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Effects of adding different doses of clonidine to intrathecal bupivacaine for spinal anesthesia in cesarean section

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Summary

Purpose: This study investigated the effects of three different doses of clonidine in combination with intrathecal hyperbaric bupivacaine on the quality of the blockade and maternal-fetal repercussions in parturients undergoing elective cesarean section. *Materials an Methods:* Following ethics committee approval, ASA I and II patients of age group 20-35 years, scheduled for cesarean section, were chosen for this study. Patients were randomly distributed into three equal groups of 35 patients in each using a computer-generated sequence of numbers. The patients received hyperbaric bupivacaine (two ml) with 15 μg of clonidine (BC15 group) or 30 μg of clonidine (BC30 group) or 60 μg of clonidine (BC60 group). Hemodynamic parameters, onset, peak and duration of sensory and motor block, sedation scores, Apgar scores, side effects, and duration of postoperative analgesia were compared. *Results:* All groups were comparable with respect to demographic profile, onset, peak and duration of sensory and motor block, and overall hemodynamic stability. The authors observed dose-dependent variability in duration of analgesia and sedation. Duration of analgesia was significantly higher in BC60 group as compared to the other two groups (577.13 ± 120.30 *vs.* 422.06 ± 112.47 and 376.21 ± 87.21 minutes, respectively). Sedation was also more in BC 60 group. *Conclusion:* Intrathecal addition of 15 and 30 μg clonidine are better options when sedation is not desirable; on the contrary, addition of 60 μg provides excellent quality of spinal analgesia when some amount of sedation is acceptable or required without any deleterious effects on the mother and baby.

Key words: Spinal anesthesia; Hyperbaric bupivacaine; Clonidine; Cesarean section; Analgesia.

Introduction

Spinal blocks with disposable, low caliber spinal needles and the use of hyperbaric bupivacaine associated with adjuvant became the technique of choice for elective cesarean sections and in urgent and emergency situations [1]. Bupivacaine, a highly lipophilic long-acting local anaesthetic, has been the most commonly used anesthetic agent in these cases. Even when a long acting local anesthetic like bupivacaine is used, the duration of spinal anesthesia (SA) is short and higher doses of analgesics are required in the postoperative period [2]. In order to improve the quality of intraoperative anesthesia, postoperative analgesia and aid early ambulation and recovery of motor block, several adjuvants have been employed such as opioids and α-2 adrenergic agonist like clonidine [3-8]. Some recent placebo-controlled studies suggest that α-2 adrenergic agonist has both analgesic and sedative properties when used as an adjuvant in local anesthesia [8-12].

Intrathecal clonidine is being extensively evaluated as an alternative to neuraxial opioids for control of pain and has proven to be a potent analgesic, free of some of the opioid-related side effects [13]. In clinical studies, addition of clonidine to local anesthetic has been shown to improve peripheral nerve blocks by reducing onset time, improves efficacy of the block during surgery, and prolongs postoperative analgesia [14-18]. Furthermore, it has been reported that clonidine also offers other beneficial effects such as antiemesis, reduced post-spinal shivering, anxiolysis, and sedation [19]. However, its use is limited due to side effect that includes impact on hemodynamic variable. In parturients at term, a higher dose of clonidine may have deleterious effects on fetus, moreover, considering the fact that Chinese population has relatively lower body weight and there is limited research with low-dose clonidine. Thus, it is important to discover the lower effective dose of clonidine to avoid its known side effects like bradycardia, hypotension, and sedation.

The objective of the present study was to assess the effectivity of three different doses of clonidine in combination with hyperbaric bupivacaine in the quality of the blockade and maternal-fetal repercussions in parturients undergoing elective cesarean sections. The study aimed to discover the lowest possible effective dose among the three doses tested. Primary outcome measure compared was duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. Secondary outcome measures compared were demographic characteristics, onset peak and duration of sensory and motor blockade, level of sedation, maternal hemodynamic parameters, and fetal parameters.

