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Clonidine (30µg) and Midazolam (2mg) as Intrathecal Adjuvants to Bupivacaine: Hemodynamic Changes

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ABSTRACT
Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tractus solitarius and locus coeruleus of the brain stem, activation of post-synaptic a2 adrenoreceptors reduces sympathetic drive. It also activates noradrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti-arrythmogenic action. Patients fulfilling the required essential criteria were selected and 90 patients were randomly allocated to following 2 groups: Group BC (45 No.)-Spinal Bupivacaine with Clonidine. Group BM (45 No.)-Spinal Bupivacaine with Midazolam. Patient allocation was made based on computer generated numbers and sealed envelope method. The study solution for spinal anaesthesia was prepared separately by a person not involved in the patient care. Patients and Anaesthesiologists were blinded to both the study groups. The mean intra-operative fall of heart rate in BC group was 14bpm (range-10-40bpm) with a mean maximum fall of 21.4±7.2bpm. On the other hand, these figures in BM group were 3 bpm (range-2-25 bpm) and 12.5±4.4 bpm only.

INTRODUCTION

Bupivacaine is highly hydrophobic and hence it is very potent. The onset of action of Bupivacaine is usually between 4-6 minutes and the maximum anaesthesia is obtained in 15-20 minutes. The duration of anaesthesia varies according to the type of block, the average duration of neuraxial block is about 3.5-5 hours and is about 5-6 hours for nerve blocks. Bupivacaine can be detected in the blood within 5mins of infiltration or following epidermal or intercostal nerve blocks. The systemic absorption of Bupivacaine is determined by the site of injection of drug used, dose and the addition of a vasoconstrictor determine. Absorption is faster in areas of high vascular supply. In plasma, drug binds avidly with protein to the extent of 70-90%. The toxic plasma concentration is set at 4-5µg/ml[1,2]. Midazolam 0.2mg/kg IV for induction of anaesthesia produces a greater decrease in systemic blood pressure and increase in heart rate. Cardiac output is not altered. In the presence of hypovolemia, it results in enhanced blood pressure lowering effects. It does not prevent blood pressure and heart rate responses evoked by intubation of trachea[3]. Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tract us solitarius and locus coeruleus of the brain stem, activation of post-synaptic α2 adrenoreceptors reduces sympathetic drive (25). It also activates noradrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti-arrythmogenic action. In the periphery it acts on presynaptic α2 adrenoreceptors at sympathetic terminals reduces the release of norepinephrine causing vasorelaxation and reduced chronotropic drive (26). The brainstem and the peripheral effects of α2 adrenoreceptors stimulation are counterbalanced by the direct peripheral vasoconstrictor through its action on α21 adrenoreceptors from the circulating concentrations of Clonidine[4].

MATERIALS AND METHODS

A prospective randomised study was conducted to compare the clinical effects of intrathecal Midazolam and Clonidine as Adjuvants to spinal Bupivacaine in patients undergoing infra-umbilical surgeries under spinal anaesthesia in Department of Anaesthesiology after approval from the Ethics Committee and patient consent. A total of 90 patients were enrolled between January 2020 to June 2021 for the study with the following inclusion and exclusion criteria. Sample size was calculated based on the study conducted by Joshi[1] considering the mean difference for duration of analgesia between Bupivacaine Midazolam (BM) and Bupivacaine Clonidine (BC) group as 60 minutes with a standard deviation of 132 and 53. The sample size was calculated with 80% power and alpha of 1.5 (95% confidence interval) and was found to be 90 with 45 cases in each group.

Inclusion Criteria:

- Patients willing to give informed written consent.
- Patients with 18-60 years of age either sex.
- ASA physical status I and II.
- Operations below umbilicus.

Exclusion Criteria:

- ASA physical status grade III and IV.
- Patients with pre-existing spinal disorder, neurological disorders, endocrine disorders, cardio-respiratory or other systemic disease.

Following ethics committee, informed consent was obtained from the patients. Detailed pre-anaesthetic check-up was done. Patients fulfilling the required essential criteria were selected and 90 patients were randomly allocated to following 2 groups:

- **Group BC (45 No.):** Spinal Bupivacaine with Clonidine.
- **Group BM (45 No.):** Spinal Bupivacaine with Midazolam.

Patient allocation was made based on computer generated numbers and sealed envelope method. The study solution for spinal anaesthesia was prepared separately by a person not involved in the patient care. Patients and Anaesthesiologists were blinded to both the study groups.

RESULTS AND DISCUSSIONS

The mean basal heart rate was comparable between the two groups (p=0.113). Intra operatively the mean heart rate in group BC dropped from 86.5-72.0 whereas in group BM the drop was 85.1-82. The range of fall was 10-40 and the mean maximum fall was 21.4±7.2 bpm in BC group. In group BM the range was 2-25 with a mean maximum fall of 12.5±4.4 bpm. There was statistically significant fall in Group BC compared to Group BM.

