Original article

Evaluation of Intrathecal Clonidine as Adjuvant to Hyperbaric Bupivacaine for Spinal Anaesthesia – Quest for the Optimal Dose

Dr. Kiran S.[1], Dr. Rajit Kumar[2]

[1]Anaesthesiologist & Intensivist, Department of Anaesthesiology & Critical Care, INHS Asvini, Colaba, Mumbai – 400 005

[2]Anaesthesiologist, Department of Anaesthesiology, AFH Kalaikunda, West Bengal

Corresponding author: Dr. Kiran S.

Abstract:

Aims: This study aims to assess the efficacy of intrathecal clonidine 75 µg as an adjuvant to hyperbaric bupivacaine for spinal anaesthesia and for postoperative analgesia and to evaluate its side effects.

Methods: The prospective study was under taken in a tertiary care hospital, enrolled 120 patients, scheduled for lower limb surgeries under spinal anaesthesia. The study population was randomly divided into two groups with 60 patients in each group. Patients in Group-I (n=60**),** received 3 ml (15mg) of intrathecal bupivacaine with 0.5 ml (75µg) of preservative free clonidine for spinal anesthesia. Patients in Group-II (n=60), received 3 ml (15mg) of intrathecal bupivacaine with 0.5 ml of normal saline for spinal anesthesia.

Results: There was no significant difference between the two groups with respect to patient characteristics. Mean onset of sensory blockade was 177.17±29.25 seconds in group I and 186±39.29 seconds in group II, the difference being statistically not significant (p=0.165). The decrease in heart rate and systolic BP, at 30 minutes, 60 minutes and at 120 minutes in the clonidine group was statistically significant (p<0.001). After 120 minutes, there was no statistically significant difference in the mean heart rate and systolic BP recorded in the two groups. Mean duration of motor blockade, was 241.83±32.29 minutes in group I and 170.33±19.98 minutes in group II, the difference being statistically significant (p<0.001). Mean duration of analgesia, was 572.83±62 minutes in group I and 218±36.92 minutes in group II, the difference being statistically significant (p<0.001). There was no statistically significant difference in incidence of bradycardia, hypotension, hypoxemia, respiratory depression, shivering, nausea and vomiting among the two groups.

Conclusion: The results of the study indicate that addition of 75µg clonidine with hyperbaric bupivacaine for spinal anaesthesia increases the duration of sensory and motor blockade. It prolongs postoperative analgesia, results in mild sedation and enhances patient comfort, with no major side effects.

Key words: Subarachnoid Block, Clonidine, Postoperative analgesia

Introduction:

Central neuraxial blockade with local anesthetics is the preferred anaesthetic technique for lower limb surgeries. Bupivacaine however, when used as the local anesthetic for spinal anesthesia, does not result in prolonged postoperative analgesia. Several adjuvants, especially opioids and α2 adrenergic agonists, have been used successfully with bupivacaine for prolonging postoperative analgesia, enhancing patient comfort in the postoperative period and for early ambulation. Clonidine, an selective α2 adrenergic agonist has been shown to result in the prolongation of the sensory blockade, with reduction in the amount or the concentration of local anesthetic required to produce postoperative analgesia.[1] Clonidine also has the ability to prolong the motor blockade produced by local anesthetics. Studies have used

varying doses of clonidine as an adjuvant to local anesthetic for producing prolonged postoperative analgesia, with minimal side effects. There is a need to study the efficacy and side effects of various doses of intrathecal clonidine, so as to use the optimal dose and ensure patient safety. This study aims to assess the efficacy and side effects, of dose of 75 µg clonidine given intrathecally as an adjuvant to hyperbaric bupivacaine.

Material and Methods:

The prospective randomised study was under taken in a tertiary care hospital over a period of one year i.e. from June 2013 to June 2014. The study was undertaken, after obtaining the approval of the hospital ethical committee, as well as informed consent from all patients. One hundred twenty patients, scheduled for lower limb surgeries under spinal anesthesia were included in the study. The study population was randomly divided into two groups with 60 patients in each group. Patients in Group I (n=60)**,** received 3 ml (15mg) of intrathecal 0.5% hyperbaric bupivacaine with 0.5 ml (75µg) of preservative free clonidine for spinal anesthesia. Patients in Group II (n=60), received 3 ml (15mg) of intrathecal 0.5% hyperbaric bupivacaine with 0.5 ml of normal saline for spinal anesthesia.

