessed.

Objectives: This study was designed to compare the effects of addition of Dexmedetomidine (5 μg) to low dose hyperbaric bupivacaine 0.5% compared to Bupivacaine 0.5%,for elective lower segment caesarean section (LSCS) in terms of 1) Sensory and motor block 2) Maternal hemodynamics 3) Post-operative analgesia and 4) Neonatal outcome.

METHODS

Trial design: This was a single center double blinded, randomized control trial conducted at tertiary care hospital in India. Full term parturients of 18 to 35 years, of ASA physical status Class I and II having height between 150-170 cm were included in the study. Patients with known hypersensitivity to any of the study drugs and or with medical and obstetric complications like anemia, heart disease, gestational hypertension, gestational diabetes mellitus, shock, septicemia and hypertension were excluded from the study. Study was conducted in S B H Government Medical College Hospital, Dhule, Maharashtra, India after Ethical committee approval wide ECR/472/Inst/MH/2013.

Study interventions: Written, informed consent in local language was taken from all study participants and was enrolled for study. population was randomly divided into two groups with 40 parturients (n=40) in each group by closed sealed opaque envelope method.Figure 1 Study drug was constituted by blinded anesthesiologist according to randomization sequence. Dexmedetomidine was constituted by diluting Dextomid50 (Neon Labs) 0.5ml up to 2 ml with normal saline. For Group D, 0.5% Hyperbaric Bupivacaine 9mg (1.8ml) + Dexmedetomidine 5μg (0.2ml of 25 μg per ml) and for Group B, 0.5% Hyperbaric Bupivacaine 10mg (2ml) were prepareed.All the participants were fasted for 6 hrs for solids and for 2 hrs for clear liquids. All Patients were premedicated on the night before surgery with tablet Ranitidine 150mg and Injection Metoclopramide 10mg IV for aspiration prophylaxis before surgery. Baseline vitals like oxygen saturation (SpO2), blood pressure, respiratory rate and heart rate were recorded. Oxygen supplementation of 3 L/min was given. Co-loading with 5ml per kg of Ringer's lactate solution was done within 10 min. Spinal anesthesia was performed in lateral position at the L3-L4 inter space with a 25 G spinal Quincke-tip needle and study drug was injected by experienced anesthesiologist. Leftward Tilt of 15 degree was immediately applied. The sensory level was tested using pinprick method with a blunt 25-G needle every1min until the peak sensory block level was achieved. Sensory onset time i.e. time to T10 level noted. Time required to maximum level was noted. Then every 10 min sensory block was tested until two segment regression. The motor block onset was assessed by the modified Bromage scale (MBS, 0 = no paralysis, 1 = inability to raise the leg, 2 = inability to flex the knee, and 3= inability to flex the ankle). Motor block of grade 3 was considered onset of block [11] After ensuring T6 sensory level, surgery was allowed to commence. [12] If patient were to complain moderate pain (visual analog score(VAS) $\geq$3) would be administered intravenous 0.5 mg/kg Ketamine. Hemodynamic parameters including blood pressure, heart rate, respiratory rate and oxygen saturation were recorded every min for first 10 min and every 5 min after that till the surgery is over Episode of hypotension (systolic blood pressure (SBP) < 90 mm Hg or drop below baseline values by 30%) was recorded and managed with intravenous 6mg of Mephenteramine. Heart rate less than 60 beats/ minute was recorded as bradycardia and treated with injection Atropine 0.6mg IV. Sedation score was assessed every 15 minutes in intra operative and hourly in the postoperative period for first 6 hours using Modified Ramsay sedation score. Neonatal APGAR scores 1 and 5 minutes were assessed by pediatrician blinded to study.

Time taken to L1 was taken as total duration of sensory blockade. Time taken to regression of motor power to Grade 2 was taken as motor recovery time. Other intra operative adverse events like nausea, vomiting and shivering were recorded. Postoperative pain was assessed using Visual analogue scale (0 – 10) at 30 minutes, then hourly for the next 6 hours and 2 hourly till 24 hours and time to first rescue analgesic request will be recorded. Inj Diclofenac Sodium 75gm intramuscular was given as rescue analgesic up to maximum 3 doses over 24 hrs.

Sample size was calculated by using online sample size calculator for randomized control trial on the basis of primary outcome, duration of sensory block. Sample size of 70 was required for 80 % power and 5% alpha error but considering failure rate of 10 %, 80 parturient were included in study.