Table 1: Distribution of Heart Rate

Heart rate (bpm)	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Baseline	86.5	8.3	85.0	5.4	.339
5mins	83.0	8.8	82.6	6.3	.826
10mins	78.1	10.9	81.4	8.9	.120
15mins	65.9	7.8	84.6	9.5	< 0.01 **
20mins	68.6	8.6	84.0	8.5	< 0.01 **
25mins	79.2	8.3	85.8	9.9	< 0.01 **
30mins	81.2	8.0	78.8	6.9	.124
35mins	83.0	7.4	78.5	7.1	< 0.01 **
40mins	83.4	8.3	78.5	6.7	< 0.01 **
45mins	83.9	8.1	79.5	6.2	< 0.01 **
50mins	83.8	8.3	79.6	6.5	< 0.01 **
55mins	83.9	7.5	80.3	6.3	< 0.05 *
60mins	84.2	7.4	81.5	6.1	.060
70mins	84.4	7.7	81.0	6.1	< 0.05 *
80mins	84.3	8.0	80.5	6.1	< 0.05 *
90mins	84.7	7.6	81.1	6.2	< 0.05 *
100mins	84.4	7.1	81.6	6.1	< 0.05 *
110mins	84.2	7.3	81.8	5.3	.074
120mins	85.1	6.8	83.1	6.1	.136

The mean basal systolic blood pressure was comparable between two groups with p=0.018. The mean systolic blood pressure fall was from 129.7-118.76 in group BC as compared to fall from 136.8-125.77 in group BM. The range of fall was from 5-62 with a mean maximum fall of 28.8±15.3mmHg in Group BC. In Group BM the range was from 4-67 with a mean maximum fall of 21.1±13.2mmHg. The fall was significant at 10-35mins (p<0.01) in Group BC compared to Group BM (p<0.05).

Table 2: Distribution of Systolic Blood Pressure

SBP(mmHg)	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Baseline	129.5	13.1	137.0	16.3	< 0.05 *
5 mins	126.5	13.4	132.2	17.6	.088
10 mins	116.0	15.5	126.6	17.6	< 0.01 **
15 mins	111.6	17.0	123.7	16.1	< 0.01 **
20 mins	109.0	18.4	123.0	16.0	< 0.01 **
25 mins	108.3	18.5	122.8	14.8	< 0.01 **
30 mins	110.3	17.2	125.5	14.2	< 0.01 **
35 mins	111.5	15.9	125.7	13.8	< 0.01 **
40 mins	121.4	8.9	127.1	13.7	< 0.05 *
45 mins	122.0	9.0	126.5	14.1	.072
50 mins	122.3	8.8	126.0	14.5	.155
55 mins	122.6	9.0	125.5	13.4	.234
60 mins	121.4	8.7	125.3	11.6	.074
70 mins	121.1	7.9	124.9	10.7	.054
80 mins	120.8	8.4	123.8	11.2	.151
90 mins	120.0	8.7	124.5	11.6	< 0.05 *
100 mins	122.5	9.3	127.5	12.1	< 0.05 *
110 mins	124.6	10.0	127.8	12.5	.191
120 mins	123.8	8.8	128.4	11.4	< 0.05 *

The mean basal DBP was comparable between two groups with p=0.875. The mean diastolic fall intraoperatively was from 81.5-73.3 (8.2) in Group BC and from 81.2-74.9(6.3) in Group BM. The range of fall was from 3-46mmHg with mean maximum fall of 20.0±12.0mmHg in Group BC whereas the range was from 5-28 with a mean maximum fall of 13.8±6.0 in Group BM. There was statistically significant difference between group BC and groups BM at 15-35 mins (p<0.01).

Table 3: Distribution of Diastolic Blood Pressure

DBP (mmHg)	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Baseline	81.5	8.3	81.2	7.7	.875
5 mins	77.4	8.0	78.8	7.8	.404
10 mins	72.2	9.0	75.5	8.6	.083
15 mins	69.5	10.1	74.8	8.0	< 0.01 **
20 mins	67.4	11.2	74.0	9.8	< 0.01 **
25 mins	68.9	9.6	74.4	9.0	< 0.01 **
30 mins	69.4	9.2	75.0	7.8	< 0.01 **
35 mins	69.8	8.8	74.7	7.0	< 0.01 **
40 mins	74.3	8.4	74.2	7.9	.979
45 mins	75.1	7.7	75.0	8.4	.948
50 mins	75.2	7.7	75.0	8.9	.910
55 mins	75.2	7.8	74.6	8.7	.742
60 mins	75.0	8.0	74.1	8.7	.589
70 mins	74.9	8.2	74.1	8.2	.625
80 mins	74.5	8.6	74.4	7.6	.948
90 mins	75.2	8.5	74.4	7.9	.636
100 mins	74.5	8.1	75.6	8.3	.556
110 mins	75.6	7.7	75.4	8.4	.948
120 mins	75.4	8.0	75.3	8.2	.928

The basal mean arterial pressure was comparable in both the groups (p=0.875). The mean fall in MAP intraoperatively was from 97.3-88.4(8.9) in group BC and from 100.3-92.2(8.1) in group BM. The range of fall was from 3-48 with a mean maximum fall of 22.0±12.4mmHg in Group BC. In Group BM the range was from 2-36 with a mean maximum fall of 15.3±7.9mmHg. There was statistically significant difference between group BC and groups BM at 15-35 mins (p<0.01).