Patients included for the study were ASA I with no comorbidities, scheduled for elective lower limb surgery, aged between 20 and 60 years. Patients who refused consent, patients with local infection of the back, coagulopathy, cardiovascular disease, preexisting neurological disease & severe deformity of spine were excluded from the study. After securing a suitable peripheral vein all patients were administered ondansetron 4 mg intravenously. All patients were administered 10 ml/kg of ringers lactate solution as crystalloid preloading. Baseline heart rate (HR), non invasive blood pressure (NIBP), respiratory rate (RR), oxygen saturation (SpO_2) and electro cardiograph (ECG) were recorded. The subjects were randomly allocated to two groups by a random number table. Under all aseptic precautions, lumbar puncture was performed with patients in sitting position using a 25G Quincke's spinal needle and the subarachnoid block (SAB) was administered.

HR, NIBP, RR, SpO_2, ECG were recorded at every 5 minutes till end of surgery and every 15 minutes in the postoperative period. Sensory block was evaluated by Hollmen scale, till complete sensory block was achieved. Onset time of sensory block was taken as the time interval from time of administration of SAB, till the time, a Hollmen score of 4, was achieved. Motor block was evaluated using modified Bromage score for lower extremity. Onset time of motor block was taken as the time interval from time of administration of SAB to the time, a modified Bromage score of 3, was recorded. Total duration of motor block was taken as the time from onset, to the time when a modified Bromage score of less than 3, was recorded in the postoperative period. Postoperatively, the patients were monitored for vital parameters, modified Bromage score for motor block, Visual Analogue Scale (VAS) score for pain on a scale of 1 to 10, hourly till the complete regression of SAB was achieved. Duration of postoperative analgesia was recorded as the time from onset, till the time the VAS score for pain was recorded more than 4. The patients with VAS>4 were administered systemic analgesics. Complications like nausea, vomiting, drowsiness, hypotension, bradycardia, shivering, itching, respiratory depression; hypoxemia and urinary retention were monitored for the first 24 hours. Other complications such as headache and neurological deficit were noted till the time of discharge.

Statistical analysis: Data was analyzed using

statistical software SPSS version 20.0. Sample size was calculated based on literature search for variation in studied data. To calculate the sample size, a power analysis of $\alpha = 0.05$ and $\beta = 0.90$, showed that 60 patients per study group were needed to detect a 30 minute difference in the duration of analgesia between the groups. With 60 patients in each group the power of study was 90%. Pearson's Chi-square tests were applied for categorical variables like level of sensory bock, sedation score and incidence of side effects. Continuous variables were compared using unpaired t test. Data are expressed in terms of mean ± standard deviation. *P* value <0.05 was considered as significant.

Results:

Maximum level of sensory block was also noted. The quality of SAB was recorded as 'Adequate' when the patient experienced total comfort and 'Inadequate' when there was patient discomfort, which required supplementation with analgesic agents. Block was considered 'Failed', if complete sensory and motor block was not achieved even after 30 minutes. Degree of sedation was closely monitored in patients of both groups. The sedation score was assessed using the Modified Observer's Assessment of Alertness/Sedation Score on a scale of 1 to 5 (As shown in **Table 1**).

There was no significant difference between the two groups with respect to patient characteristics such as age and weight distribution. The differences in the base line data of HR, NIBP, RR and SpO_2 of both groups were statistically not significant ($p>0.05$). The mean duration of surgery was 78±15.3 minutes in group I and 75.5±15.2 minutes in group II. The difference in duration of surgery between the two groups was statistically not significant ($p=0.371$) (As shown in **Table 2**).

Mean onset of sensory blockade was 177.17±29.25 seconds in group I and 186±39.29 seconds in group II. The difference in mean onset of analgesia between the groups was statistically not significant ($p=0.165$) (As shown in **Table 3**).