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Table 1. — *Demographic profile of the subjects (mean ± SD).*

S. No	Variables	BC15 group, n=35	BC30 group, n=35	BC60 group, n=35	*p*-value
1	Age (years)	23.8 ± 2.56	25.2 ± 3.14	22.9 ± 2.9	> 0.05
2	Weight (kg)	55 ± 3.39	52 ± 5.20	54 ± 4.61	> 0.05
3	Height (cm)	150.2 ± 5.26	149.6 ± 4.09	148.4 ± 4.91	> 0.05
4	Duration of pregnancy (weeks)	38.96 ± 1.54	38.78 ± 1.01	38.61 ± 1.13	> 0.05
5	ASA I/II	17/13	19/11	21/9	NA
6	Systolic BP	118.69 ± 12.84	120.18 ± 13.22	119 ± 9.36	> 0.05
7	Diastolic BP	77.14 ± 8.23	78.02 ± 5.62	76.08 ± 7.74	> 0.05
8	Duration of surgery (minutes)	79.89 ± 5.07	81.01 ± 4.31	80.11 ± 5.20	> 0.05

NA = not applicable, SD = standard deviation.

Materials and Methods

This double-blind prospective investigation was conducted from January 2014 to September 2014. Following approval from the institutional review board, written informed consent was obtained from the subjects. A total of 105 patients aged between 20-35 years, assessed as ASA class I or II scheduled to undergo lower segment cesarean section under subarachnoid block, were enrolled double-blind prospective randomized controlled trial. Exclusion criteria included complicated or multiple pregnancy, history of hypersensitivity to clonidine, diabetes mellitus, psychiatric or neurologic diseases, morbid obesity (body mass index > 40), coagulation disorders, infection at the site of injection, and patient's refusal of regional anesthesia. The demographic profile, medical history, ASA physical status, and allergies of subjects were recorded prior to surgery and all subjects were made familiar with the study plan and visual analogue scales (VAS) to be used in the assessment. Throughout the preoperative period, respiratory rate, arterial blood pressure, peripheral arterial saturation, and heart rate were recorded for all patients. Sedatives and hypnotics were avoided in pre-, intra-, and postoperative periods. All subjects were pre-medicated with antiemetic agent – inj. ondansetron (four mg intravenously [i.v.]). In addition, Ringer's lactate solution ten ml/kg was infused to all patients.

The subjects were randomized into three groups of 30 patients each by using a computer-generated sequence of numbers and sealed envelopes were used for allocation. The three groups underwent the following treatments: group 1 (BC15) (n=35): two ml of 0.5% hyperbaric bupivacaine + 15 µg clonidine, group 2 (BC30) (n=35): two ml of 0.5% hyperbaric bupivacaine + 30 µg clonidine, and group 3 (BC60) (n=35): two ml of 0.5% hyperbaric bupivacaine + 60 µg clonidine.

Spinal anesthesia was performed at L_{3-4} or L_{4-5} using 26G Quincke's spinal needle in sitting or lateral decubitus position under all aseptic precautions. Respective agents were injected depending on the groups assigned. The total volume of the drug injected was made up to 3.0 ml in each by adding saline wherever needed. All the drugs were prepared just before the spinal anesthesia by an experienced anesthesiology resident blinded to the study. The assessments of the haemodynamic parameters were noted. Onset of sensory block was tested by pin-prick method every two minutes until T6 level was achieved. Motor blockade was assessed by using modified Bromage scale. An experienced anesthesiologist, who was unaware of the drug administered, evaluated the spinal block and other physiological parameters. Following parameters were observed and recorded: T0 – time of spinal anesthesia, T1 – time of onset of sensory block, T2 – time of onset of motor block, T3 – time of peak sensory block, T4 – time of peak motor block, T5 – time of two segment regression of sensory block, and T6 – time to first dose of postoperative rescue analgesia.

Whenever patient's VAS score crossed 7, postoperative analgesic drugs were given and this time was considered as the time of wear off of analgesia. Inj. diclofenac 75 mg was given intramuscularly as rescue analgesia.

Side effects such as hypotension (systolic blood pressure less than 20% of the baseline value), bradycardia (heart rate < 50 beats per minute), nausea, pain, vomiting, pruritis, shivering, respiratory discomfort, and sedation were recorded and treated with appropriate drugs if needed. The maternal sedation was recorded using the 4-point ordinal sedation scale (1 = wide awake and alert, 2 = awake but drowsy, responding to verbal stimulus, 3 = arousable, responding to physical stimulus, 4 = not arousable, not responding to physical stimulus) at five, 15, 30, 45, 60, and 90 minutes of drug administration. Umbilical artery blood pH and pO_2 were measured at delivery and newborn's Apgar scores were determined by a pediatrician not otherwise involved in the study at one, five, ten and 15 minutes. Assessment of block characteristics and hemodynamics were the primary outcome and the intraoperative side effects and postoperative pain were secondary outcome measures.

