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ORIGINAL RESEARCH

Comparison of Hyperbaric Bupivacaine Alone and Combination of Hyperbaric Bupivacaine with Clonidine in Cesarean Section: A Prospective Randomized Clinical Trial

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ABSTRACT

Introduction: Spinal anaesthesia using hyperbaric bupivacaine with adjuvants such as clonidine is now the routine and preferred technique for majority of the surgical cases.

Aim: to compare various block characteristics alongwith materno-fetal outcome in patients scheduled for caesarean section under subarachnoid block (SAB), following administration of hyperbaric bupivacaine alone and in combination with clonidine intrathecally.

Methods: In this randomized clinical trial, 90 patients undergoing elective cesarean section were randomly allocated to two groups. The patients of Group A received intrathecal 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of normal saline and Group B received intrathecal 0.5% hyperbaric Bupivacaine (10 mg) + 0.2 mL of clonidine (30 µg). Various block characteristics and materno-fetal outcome were compared between the groups.

Results: Group B had quicker sensory onset (3.17 ± 1.05 min vs. 3.50 ± 0.94 min), longer duration of sensory and motor block (209.73 ± 30.70 min and 147.50 ± 23.00 min), longer time for rescue analgesia demand (298.83 ± 44.68 min) in comparison to Group A.

Conclusion: Intrathecal clonidine provided better block characteristics and outcome measures in terms of prolonged sensory as well as motor blockade, longer duration of analgesia, greater intraoperative relaxation and minimal or no adverse incidences.

Keywords: Clonidine, Hyperbaric Bupivacaine, Spinal Anaesthesia, Randomized Controlled.

INTRODUCTION

Currently, spinal anaesthesia is the chosen procedure and can be regarded as a gold standard technique for caesarean section, owing to its simplicity and efficacy, also the speed at which it develop sufficient amount of analgesia.[1,2]Various intrathecal agents from opioids and non-opioids class of drugs have been used to prolong analgesia following surgery.[3]Intrathecal opioids however, are associated with incidences of side effects such as pruritus, nausea,

vomiting, urinary retention and respiratory depression, which often outweighs their advantage as an intrathecal adjuvant. This led to further studies into nonopioid class of drugs as an intrathecal adjuvant which are devoid of opioid related side effects.[4,5] Also, with use of a long-acting local anaesthetic such as bupivacaine, higher doses are required to meet the demand of longer surgical durations and fair postoperative analgesia. But, high doses ofbupivacaine are associated with extreme hemodynamic variations leading to patient compromise.[6,7] Clonidine is an selective alpha-2 adrenoreceptors agonist and is a better alternate to widely used opioids with its quality to improve degree of sensory and motor blockade with local anaesthetic agent.[8,9] The addition of clonidine as an intrathecal adjuvant to bupivacaine curtails the requirement of bupivacaine and promises to offer efficient and sustained.[10,11]In this study, we aimed to compare various block characteristics and overall materno-fetal outcome offered by intrathecal bupivacaine alone and with clonidine as an adjuvant to it in patients scheduled for elective cesarean section under spinal anaesthesia.