Sensory block reached up to T7 level, in 41 patients in group I and 44 patients in group II. Sensory block reached up to T8 level, in 19 patients in group I and 16 patients in group II. Level of sensory block obtained in both groups was statistically not significant ($p=0.547$). Mean onset of motor blockade was 291.5±51.68 seconds in group I and 298.67±53.25 seconds in group II. The difference in mean onset of motor blockade among both the groups was not significant statistically ($p=0.456$). Motor block was complete in all patients included in the study. All patients reached a modified Bromage score of 3 in both groups (As shown in **Table 4**).

The mean heart rate was compared at baseline and at every 30 minutes thereafter in both groups upto 8 hours post SAB (**Figure 1**). Though there was no difference in baseline, there was a significant fall in heart rate at 30 minutes, 60 minutes and at 120 minutes in the clonidine group ($P<0.001$). However there was no incidence of symptomatic bradycardia. After 120 minutes, there was no difference in the mean heart rate recorded in the two groups (As shown in **Table 5**).

The mean systolic BP was compared at baseline and at every 30 minutes thereafter in both groups up to 8 hours post SAB (**Figure 2**). Though there was no difference in baseline, there was a significant fall in systolic BP at 30 minutes, 60 minutes and at 120 minutes in the clonidine group ($P<0.001$). After 120 minutes, there was no difference in the mean systolic BP recorded in the two groups (As shown in **Table 6**).

The level of sedation, which was assessed using the modified Observer's Assessment of Alertness/Sedation (OAA/S) Scale, showed that 20 (33.33%), 34 (56.67%) and 6 (10%) patients

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recorded an OAS/S score of 5, 4 and 3 respectively in group I. No patients recorded an OAA/S Score of 1 or 2. In group II, 59 (98.33%) patients out of 60 recorded an OAA/S score of 5 and only 1 (1.67%) patient recorded an OAA/S score of 3. Difference in the level of sedation between the groups was statistically significant, with clonidine group recording a higher level of sedation (P>0.001) (As shown in **Table 7**). However, all patients recorded RR of more than 12 breaths per minute and SpO_2 more than 97%. There were no differences from the baseline values of RR and SpO_2 of both the groups recorded at various time intervals.

Mean duration of motor blockade, when a modified Bromage score of less than 3, was recorded was 241.83 ± 32.29 minutes in group I and 170.3±19.98 minutes in group II. The difference in the mean duration of motor blockade between the two groups was statistically significant (P<0.001). Mean duration of analgesia, till a VAS score for pain of more than 4 was recorded in the post operative period, was 572.83±62 minutes in group I and 218±36.92 minutes in group II. The difference in the mean duration of postoperative analgesia between the two groups was statistically significant (P<0.001). Mean VAS scores for pain recorded in the postoperative period were significantly lower in group I as compared to group II. Most patients in group I, did not reacha VAS score of 4 in the post operative period even at 08 hours and did not need systemic postoperatively (As shown in **Table 8**).

Bradycardia (HR<60/min) occurred in 6.67% cases in group I and in a similar number of cases in group II. There was no statistically significant difference in incidence of bradycardia in the clonidine group (P=1.02). Incidence of hypotension defined as decrease of mean arterial pressure >20% from baseline or systolic BP<90 mm Hg was 8.33% in group I and 6.67% in group II. Incidence of hypotension was not statistically significant between the groups (P=0.729). Shivering occurred in 6.67% of cases in both groups and the incidence of nausea and vomiting was 3.33% in both groups. There was no statistically significant difference in the incidence of shivering, nausea and vomiting among the two groups (P=1) (As shown in **Table 9**).