Statistical analysis

One-way analysis of variance (ANOVA) was conducted to analyze continuous variables and Chi-square (χ^2) test was conducted to analyze categorical variables. If the significant group differences were observed, HSD Turkey *post hoc* test was conducted to assess the differences between individual groups. The data analysis was conducted using SPSS version 20.0. Moreover, descriptive statistics such as mean, standard deviation, and percentage were calculated. A *p*-value less than 0.05 was considered statistically significant.

Results

A total of 105 patients were divided randomly into three groups with 35 patients each were studied As shown in Table 1, patient characteristics e.g., age, weight, height, ASA physical status, systolic and diastolic BP, duration of pregnancy, and duration of surgery were comparable in all three groups and differences among them were not statistically significant. The baseline systolic and diastolic pressures were normal and are recorded in Table 1.

Block characteristics are presented in Table 2. Results show that the time for onset of sensory blockade and time for onset of motor blockade of the three groups were sta-

Table 2. — *Sensory and motor block characteristics.*

	BC15 group	BC30 group	BC60 group	*p*-value
Time for onset of sensory blockade (minutes)	0.92 ± 0.38	0.91 ± 0.45	0.89 ± 0.46	> 0.05
Time for onset of motor blockade (minutes)	1.61 ± 0.66	1.49 ± 0.39	1.39 ± 0.47	> 0.05
Time for peak of sensory blockade (minutes)	7.21 ± 1.47	6.74 ± 1.32	6.41 ± 1.19	< 0.05
Two segment regression time for sensory blockade (minutes)	122.23 ± 10.87	132.63 ± 13.14	148.14 ± 12.62	< 0.05
Time for wearing off of motor block (minutes)	174.03 ± 11.14	176.31 ± 11.74	180.01 ± 13.53	> 0.05
Time for first rescue analgesia (minutes)	376.21 ± 87.21	422.06 ± 112.47	577.13 ± 120.30	< 0.02

Note: values are mean ± SD.

Table 3. — *Hemodynamic parameters and complications.*

Parameters		BC30 group	BC60 group	*p*-value
Heart rate (bpm)	82.8 ± 11.2	81.4 ± 10.8	80.5 ± 10.2	> 0.05
Bradycardia (< 50 bpm)	3	3	3	> 0.05
Systolic blood pressure (mmHg)	115.25 ± 10.87	102.63 ± 13.14	99.14 ± 12.62	< 0.05
Number of patients with SBP < 20% of baseline (n)	3	4	4	< 0.05
Diastolic blood pressure (mmHg)	65 ± 9.55	57 ± 8.95	54 ± 8.81	< 0.05

Note: values are mean ± SD.

tistically comparable and similar, however the BC60 group seemed to reach sensory block slightly earlier than BC30 and BC15, but the difference was not significant on statistical evaluation. The time to onset of motor block was similar in all groups with no significant variation among the three groups. Sensory block reached its peak at an earliest in BC60 group in 6.41 ± 1.19 minutes followed by BC30 in 6.74 ±1.32 minutes and the latest by BC15 in 7.21 ± 1.47 minutes. There was a significant difference in time taken to reach peak sensory block at $p < 0.05$ among the three groups. The exact trend was observed in regression time for sensory blockade of the three groups, wherein the maximum regression time was taken by patients in BC60 followed by BC30 and the last by BC15. A statistical significant difference was observed in the regression time with $p < 0.05$.

Motor block wearing-off time was similar in all the three groups with no significant difference, although patients in BC60 were slower in gaining motor control than other two groups, however this revealed no difference upon statistical evaluation. BC60 group required the least instances of postoperative analgesia than other two groups. The time for first rescue analgesia varied greatly among the three groups. The first rescue analgesia was administered on an average time of 577.13 ± 120.30 minutes in BC60 group, 422.06 ± 112.47 minutes in BC30 group, and 376.21 ± 87.21 minutes in BC15 group. The BC15 group required an earliest rescue analgesia among the three groups. The time for first rescue analgesia showed a statistically significant difference at $p < 0.02$.

Heart rates were statistically similar throughout the procedure with incidence of bradycardia observed in all groups which was, however, also statistically similar among all the groups. Systolic blood pressure was higher in BC15 group as compared to BC30 and BC60. BC30 and BC60 showed no significant difference in systolic blood pressures. The number of patients with SBP < 20% of baseline was alternatively higher in BC60 (n=4) group and BC 30 (n=4) group as compared to BC15 (n=3). Diastolic blood pressure was higher in BC15 group as compared to BC30 and BC60 group; however, diastolic blood pressure of patients in BC30 and BC60 showed no significant difference (Table 3).