METHODS

This prospective randomized double-blinded study was conducted at Mahatma Gandhi Medical College and Hospital, Jaipur after obtaining required permission from the institutional ethics committee (reference number: MGMCH/IEC/JPR/2020/32), and Clinical Trials Registry-India (registration no.: CTRI/2021/02/031199). Written informed consent was obtained from all the patients enrolled in the study. All the patients were explained about the procedure, the drug, the advantage, and the disadvantages and that they have the right to deny. Those denying the consent were not included in the study.Ninety patients aged 18-40 years belonging to the American Society of Anaesthesiologists (ASA) physical status class I/II and scheduled for elective lower segment caesarean section with a singleton fetus and term pregnancy were enrolled in the study. Exclusion criteria were parturients with maternal cardiac, hepato-renal, haematological disease, diabetes, eclampsia, foetal distress, foetal anomaliesand drug allergy. Likewise, unwilling patients and emergency surgeries were excluded from the study.All the enrolled patientswere randomly divided into two equal groups using a computer-generated list. The group assignment was enclosed in anopaque and sealed envelope to ensure adequate concealment of allocation sequence. The sealed envelope was opened only by an anaesthesiologistwho was not involved in the study but according to randomization prepared the drug solution. The anaesthesiologistresponsible for performing the block procedure and observing the study outcomes was blinded to the treatment group. Anaesthesiologist responsible for data collection was also unaware of the group allocation. Patients were assigned randomly to one of the two equal groups. Group Areceived2 ml of 0.5% hyperbaric bupivacaine (10 mg)+0.2 ml normal saline. Group Breceived 2 ml of 0.5% hyperbaric bupivacaine (10 mg)+0.2 ml clonidine 30 mcg.All the patients received oral alprazolam 0.5 mg a night before surgery.On the day of surgery, standard 5 leads ECG, non-invasive blood pressure and pulse oximetry were attached, and baseline parameters were recorded. Venous access was secured using an 18 G cannula on the dorsum of the hand and an injection of Ringer's lactate was begun. Under all aseptic precautions, lumbar puncture at L3-L4 interspace using a 25G spinal needle with the patient in the left lateral position was performed. The study drug was injected into the subarachnoid space after aspiration of the clear free flow of CSF; at the rate of 1ml in 3 seconds with the operating table being flat. After the injection of the spinal medication, the patients were immediately made to lie in supine position with wedge placed under the right hip and a pillow under the head. The time at which intrathecal injection was completed was considered as time zero(t=0).Each patient was assessed at various predetermined time-points for 3 hours post-spinal injection of test drugs for assessment of various parameters.Assessment of sensory and motor blockade was done for every 5 min post block performance till 30 min and then at an interval of 30 min

post-surgery or until the block had worn off completely.
Assessment of sensory blockade was done bilaterally by impairment of the sense of the pin prick along the midclavicular axis using a 3-point scale:1-no block, 2-loss of sensation to pin-prick, 3-loss of touch sensation.Onset of sensory blockade was defined as the time period between the point of the end of injection of drug and evidence of sensory blockade by attainment of loss of sensation to pin-prick or by a pin-prick response grade 2.The duration of the sensory block was defined as the time period between the appearance of a grade-2 block on pin-prick to the point to regression from complete grade-3 sensory block to grade-1 block on pin-prick.The duration of analgesia was evaluated as the time period between the onset of the sensory blockade and the first dose of analgesic administered to the patient.
Assessment of motor blockade was done by modified bromage scale:1 patient can move hip, knee & ankle, 2 cannot move hip, but can move knee & ankle, 3 cannot move hip and knee but can move ankle, 4 cannot move hip, knee & ankle. The onset of motor blockade was defined as the time period between the point of the end of injection of drug and attainment of inability to move hip and knee (grade 3).The duration of the motor blockade was defined as the time point between the maximum motor blockade and point of complete movement of the knee and ankle joint.A complete block was considered when grade-3 sensory anaesthesia with a grade-3 motor block was achieved and only these patients were considered for further study. Patients with a sensory block of grade-1, 2 or motor block of grade-0, 1 and 2 were considered as block failure and were converted to general anaesthesia and hence were excluded from further analysis. Assessment of haemodynamic stability in terms of pulse rate, systolic, diastolic, and mean blood pressure, Surgeon's and patient's satisfaction score in terms of the quality of muscle relaxation and degree of intraoperative comfort respectively were recorded as good, fair or bad.Assessment of analgesic requirements in the early postoperative period using the visual analogue scale (VAS) score.Post-operative pain assessment was done using a visual analogue scale (VAS) (0-no pain to 10-worst possible pain) for every hourly until the block lasted. Rescue analgesia was provided using an intravenous (IV) tramadol 2mg/kg (max 100 mg) when the VAS score was above or equal to 4.Assessment of intraoperative and postoperative complications (bradycardia, hypotension, respiratory depression, etc.) as Bradycardia was defined as a reduction in heart rate by 20% from the baseline value or an absolute heart rate <50 beats per min; which was treated by IV bolus of atropine 1 ml. Hypotension was defined as a decrease in blood pressure by 20% from the baseline or an absolute mean blood pressure <65 mmHg; which was treated by administration of IV crystalloids (200 ml bolus) or incremental dosage of mephentermine 3 mg IV. Respiratory depression was defined as SpO2 < 90% on room air; which was treated by the administration of supplemental oxygen through a nasal cannula at 4 L/min.Shivering; which was treated by administration of IV tramadol 0.5 mg/kg.Nausea and vomiting; were treated by administration of IV ondansetron 4 mg.Fetal outcome in terms of APGAR scores at 1st and 5th minutes were evaluated and recorded.