Discusssion:

The synergism between local anaesthetic agents such as bupivacaine and α2 adrenergic agonists such as clonidine is well established. Various studies conclude that duration of sensory analgesia, motor blockade and sedation was longer with addition of clonidine to bupivacaine intrathecally.[2,3]

Clonidine has been demonstrated to be an effective sedative and analgesic agent, which reduces the amount of anaesthetic agents required when used as part of anaesthetic technique. It acts on both presynaptic and postsynaptic nerve terminal by decreasing the sympathetic outflow and norepinephrine release, leading to sedation, anxiolysis and analgesia. It produces analgesia by depressing the release of C- fiber transmitters and by hyperpolarization of post synaptic dorsal horn neurons. The prolongation of motor block is the result of binding to the motor neurons in the dorsal horn. Studies have shown that both oral and intrathecal clonidine in doses of 150µg resulted in prolongation of the time until the first request for supplemental analgesics. Intrathecal clonidine was however better than oral clonidine due to the higher quality of postoperative analgesia and lower degree of hypotension and sedation compared to oral clonidine.[1]

The dose of intrathecal clonidine, which produces prolonged analgesia with minimal side effects, has not been well established. Literature search reveals

that different studies have used different doses of clonidine, ranging from 15µg to 200µg intrathecally. Chiari A et al.[4] reported dose dependent analgesia, when 50µg to 200µg clonidine was administered intrathecally as sole an agent in labour. They found that risk of hypotension is higher with use of higher doses. Studies with higher doses of 2µg/kg body weight of clonidine added to 0.5% hyperbaric bupivacaine for spinal anesthesia in children shows that intrathecal clonidine 2µg/kg body weight is associated with extending duration of postoperative analgesia with moderate side effects.[5]

Addition of low dose clonidine 15µg, with ropivacaine for ambulatory arthroscopy significantly improves the quality of postoperative and analgesia, without compromising early mobilization or causing systemic side effects.[6] Other studies comparing different doses of 15µg and 30µg of intrathecal clonidine added to bupivacaine for inguinal herniorrhapy concluded that use of clonidine and increases the duration of analgesia and is effective for ambulatory herniorrhapy.[7] In elderly patients, clonidine when used intrathecally in doses of 15µg or 30µg with bupivacaine, significantly potentiates the sensory block and duration of analgesia and does not affect the trend of systolic blood pressure as compared to bupivacaine alone.[8] Strebel S et al studied the dose response of intrathecal clonidine 37.5µg, 75µg and 150µg when added to bupivacaine.The study concluded that doses of intrathecal clonidine less than 150µg, dose dependently prolongs both the sensory blockade of spinal anesthesia and time interval to first request for supplement alanalgesia.[9]

The aim of this study was to study a dose of intrathecal clonidine, as adjuvant to hyperbaric bupivacaine that will produce maximum benefit with no side effects. Based on the review of literature, doses of 15 to 37.5µg were shown to be effective for surgeries requiring early ambulation, elderly patients or short duration surgeries. Most studies with doses of 100µg to 200µg reported minimal to moderate side effects of clonidine. A dose of 75µg of preservative free clonidine as an adjuvant to intrathecal bupivacaine for spinal anaesthesia was chosen for this study to evaluate its efficacy for prolonged analgesia and record its side effects. In this study, there was no difference in the mean time for onset of sensory block on adding intrathecal clonidine. Maximum level of sensory blockade reached T7 or T8 dermatome in all cases in both the groups suggesting that addition of clonidine did not heighten the level of SAB. The mean time taken for maximum motor blockade also did not differ in both the groups. Both the groups had a motor blockade of modified bromage score of 3. This is consistent with the studies done by Sethi et al.[3] who observed the complete motor blockade of the lower extremity in all patients.

The mean duration of analgesia was longer in the clonidine group compared to the plain bupivacaine group and this difference was statistically significant. Mean analgesia with addition of 75µg intrathecal clonidine, lasted for 241.83±32.29 minutes in the clonidine group which concurs with the study conducted by Grandhe PR et al[10] who observed the mean duration of analgesia of 6.3±0.8 hours when using clonidine of 1µg/kg. Combination of clonidine with a local anesthetic improves the quality of analgesia during surgery, significantly improved postoperative analgesia, improves immediate postoperative pain scores and prolongs time to the first analgesic request.[11,12] These effects of clonidine are valuable inanticipated prolonged procedures. For prolonged surgeries, it is beneficial to use an adjuvant like clonidine, which results in an

extended duration of analgesia and motor block, without serious side effects. The mean duration of motor blockade was longer in the clonidine group compared to the plain bupivacaine group and this difference was statistically significant. Intrathecal clonidine alone does not induce motor block or weakness. In contrast, intrathecal clonidine combined with local anaesthetics, significantly potentiates the intensity and duration of motor blockade. The explanation could be that α2 adrenergic agonists induce motor neuron hyperpolarisation in the ventral horn of the spinal cord and facilitate local anaesthetic action.[7]