Table 4. — *Sedation scores.*

Time (minutes)	BC15 group	BC30 group	BC60 group	*p*-value
5	1 (1-3)	2 (1-3)	2 (1-2)	> 0.05
15	1 (1-3)	2 (1-3)	2 (1-2)	< 0.001
30	1 (1-2)	1 (1-3)	2 (1-2)	< 0.001
60	1 (1-1)	1 (1-3)	1 (1-3)	< 0.001
90	1 (1-1)	1 (1-1)	1 (1-1)	> 0.05

Scores are median (range).

Sedation scores among the three groups did not differ statistically at five and 90 minutes of drug administration (Table 4). At 15 and 30 minutes, BC60 and BC30 groups had more sedation as compared to BC15. A comparison between BC30 and BC60 at 15 and 30 minutes revealed no significant difference although the range of the sedation scores varied between the groups, which proved to be statistically insignificant. At 60 minutes, the sedation scores in BC30 and BC60 were statistically similar in frequency and ranges but altogether significantly different from sedation scores of BC15. The neonatal Apgar scores at one and five minutes, umbilical artery pH, oxygen partial pressure, and carbon dioxide partial pressure were statistically similar in all the three groups (Table 5).

Table 5. — *Neonatal APGAR scores.*

	BC15 group	BC30 group	BC60 group	*p*-value
APGAR score at one minute	8 (7–10)	8 (7–10)	8 (8–10)	> 0.05
APGAR score at five minutes	10 (9–10)	10 (9–10)	10 (9–10)	> 0.05
Oxygen partial pressure (mmHg)	20.17 (10–43)	20.13 (11–44)	21.15 (11–36)	> 0.05
Umbilical artery pH	7.2 (0.2)	7.3(0.2)	7.3(0.3)	> 0.05
Carbon dioxide partial pressure (mmHg)	50.13 (37–70)	52.15 (36–71)	50.30 (39–75)	> 0.05

Scores are median (range).

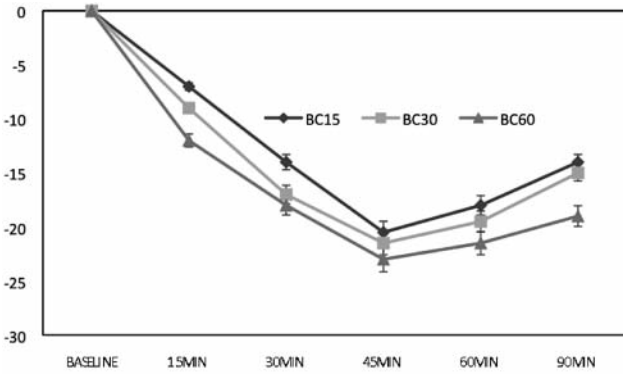

Figure 1. — Percentage change in mean intraoperative systolic pressure (SBP) as compare to baseline.

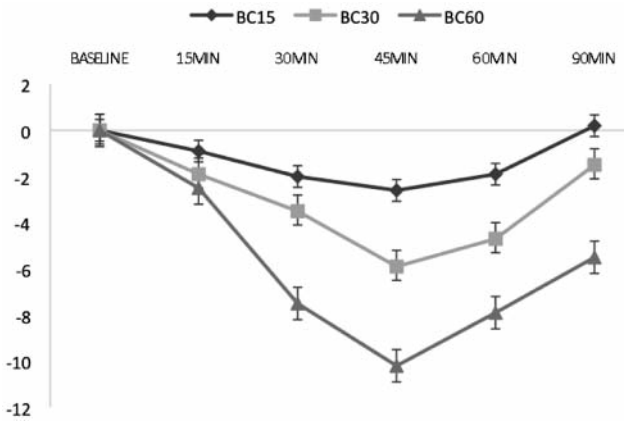

Figure 2. — Percentage change in mean intraoperative diastolic pressure (DBP) as compare to baseline.