Randomization: Random sequence was generated by computer. Randomization was done using sealed opaque envelop method. Junior resident had assessed the patients for enrollment. Principal investigator enrolled the cases and obtained consent in local language. Nurse assigned the participant according to envelope. Blinded anesthesiologist prepared the study drug. The person who gave drug, participant and person monitoring and collecting the data, all were blinded. Total 106 patients were assessed for eligibility. 26 patients were excluded as 14 were not meeting the inclusion criteria and 12 had refused to participate in study. As no patient was excluded, all 80 patients were assessed and analyzed for final result. The study population was randomly divided into 2 groups with 40 parturients (n=40) in each group by closed sealed opaque envelope method.

Statistics: The result of the study were analyzed by 't' test for independent samples and repeated measure ANOVA using SPSS for windows (version 16.0). p value of <0.05 was considered statistically significant.

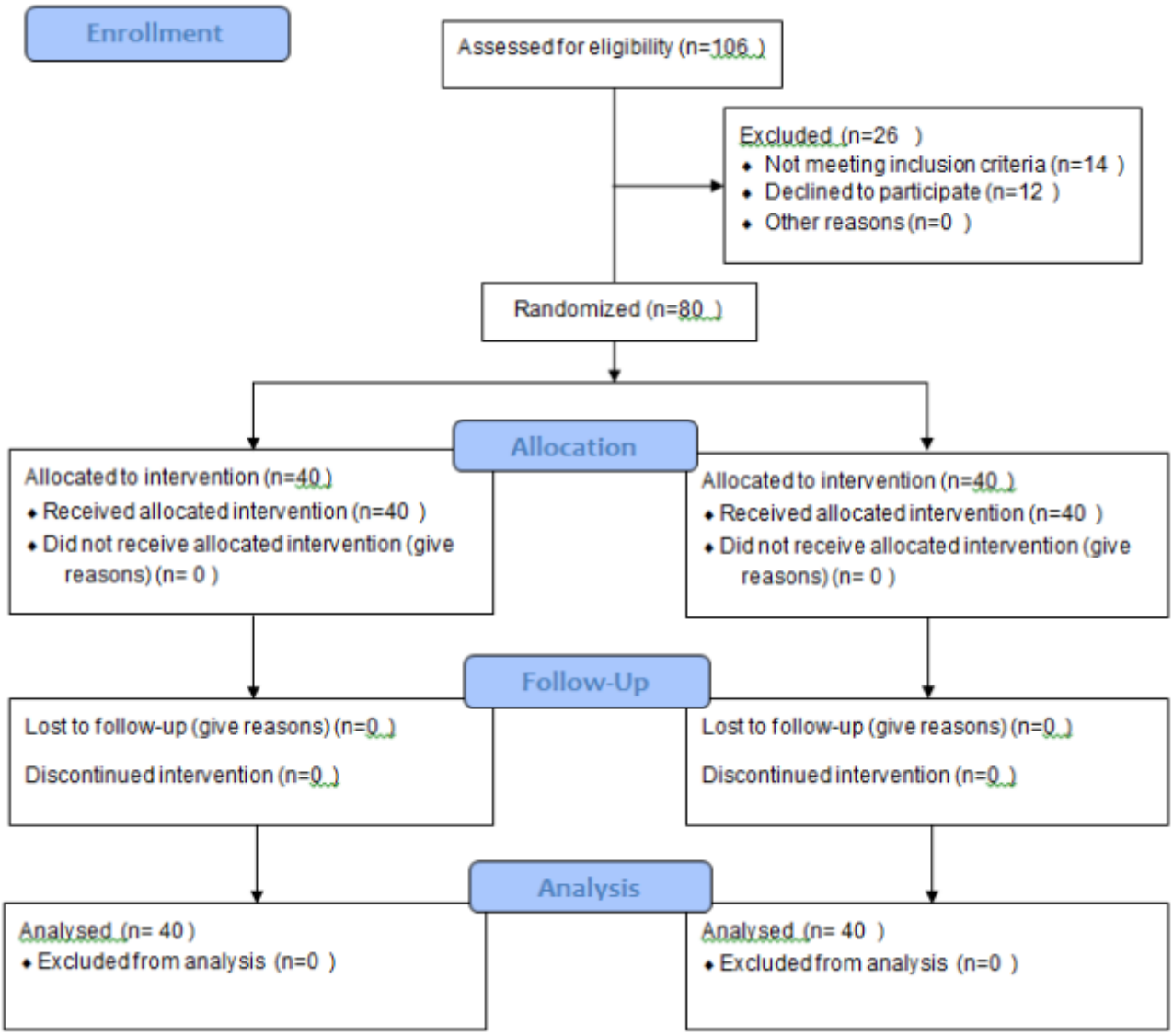

Figure 1: Consort Flow chart of study

RESULTS

Total 106 patients were assessed for eligibility. 26 patients were excluded as 14 were not meeting the inclusion criteria and 12 had refused to participate in study. Collection was commenced in Aug 2017 and completed by Aug 2018. No Significant difference was observed in demographic, ASA physical status, obstetric data and duration of surgery was between the 2 groups. Table 1 As no patient was excluded, all 80 patients were assessed and analyzed for final result.