STATISTICAL ANALYSIS

Assuming, a 30 min difference in prolongation of sensory analgesia and taking the power of study at 90% by keeping type I error ($\alpha = 0.05$) and type II error (β) at 0.1, the sample size was calculated at 43 patients in each group. We enrolled 45 patients in each group for better validation of study results.Statistical analysis was performed using SPSS, version 19.0 for Windows statistical software package (SPSS Inc, Chicago, IL, USA). A chi-square test was applied categorical data.Unpaired t-test was applied for quantitative data. P-value was considered significant if <0.05 and highly significant if <0.001.

RESULTS

A total of ninety patients were enrolled in our study and none were excluded as shown in the consort chart [Figure 1]. Demographic data, various block characteristics (such as:sensory and motor block onset, duration, time for rescue analgesia, VAS score, and hemodynamic variations), and materno-fetal outcome in terms of APGAR score, incidences of complications and quality of anaesthesiawere recorded for each patient. Patients between the two groups were demographically comparable[Table 1].

The onset of sensory block was comparatively quicker in Group B (3.17 ± 1.05 min vs. 3.50 ± 0.94 min), while the onset of motor block was comparatively quicker in Group A (5.90 ± 0.85 min vs. 6.20 ± 0.85 min). However, the differences with the onset of sensory and motor block were statistically insignificant (P = 0.1198 and 0.0977) [Table 2]. The duration of sensory and motor block was significantly longer in Group B (209.73 ± 30.70 min and 147.50 ± 23.00 min) than Group A (162.59 ± 17.34 min and 104.67 ± 14.85 min); (P<0.00001) [Table 2]. Also, the time for rescue analgesia was significantly long in Group B (298.83 ± 44.68 min vs. 250.17 ± 30.89 min); (P<0.00001). [Table 2]

The mean VAS score was significant at majority of time points between both groups. In Group A, it ranged from maximum of 3.1 ± 1.6 min at 4th hour to minimum of 0.0 min at 6th hour; while in Group B, it ranged from maximum of 2.4 ± 1.22 min at 4th hour to minimum of 0.0 min at 8th hour [Table 3a]

The APGAR score at 1min in Group A vs. Group B were 8.70 ± 0.47 min vs. 8.50 ± 0.51; (P<0.1177), and APGAR score at 5min was 9.00 ± 0.00 min in both the groups. [Table 3b]

The haemodynamic parameters (heart rate, systolic, diastolic and mean blood pressure) were well maintained within the presumed range of significant variation, i.e., 20% from baseline throughout the surgery. There was no significant difference in haemodynamic parameters in both the groups at any time point [Table 4a, 4b, 4c, 4d].

The incidences of complications and quality of anaesthesia were almost similar in both the groups without much differences [Table 5, fig.1]. Out of the total fourty five participants included in each study group, none had to be dropped off.

Table 1: Distribution of demographic data among the studied groups

Parameters	Mean±SD		P
	Group BD (n=45)	Group BF (n=45)	
Age (years)	29.4±15.3	28.2±13.9	0.697*
Sex (%)			
Male	40	39	0.606*
Female	5	6	
Weight (kg)	69.4±8.6	68.9±8.2	0.778#
Duration of surgery (min)	48.9±10.4	50.2±9.6	0.539#
ASA grade (%)			
I	32	31	0.606*
II	13	14	

*Chi-square test; #Unpaired t-test. n – Number of patients; SD – Standard deviation; ASA – American Society of Anesthesiologists

Table 2: Comparison of block outcomes in between the groups

	Group A		Group B		P*
	Mean	SD	Mean	SD	
Onset of sensory block	3.17	1.05	3.50	0.94	0.1198
Onset of motor block	5.90	0.85	6.20	0.85	0.0977
Duration of sensory block	162.59	17.34	209.73	30.70	<0.00001

Duration of motor block	104.67	14.85	147.50	23.00	<0.00001
Time for rescue analgesia	250.17	30.89	298.83	44.68	<0.00001

*Unpaired t-test. SD – Standard deviation, SE –Standard error.