Table 4: Distribution of Mean Arterial Pressure

MAP (mmHg)	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Baseline	81.5	8.3	81.2	7.7	.875
5 mins	77.4	8.0	78.8	7.8	.404
10 mins	72.2	9.0	75.5	8.6	.083
15 mins	69.5	10.1	74.8	8.0	< 0.01 **
20 mins	67.4	11.2	74.0	9.8	< 0.01 **
25 mins	68.9	9.6	74.4	9.0	< 0.01 **
30 mins	69.4	9.2	75.0	7.8	< 0.01 **
35 mins	69.8	8.8	74.7	7.0	< 0.01 **
40 mins	74.3	8.4	74.2	7.9	.979
45 mins	75.1	7.7	75.0	8.4	.948
50 mins	75.2	7.7	75.0	8.9	.910
55 mins	75.2	7.8	74.6	8.7	.742
60 mins	75.0	8.0	74.1	8.7	.589
70 mins	74.9	8.2	74.1	8.2	.625
80 mins	74.5	8.6	74.4	7.6	.948
90 mins	75.2	8.5	74.4	7.9	.636
100 mins	74.5	8.1	75.6	8.3	.556
110 mins	75.6	7.7	75.4	8.4	.948
120 mins	75.4	8.0	75.3	8.2	.928

The mean intra-operative fall of heart rate in BC group was 14 bpm (range-10-40 bpm) with a mean maximum fall of 21.4±7.2 bpm. On the other hand, these figures in BM group were 3 bpm (range-2-25 bpm) and 12.5±4.4 bpm only. Sethi[5] who used Clonidine reported a heart rate fall from 45mins until the end of 6 hours with a maximum fall of 35 bpm. Joshi[6] also observed the mean intraoperative fall in BC group to be 15 bpm as compared to BM group in which there was no considerable fall. In our study bradycardia requiring treatment with Atropine was seen in 33.3% of patients in BC group and 2.2% in BM group. Saxena[7] observed bardycardia in 20% of cases with same dose of Clonidine. Joshi[6] reported bardycardia in 36% in BC compared to none in Group BM. Clonidine causes decrease in heart rate is due to presynaptic mediated inhibition of norepinephrine release and direct depression of AV nodal conduction after systemic absorption. We found that in Group BC the mean intra-operative fall of MAP was 8.9mmHg (range 3-48mmHg) with a mean maximum fall of 22.0±12.4mmHg and 8.1mmHg (range 2-36mmHg) with a mean maximum fall of 15.2±7.9mmHg in Group BM. Dobrydnjov[8] recorded a significant decrease in MAP with a fall of 15-20mmHg after spinal injection with 30mcg Clonidine. Thakur[9] also observed significant fall of 20mmHg in MAP with Clonidine. Nanjegowda[10] observed no hemodynamic changes with 2mg Midazolam. Clonidine affects arterial blood pressure in a complex manner because of opposing action at multiple sites. The α2-adrenergic agonists produce sympatholysis and reduce arterial blood pressure through effects at specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal

cord. These effects are counteracted by direct vasoconstrictor resulting from action on peripheral vasculature. In our study 60% of patients in Group BC had hypotension, requiring treatment with vasopressors (Mephentermine or Ephedrine) in addition to intravenous fluid compared to 17.8% in Group BM. Saxena[7] who used 30mcg Clonidine reported hypotension in 20% of patients. Similarly, Thakur[9] reported hypotension in 28% of patients. Joshi[10] observed hypotension in 44 % in Group BC and 16% in Group BM. The observations regarding heart rate and blood pressure show that patients were more stable in BM group than BC group. This is also in consonance with the fact that Benzodiazepines administered even systemically are credited with hemodynamic stability. It is found that sympathetic nervous system remains intact after intrathecal administration of Midazolam. Our findings are in agreement with the above cited investigators studying cardiovascular responses of these drugs.

CONCLUSION

- The mean of maximum fall in HR (bpm) in Group BC was 21.4±7.2 whereas in Group BM it was 12.2±4.4. The mean of the maximum fall (mm Hg) in MAP was 22.0±12.4 in Group BC and 15.2±7.9 in Group BM. All these values were statistically significant.
- Hypotension, requiring treatment with vasopressors was seen in 25 patients in Group BC and 7 patients in Group BM ($p<0.01$). Bradycardia, requiring treatment with Atropine was observed in 15 patients in Group BC compared to 1 patient in Group BM ($p<0.01$).

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