Primary outcomes: The onset time of sensory block was significantly less in D group as compared to B groups (3.7±1.1vs 4.5±1.2). Onset of motor block was also shortened in D group compared to B group was statistically significant (3.8±2.0 vs 4.9 ±1.9). The highest block level (T5 [T3–T6] vs T5 [T3-T6]) and the time to the highest block level (15.7±4.5 vs 15.3±4.2) were similar between the 2 groups. There was significant difference in the duration of sensory block between group D and group B (112±27.0 vs 70.5±31.5). The duration of spinal analgesia was more extended in D group than in C group (230.5±40.5 vs 145.1±28.5). The duration of motor blockade was more in D group than in C group (180±22.5 vs 143±10.5).

The total number of rescue analgesics dose required for postoperative analgesia in D group were significantly lower than in B group (2±1 vs 3±1)Table 2. Shivering was found significantly reduced. There was no difference in the occurrence of adverse outcomes like hypotension, bradycardia, nausea, vomiting, respiratory depression, pruritus, sedation score and neonatal outcomes between the 2 groups.Table 3

Variable	Group D (40)	Group B (40)	P
Age	22 ± 4	23 ± 5	0.284
Height	160 ± 7	162 ± 5	0.145
Weight	63 ± 6	64 ± 4	0.383
ASA status			0.347
I	28	24	-
II	12	16	-
Gestational age	39 ± 1	39 ± 1	1
Duration of surgery	50 ± 12	55 ± 15	0.10

Data presented as mean ± SD, p test using unpaired student t test.
Gestational age in weeks, weight in kilograms, height in centimeters, Age in years, Duration of surgery in minutes

Table 1: Participants demographic, obstetric and surgical data.

Outcome Variable	Group D	Group B	p value
Highest sensory level	T5 (T3 – T6)	T5 (T3 – T6)	0
Onset time (Sensory)	3.7 ± 1.1	4.5 ± 1.2	< 0.001
Time to peak level	15.7±4.5	15.3 ±4.2	>.05
Onset time (Motor)	3.8 ± 2.0	4.9 ± 1.9	<.05
Duration of Analgesia	222.5 ± 42	152 ± 24	< 0.001
Duration of sensory block	112 ± 27.0	70.5 ± 31.5	< 0.001
Duration of motor block	180 ± 22.5	143 ± 10.5	< 0.001
Analgesic dose requirement	2 ± 1	3 ± 1	< 0.001

Table 2: Characteristics of spinal anesthesia in patients with respect to objectives

Variable	Group D	Group B	p value
Hypotension	8 (20)	12(30)	> 0.05
Nausea vomiting	7 (18)	9 (23)	> 0.05
Bradycardia	0	0	> 0.05
Shivering	1 (4)	7 (18)	< 0.05
Respiratory depression	0	0	NA
Pruritus	0	0	
Sedation score	3 ± 1	3± 1	1
APGAR score			
At 1 min	8 ± 1	8 ± 1	> 0.05
At 5 min	9 ± 1	9 ± 1	> 0.05

Table 3: Maternal and neonatal outcomes

DISCUSSION

Spinal anesthesia for LSCS is most popular, due to decreased maternal morbidity with regional anesthesia. [1]It provides ease and reliability, rapid onset of analgesia, motor blockade and muscle relaxation.Hyperbaric bupivacaine 0.5%, 10 to 12 mg is commonly used to achieve an adequate (T4) sensory level. In our institution, we use 0.5% hyperbaric bupivacaine in dose of 10 to 12 mg for spinal anesthesia for lower segment cesarean section.

Spinal hypotension is most common complication. Reduction in dose to reduce the hypotension is not possible due to increasing risk of inadequate block. Visceral pain, nausea, and vomiting are the most common causes of discomfort during cesarean sections, if done under spinal anesthesia. Administering spinal anesthesia, using only local anesthetic in usual dose has shown shorter duration of action, and is ineffective in preventing the above side effects during uterine manipulation and peritoneum closure. It causes early and increased postoperative analgesic consumption. Increasing the doses may intensify the block but at the cost of increased hypotension. Bupivacaine doesn't obliterate visceral pain and does not provide prolonged postoperative analgesia in spite being long acting with high-potency and differential sensorial-motor blockade. [13]

Fentanyl is the most commonly used adjuvants to improve the quality of block. But in India it is not widely available and also not devoid of discomforting side effects like pruritus. Use of Clonidine, a non-selective α2-agonists, as an intravenous supplement was found to be free from opioid related side effects like respiratory depression and pruritus, with improved perioperative analgesia and conscious sedation.