Table 3a: Comparison of VAS score in between the groups

Time interval (hour)	Group A		Group B		P*
	Mean	SD	Mean	SD	
0	0.00	0.00	0.00	0.00	-
0.5	0.00	0.00	0.00	0.00	-
1	0.13	0.35	0.07	0.25	0.398
2	1.13	0.35	0.47	0.63	<0.0001
3	2.43	0.82	1.37	1.07	<0.0001
4	3.1	1.60	2.4	1.22	0.0219
5	1.22	1.22	2.1	1.73	0.0065
6	0.00	0.00	0.83	1.56	-
7	0.00	0.00	0.167	0.75	-
8	0.00	0.00	0.00	0.00	-
12	0.00	0.00	0.00	0.00	-

*Unpaired t-test. SD – Standard deviation

Table 3b: Comparison of APGAR score in between the groups

APGAR score	Group A		Group B		P*
	Mean	SD	Mean	SD	
1 min	8.70	0.49	8.50	0.51	0.0611
5 min	9.00	0.00	9.00	0.00	-

*Unpaired t-test. SD – Standard deviation

Table 4a: Comparison of heart rate in different time interval in between groups

Time interval (min)	Heart rate				P*
	Group A		Group B		
	Mean	SD	Mean	SD	
0	89.50	12.87	90.70	17.05	0.7072
2	98.83	22.93	94.77	18.31	0.3559
4	98.90	0.80	99.07	0.64	0.2687
8	96.20	21.25	90.73	21.51	0.2282
10	92.50	17.77	88.10	17.16	0.2354
20	95.97	5.79	93.87	12.22	0.3004
30	91.70	14.51	93.93	15.48	0.4826
40	89.37	16.44	89.67	16.02	0.9303
50	87.41	12.37	86.86	14.02	0.8440
60	84.62	10.28	85.76	11.18	0.6159

*Unpaired t-test. SD – Standard deviation

Table 4b: Comparison of SBP in different time interval in between groups

Time interval (min)	SBP				P*
	Group A		Group B		
	Mean	SD	Mean	SD	
0	128.07	11.01	127.17	14.48	0.7408
2	122.10	10.43	120.57	15.90	0.5907

4	115.83	14.74	113.63	17.69	0.5232
8	115.77	10.01	112.43	15.25	0.2226
10	114.77	11.96	116.17	13.87	0.6094
20	115.60	8.25	115.47	9.83	0.9460
30	113.17	9.95	115.63	9.58	0.2354
40	114.00	10.95	114.77	10.55	0.7349
50	115.28	10.62	116.04	10.92	0.7387
60	115.65	9.61	118.63	8.17	0.1166

*Unpaired t-test. SBP – Systolic blood pressure, SD - Standard deviation

Table 4c: Comparison of DBP in different time interval in between groups

Time interval (min)	**DBP**				**P***
	Group A		**Group B**		
	Mean	**SD**	**Mean**	**SD**	
0	77.00	6.37	77.43	10.10	0.8097
2	72.90	7.91	70.93	11.88	0.3570
4	67.80	10.41	65.90	13.86	0.4641
8	67.03	8.59	67.30	12.43	0.9049
10	66.57	9.89	67.47	10.69	0.6795
20	66.43	7.33	64.90	8.86	0.3745
30	64.27	9.23	64.00	7.31	0.8781
40	64.93	8.19	63.20	7.10	0.2872
50	66.90	8.34	65.82	10.90	0.5989
60	67.62	7.07	66.28	7.92	0.3995

*Unpaired t-test. DBP – Dystolic blood pressure, SD - Standard deviation

Table 4d: Comparison of MBP in different time interval in between groups.