A decrease in the mean HR was recorded in both the groups up to 120 minutes post SAB [Figure 1]. On analysis of the decrease in the mean HR between clonidine and plain bupivacaine group at different time intervals, the decrease was in mean HR statistically significant from 30 minutes to 120 minutes. After 120 minutes the difference between both the groups was not statistically significant. It suggests that intrathecal clonidine causes a decrease in HR that mainly occurs in the initial 120 minutes and then the HR returns to the baseline values. Clonidine reduces HR partly by decreasing the norepinephrine release at the presynaptic nerve terminal and partly by a vagomimetic effect.[13] However, in the study, the incidence of bradycardia, defined as a HR less than 60/minute, was around 6.6% in both the groups. In a study conducted by Kaabachi O et al.[5] the authors observed the incidence of bradycardia to be 30%, inintrathecal clonidine 2µg/kg group, which is higher compared to our study. This is probably due to higher dose of clonidine of 2µg/kg used compared to this study.

Adecrease in the mean systolic BP was observed in both groups up to 120 minutes post SAB, even after perloading with ringer lactate 10 ml/kg [Figure 2]. On analysis of the decrease in the mean systolic BP between clonidine and plain bupivacaine group at different time intervals, the decrease in the mean systolic BP was statistically significant from 30 minutes to 120 minutes. After 120 minutes the difference between both the groups was not statistically significant. It suggests that decrease in systolic BP caused by intrathecal clonidine 75µg occurred for first 120 minutes after administration. There was no difference in values of systolic BP after 120 minutes, suggesting that intrathecal clonidine did not cause sustained fall in systolic BP.

Incidence of hypotension, defined as a fall in mean arterial pressure more than 20% of baseline or a systolic BP<90 mm Hg, was comparable in both the groups. The difference in incidence of hypotension was not statistically significant between the two groups. Hypotension responded to treatment with intravenous fluids and ephedrine and there was no incidence of prolonged hypotension recorded. This makes 75µg intrathecal clonidine safe to administer, without fear of bradycardia or significant hypotension in the postoperative period, where the level of monitoring is less compared to intraoperative period. Clonidine produces dose-dependent sedation with an onset of action of 20 minutes regardless of route of administration. Sedation commonly accompanies the use of clonidine for regional anesthesia, mainly due to action on the locusceruleus.[13]

In this study, after administration of intrathecal clonidine 75µg, 66% of patients reached a OAA/S score of 4 or 3, were mildly sedated and responded slowly to voice or after calling out loud. Addition of clonidine improved sedation after the SAB, which is often a desirable effect during the intra operative period. Also, all of the patients sedated, did not record respiratory depression or desaturation. The sedation induced by intrathecal

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clonidine enhanced patient comfort intraoperatively. The incidence of shivering, nausea and vomiting was not different between the two groups. There was no incidence of itching, urinary retention, headache or any neurological complications in both the groups.

Conclusion:

The results of the study indicate that addition of 75µg clonidine with hyperbaric bupivacaine for spinal anaesthesia increases the duration of sensory and motor blockade. It produces excellent and prolonged postoperative analgesia and can be considered as a method of preemptive analgesia to avoid the multiple injections for analgesia in the postoperative period. Clonidine 75µg intrathecally resulted in mild sedation and patients were comfortable throughout the surgical procedure with no adverse effects.