Clonidine as an adjuvant with bupivacaine up to a dose of 1 μg/kg has been used for various surgeries. Intrathecal Clonidine as an adjuvant with local anesthetics for LSCS has been found without significant adverse maternal and neonatal outcomes. [14] Usual dose of clonidine (15-150μg) can cause significant bradycardia, hypotension and sedation. [2]Dexmedetomidine is a highly selective α2-agonistwith a selectivity ratio for the α2 receptor to α1receptor of 1600:1, as compared with a ratio of 220:1for clonidine. [15] It acts pre-junctionaly to reduce neurotransmitter release and post-junctionaly to cause hyperpolariza-

tion and reduction of impulse transmission. Intrathecal α2 receptor agonism in the dorsal horn of the spinal cord can produce antinociceptive action for both somatic and visceral pain. [16] Highly selective α2 agonism of Dexmedetomidine produces better hemodynamic stability and preserves baroreceptor reflex and heart rate response to pressors.

Intravenous Dexmedetomidine has been reported to produce favorable maternal and fetal outcome in labor analgesia and cesarean delivery. [17] Intravenous administered Dexmedetomidine in a pregnant patient undergoing neurosurgery as well as in Klippel-Feil syndrome with difficult airway patient was successfully used before administration of general anesthesia without any untoward maternal and neonatal effects. [18, 19]

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. [20] This may be advantageous in labor analgesia and anesthesia for cesarean delivery. As such, Dexmedetomidine, by virtue of itα2 selectivity, has limited effects on uteroplacental blood flow and minimal placental transfer is advantageous over clonidine.

Zhang H et al. [21]studied the molecular mechanisms responsible for the analgesic property of intrathecal Dexmedetomidine and evaluated its neurotoxicity in vivo and in vitro experimental study on mice. It has shown to cause to prolongation of analgesia. They observed that Dexmedetomidine is neuroprotective and has a potential protective effect on neurotoxicity due to local anesthetics. The optimal dose of intrathecal Dexmedetomidine has not been established. Clonidine and Dexmedetomidine were added as an adjuvants to local anesthetics and effect were compared, based on the effects on α2 receptors and the characteristics of neuraxial block it is claimed that, 3 μg of Dexmedetomidine is equipotent to 30 μg of clonidine intrathecally. [7] Intrathecal Dexmedetomidine dose necessary for sensory and motor blockade appears to be in between 2.5 μg and 10 μg. Dose of 5 μg of Dexmedetomidine apperars to be optimum. [4] Hence for the present study we selected 5 μg Dexmedetomidine as an adjuvant. Various studies has been performed using intrathecal Dexmedetomidine (dose ranging from 3 to 15 μg) for orthopedic, endourological, lower abdominal and perianal surgeries without any adverse neurological symptoms or signs on short term follow up. [5, 6]Ogan S. et al. used low dose bupivacaine with Dexmedetomidine for single-shot intrathecal labor analgesia and found that it increases analgesia without significantly compromising limb power and adverse neonatal effects. [21]

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. The faster onset 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. [22] We also found significant prolongation in duration of motor block which has been reported by most authors [9]Li Z et al. only differed as he found no significant prolongation of motor block. [23] The hemodynamic stability and minimal sedation with Dexmedetomidine in the present study correlates with similar findings by other investigators. [3, 23]Neonatal outcome based on APGAR scores at 1 and 5 min in was not affected present study. These findings were consistent with the other authors. [3, 4, 21, 23] Umbilical artery blood gas analysis was not done due to unavailability of facility.

Limitations: Inability to record umbilical vein blood gas analysis and blood Dexmedetomidine levels are the limitations of this study. Long term follow up was also required. Further reduction in Bupivacaine dose as well as higher dose of Dexmedetomidine can be studied.

CONCLUSION

5 μg Dexmedetomidine as an intrathecal adjuvant to 0.5% hyperbaric Bupivacaine causes reduction in Bupivacaine dose for cesarean section. It also hastens sensory and motor block onset and prolonged postoperative analgesia and motor blockade, without adversely affecting hemodynamics, alertness and neonatal well-being.

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