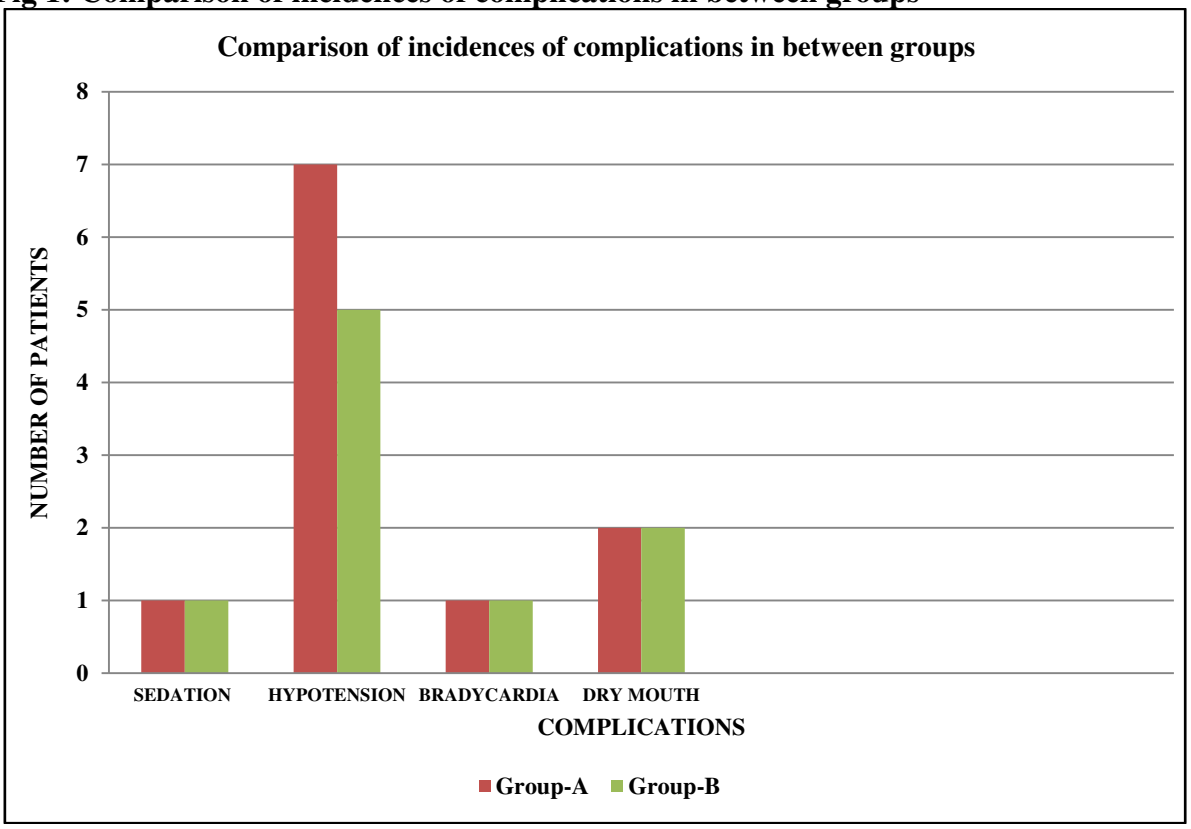
Time interval (min)	**MBP**				**P ***
	Group A		**Group B**		
	Mean	**SD**	**Mean**	**SD**	
0	95.97	5.79	93.87	12.22	0.3004
2	90.40	7.75	87.27	13.41	0.1787
4	84.57	10.60	82.13	13.52	0.3433
8	84.03	7.31	81.93	12.41	0.3307
10	84.23	9.57	83.77	9.86	0.8228
20	84.83	6.32	83.73	8.95	0.5024
30	81.93	8.50	83.03	7.47	0.5160
40	82.93	8.05	82.77	8.22	0.9259
50	84.34	7.73	80.18	16.53	0.2485
60	84.23	7.78	84.80	6.81	0.7124

*Unpaired t-test. MBP – Mean blood pressure, SD - Standard deviation

Table 5: Comparison of quality of anaesthesia in between groups

	Group A		**Group B**	
	Good	**Fair**	**Good**	**Fair**
Surgeon's satisfaction	40	5	41	4
Patient's satisfaction	38	7	40	5

Fig 1: Comparison of incidences of complications in between groups



DISCUSSION

The preferred technique for elective lower segment caesarean section is spinal anaesthesiausingcombinations of intrathecal analgesics. Apart from being easy, economical, and safe technique it provides rapid and adequate anaesthesia. Various side effects such as unpredictable respiratory depression, and varying degree of gastro-intestinal complications with opioid class of adjuvants have diverted the research to explore the nonopioid analgesics as intrathecal adjuvants. From the nonopioid ones, clonidine has been extensively evaluated as an alternative to neuraxially administered opioids and has proven to provide potent analgesia whilst being free from opioids related adverse effects.[12,13] Bupivacaine, a local anaesthetic agentblocks voltage-gated Na + channels in axonal membrane andinterferes with the synaptic transmission by inhibition of presynaptic Ca ++ channels along with their effect on nerve signal conduction. On other hand, clonidine being a α-2 receptor agonist; alters the transmission of pain by binding to nociceptive presynaptic terminals of Aδ and C fiber, and postsynaptic hyperpolarization of dorsal horn's second order neurons.[14] Therefore, the synergism found in our study between bupivacaine and clonidine can be explained by combination of these effects.