Table 1: Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5 (alert)	Responds readily to voice with normal tone
4	Responds slowly to voice with normal tone
3	Responds after calling loudly or repeatedly
2	Responds after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to pain

Table 2: Patient characteristics

Particulars	Group I	Group II	*P*-value	Significance
	Mean ± Std. Deviation	Mean ± Std. Deviation		
Age (in years)	34.6 ± 7.84	34.38 ± 7.22	0.875	Not Significant
Weight (in kgs)	63.63 ± 5.52	62.07 ± 5.27	0.114	Not Significant
Heart rate (per min)	83.4 ± 9.22	84.53 ± 9.09	0.499	Not Significant
Systolic BP (mm Hg)	124.43 ± 11.02	127.9 ± 11.77	0.099	Not Significant
Respiratory rate (per min)	16.12 ± 0.88	16.05 ± 0.83	0.671	Not Significant
Oxygen saturation (%)	98.53 ± 0.5	98.68 ± 0.47	0.094	Not Significant
Duration of surgery (minutes)	78 ± 15.3	75.5 ± 15.2	0.371	Not Significant

Table 3: Initial block characteristics

Initial block characteristics	Group I	Group II	*P*-value	Significance
	Mean ± Std. Deviation	Mean ± Std. Deviation		
Mean onset of sensory blockade (in seconds)	177.17 ± 29.25	186 ± 39.29	0.165	Not Significant
Mean onset of motor blockade (in seconds)	291.5 ± 51.68	298.67 ± 53.25	0.456	Not Significant

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Table 4: Level of sensory bock and quality of motor block

Particulars	Group I	Group II	Total	*P*-value	Significance
Level of Sensory Block upto T7	41 (68.33%)	44 (73.33%)	85 (70.83%)	0.547	Not Significant
Level of Sensory Block upto T8	19 (31.67%)	16 (26.67%)	35 (29.17%)		
Modified Bromage Score 0	0	0	0	-	-
Modified Bromage Score 1	0	0	0		
Modified Bromage Score 2	0	0	0		
Modified Bromage Score 3	60 (100%)	60 (100%)	120 (100%)		
Total	60	60	120		

Table 5: Variation of Heart Rate

Period of observation	Group I (per min)	Group II (per min)	*P*-value	Significance
0 minutes	83.4 ± 9.22	84.53 ± 9.09	0.499	Not Significant
30 minutes	69.83 ± 7.85	83.63 ± 10.07	<0.001	Significant
60 minutes	71.8 ± 7.53	85.1 ± 7.43	<0.001	Significant
120 minutes	78.9 ± 8.91	84.07 ± 6.38	<0.001	Significant
240 minutes	83.25 ± 7.54	83.83 ± 6.26	0.646	Not Significant
360 minutes	83.55 ± 7.21	83.7 ± 5.71	0.900	Not Significant
480 minutes	84.62 ± 6.27	84.43 ± 5.13	0.861	Not Significant

Table 6: Variation of Systolic Blood Pressure

Period of observation	Group I (mm Hg)	Group II (mm Hg)	*P*-value	Significance
0 minutes	124.43 ± 11.02	127.9 ± 11.77	0.099	Not Significant
30 minutes	107.87 ± 10.39	115.9 ± 11.29	<0.001	Significant
60 minutes	109.83 ± 10.11	118.5 ± 11.03	<0.001	Significant
120 minutes	110.53 ± 9.26	121.4 ± 9.64	<0.001	Significant
240 minutes	119.8 ± 7.42	122 ± 7.99	0.121	Not Significant
360 minutes	122.47 ± 9.35	123.87 ± 8.25	0.386	Not Significant
480 minutes	126.77 ± 8.49	125.33 ± 8.89	0.368	Not Significant

Table 7: Comparison of sedation scores

Sedation score	Group I	Group II	Total	*P*-value	Significance
5	20 (33.33%)	59 (98.33%)	79 (65.83%)	<0.001	Significant
4	34 (56.67%)	0(0)	34 (28.33%)		
3	6 (10%)	1 (1.67%)	7 (5.83%)		
2	0	0	0		
1	0	0	0		
Total	60 (100%)	60 (100%)	120 (100%)		