Discussion

In the present study, the effects of addition of different doses of clonidine as an adjuvant to bupivacaine were observed to discover the effective lowest dose among them by evaluating the effects versus side effects. During the recent past, clonidine which is a selective partial agonist for α-2 adrenoreceptor has been used to prolong spinal anaesthesia. Various studies have demonstrated that addition of clonidine to bupivacaine significantly improves the onset of both sensory and motor block of local anaesthetics [14, 15, 20]. This action of clonidine is because of spinal cord antinociception via post-junctional α-2 adrenoreceptor mediated noradrenaline release in the dorsal horn [21-23]. Furthermore, clonidine has cholinergic effects and increases the amount of acetylcholine available for modulating analgesia [24]. Literature reports many studies using different doses of clonidine (15-300) intrathecally as adjuvant to bupivacaine with reasonable results. Although, the earlier use of large doses of clonidine have been replaced by smaller doses to reduce the adverse effects, the optimum dose of clonidine remains unknown. Therefore, current study compared three different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia in patients undergoing cesarian section, aiming to discover the lowest possible effective dose among them.

There were very few incidences of hypotension or bradycardia in all three groups. Only two out of a of total six patients required drug intervention to correct bradycardia and both patients responded well to the atropine. It was discovered that there was no statistical difference between these three groups in terms of bradycardia. Similar findings were reported by previous studies which reported very few incidences of hypotension and bradycardia requiring intervention [14, 15, 20]. It has also been discovered that incidence of hypotension and bradycardia depended on multiple confounding factors such as type of surgery, dose of LA used, hydration status, level of sympathetic block, etc. [14, 20]. Furthermore, previous studies have shown that incidence of both hypotension and bradycardia was more in bupivacaine group than in bupivacaine with clonidine group up to 50 µg [14]. Thus, due to low doses of clonidine and bupivacaine used in this study, there was no significant difference regarding hypotension and bradycardia among the three groups.

There was no significant difference in the onset and duration of sensory and motor block in all the three groups but time to reach peak sensory block and duration of analgesia showed significant dose dependent variation. The duration of analgesia was significantly higher in BC60 group than BC30 and BC15 group at 0.05 significance level. This re-

flects that there is an increase in analgesia with increasing doses of clonidine. This result is similar to the findings reported in previous studies which concluded dose dependent variability in analgesia [25, 26]. In addition, dose dependent variability was also observed in sedation. There was an increase in sedation with increasing dose of clonidine. Sedation was observed in five patients at five and 15 minutes which reduced to four and three patients at 30 and 60 minutes, respectively, but there was no respiratory depression or fall in saturation. None of the patients from any group required active oxygen supplementation. This result is similar to the findings reported in Bhure *et al.* and Bhushan *et al.* [27, 28].

The decrease in the SBP observed after 15, 30, 45, 60, and 90 minutes of infusion were similar in all three groups, indicating that there was no significant dose dependent effect on SBP; however, significant time and interaction effects were found (Figure 1). Large decrease in SBP of all three groups was observed after 45 minutes of infusion of clonidine. On the other hand, a significant dose dependent effect on DBP was observed after 15 minutes of clonidine administration. The decrease in DPB 45 minutes after infusion of clonidine was significantly larger in BC60 group, followed by BC30 and BC15 groups (Figure 2). There was a gradual return to the baseline values within 60 minutes after infusion in all three groups. The BC15 group having lowest dose of clonidine was not statistically different from BC30 (Figure 2). This reflects dose dependent variation in DBP, suggesting increasing dose of clonidine causes greater decrease in DPB. This finding is in accordance with previous studies which indicated no differences in SBP and DPB responses to low doses but responses to higher doses are significantly different [29]. Furthermore, results indicate that there was no statistical significant difference in umbilical artery pH, oxygen partial pressure, and carbon dioxide partial pressure across the groups. In all the three groups, newborns showed no fetal signs of distress which is evident from Apgar scores at one and five minutes, thus confirming the safety adding three different doses of clonidine as adjuvant to bupivacaine

Conclusion

The present study demonstrated that addition of clonidine to bupivacaine significantly improved the onset and duration of sensory and motor block. It is concluded that intrathecal addition of 60 µg of clonidine to bupivacaine prolongs postoperative analgesia for longer duration than 30 or 15 µg of clonidine. However, sedation is more in addition of 60 µg clonidine whereas, less sedation was observed in 30 and 15 clonidine groups, with fairly good quality of analgesia. Hence, the authors suggest that addition of 15 and 30 µg clonidine are better options when sedation is not desirable; on the contrary addition of 60 µg provides excellent quality of spinal analgesia when some amount of sedation is acceptable or required without any deleterious effects on the mother and baby.

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