Further, Kothari et al.[15]also observed that higher dosesof bupivacaine was needed to prolong the duration of postoperative analgesia but, addition of clonidine to bupivacaine resulted into longer postoperative analgesia at lower dose of bupivacaine. They also observed that the onset of sensory block was faster with clonidine while, no such effects was observed with onset time of motor block, concluding that clonidine as an adjuvant does not alter the onset of motor block after spinal anaesthesia. Consistent with this, in our study, the onset of sensory block was significantly faster with clonidine and the onset of motor block remained statistically indifferent.

Our findings of prolonged duration of both sensory and motor block were in terms with studies conducted by Kothari et al.[15] and Sethi et al.[16]Theirindividual observations concluded

that clonidine prolongs the effective duration of both sensory block as well as motor block in a dose dependent fashion.Furthermore, Eisenach et al. [13] in their clinical review of clonidine for regional anesthesia confirmed the property of clonidine to enhances both sensory and motor blockade of local anesthetic agents. They also affirmed that clonidine does notincrease chances of hypotension during surgical epidural anesthesia. We also didn't observe any significant hemodynamic fluctuation with clonidine and the possible explanation for this could be the hyperpolarization of motor neuron as a part of cellular modification of ventral horn of spinal cord due to α-2 adrenergic agonism of clonidine, as observed by Bonnet et al. [17] Superior perioperative analgesia with clonidine as an adjuvant to bupivacaine was possibly due to thesynergistic inhibitionof clonidine (via α-2 adrenergic agonism) and bupivacaine on presynaptic and postsynaptic, Aδ and C-fiber conduction, respectively.

Clonidine potentiates the prolongation of neuronal block by local anesthetic, by decreasing vascular uptake and hence maintaining greater concentrations of local anaesthetic drugcloser to neuronal tissues for maximalperiod of time thereby providing greater degree of surgical relaxation and prolonged analgesia.[18]Likewise in our study,clonidine provided better maternal satisfaction in terms of prolonged analgesia and surgeon's satisfaction in terms of greater relaxation.

We also observed that Group A required rescue analgesic around 4th hour and Group B required rescue analgesic around 5th to 6th hour. Our results of significantly longer time for rescue analgesia and curtailed VAS score at most of the time-points with clonidine were supported by Van Tuijl et al., [19]where they concluded that addition of clonidine to hyperbaric bupivacaine prolongs duration of spinal analgesia therefore decreasing rescue analgesic requirement. They also stated that this effect was achieved without clinically relevant materno-fetal side effect which was also observed in our study with statistically insignificant difference in the APGAR score. Gautier et al., [20]also observed that 30 µg clonidine was not detected at delivery in foetal circulation hence the relatively comparable APGAR score obtained in our study were justified.

Bradycardia is a worrisome side effect of clonidine. However, we did not observe any significant decrease in heart rate with clonidine. One patient of each group had bradycardia incidencebut was easily treated with IV atropine. Although the incidence of hypotension was morewith clonidine, this apparently was not important clinically, as the total dose of ephedrine used in treatment was minimallydifferent between the groups. Moreover, the fall in systolic blood pressure was more frequent at either 3-6 min after spinal anaesthesia or at 5-10 min post delivery in our study. The fall in systolic blood pressure, 3-6 min post spinal anaesthesia was most likely due to bupivacaine induced sympatholysis.[11]While the fall in systolic blood pressure, 5-10 minutes post delivery coincided with the blood loss due to placental separation and the use of IV oxytocin at the same time. Thus, clonidine didn'taugmentsignificant hemodynamic effect in any of our patient.

In our study, the incidences of nausea were insignificant among both the groups which was validated by results of Kothari et al.[15] They observed that higher doses of bupivacaine was responsible for increased incidences of nausea rather than co-administration of clonidine with bupivacaine.Although dryness of mouth and sedation are known adverse effects of clonidine, we observed that dryness of mouth was equally present in patients ofboth the groups. Probably, this dryness of mouth was due to patient being kept nil orally in the postoperative period and not attributed to clonidine itself.

CONCLUSION

In conclusion, clonidine as an adjuvant tointrathecal bupivacaine offers improved block characteristics and materno-fetal outcome in terms of prolonged sensory as well as motor blockade, longer duration of analgesia, greater intraoperative relaxation and minimal or no

adverse incidences.

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