Table 8: Block characteristics and mean VAS scores

Duration in hours	Group I	Group II	*P*-value	Significance
	Mean ± Std. Deviation	Mean ± Std. Deviation		
Mean duration of motor blockade (in minutes)	241.83 ± 32.29	170.33 ± 19.98	<0.001	Significant
Mean duration of analgesia (in minutes)	572.83 ± 62	218 ± 36.92	<0.001	Significant
VAS score at 120 mins	0 ± 0	1.59 ± 0.57	<0.001	Significant
VAS score at 240 mins	0.12 ± 0.25	5.11 ± 0.65	<0.001	Significant
VAS score at 360 mins	0.75 ± 8.9	7.32 ± 0.75	<0.001	Significant
VAS score at 480 mins	1.9 ± 1.59	8.32 ± 0.55	<0.001	Significant

Table 9: Incidence of side effects

Side Effects	Group I	Group II	Total	*P*-value	Significance
Bradycardia	4 (6.67%)	4(6.67%)	8 (6.67%)	1.000	Not Significant
Hypotension	5 (8.33%)	4(6.67%)	9 (7.5%)	0.729	Not Significant
Shivering	4 (6.67%)	4(6.67%)	8 (6.67%)	1.000	Not Significant
Nausea / Vomiting	2 (3.33%)	2(3.33%)	4 (6.67%)	1.000	Not Significant

Figure 1: Variation of Heart Rate

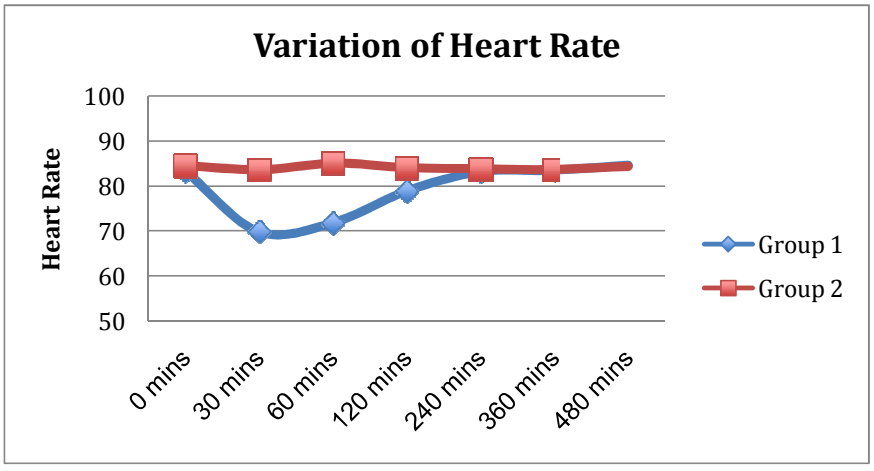
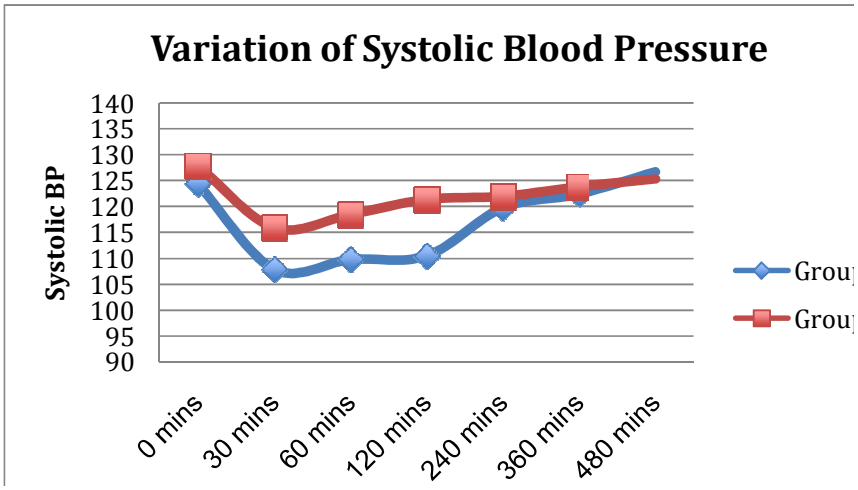


Figure 2: Variation of Systolic BP



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