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"A Comparative Study of Intrathecal Dexmedetomidine 10mcg and Fentanyl 25mcg as Adjuvants To 0.5% Hyperbaric Bupivacaine in Spinal Anaesthesia with a Control Group''

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Abstract: *To compare the effects of intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine with a control group with regards to time of onset of sensory and motor blockade, Duration of sensory blockade and motor blockade, Two segment sensory regression time, Duration of effective post-operative analgesia and incidence of side effects. A randomized, prospective study, after obtaining ethical committee approval in R.L. Jalappa hospital and research center and written informed consent of patients was conducted on 90 Adult Patients of either sex, aged between 20 to 45 years, of physical status ASA Grade I and Grade II undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia. Patients were divided into 3 groups of 30 each. Group D received 15mg hyperbaric bupivacaine with 10mcg dexmedetomidine in 0.5ml of normal saline. Group F received 15mg hyperbaric bupivacaine with 25mcg fentanyl. Group C received 15mg hyperbaric bupivacaine with 0.5ml of normal saline. The time of onset of sensory and motor blockade and the duration of two segment sensory regression time, sensory, motor blockade and duration of effective post op analgesia was statistically significant in group D compared to group C and F. Intrathecal Dexmedetomidine is associated with faster onset of sensory and motor blockade, with significantly prolonged sensory and motor blockade and less requirement of rescue analgesia compared to fentanyl and control group.*

Keywords: *α2, adrenoreceptor agonists, bupivacaine, fentanyl, spinal anaesthesia*.

I. Introduction

Spinal anaesthesia is a simple technique which is easier to perform with rapid onset of anaesthesia, providing adequate analgesia both intra operatively and post operatively. Spinal anaesthesia can be provided with a wide range of local anesthetics and additives that allow control over the level, time of onset and duration of spinal anaesthesia. Postoperative pain control is a major problem, as using only local anesthetics is associated with relatively short duration of action and thus early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as clonidine, midazolam, and others have been studied to prolong the effect of spinal anesthesia. Opioids produce intense and prolonged analgesic action without gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid space[1].

Fentanyl a highly lipophilic opioid has rapid onset of action and lesser side effects compared to morphine. Duration of effects of intrathecal fentanyl is dose independent. Side effects include pruritus, nausea and vomiting and rarely serotonin syndrome[2]. Recently intrathecal administration of α-2 adrenoreceptor agonist as adjuvants to local anaesthetics has shown to have sedative, analgesic, hemodynamic stabilizing effect with prolonged duration of spinal block[3]. It's a highly specific, selective α-2 adrenoreceptor agonist with 8 times more affinity for α-2 adrenoreceptors than clonidine[4]. Based on earlier human studies, it is hypothesized that intrathecal 10 µg dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects. Till date, there are only few studies done that compare the effects of addition of 10 µg dexmedetomidine to hyperbaric bupivacaine and 25 µg fentanyl to hyperbaric bupivacaine with a control group.

II. Methodology

This study was conducted on patients admitted to R.L. Jalapa hospital. Approval from institutional ethics committee was taken. Inclusion criteria were patients of either sex, aged between 20 to 45 years of American Society of Anesthesiologists (ASA) physical status I or II undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia. Exclusion criteria were patients with known liver, renal, cardiac problems, allergic to drug, patients using adrenergic receptor blockers or calcium channel blockers, patients with weight >120kg or height <150cms, patients posted for emergency surgeries.

After obtaining informed written consent, 90 patients undergoing lower limb and lower abdominal surgeries under spinal anaesthesia were selected. They were randomly divided into 3 groups of 30 each. Randomization was done using simple sealed envelope technique. Group C: Control group, Group D: Dexmedetomidine group, Group F: Fentanyl group.

All patients were examined a day before surgery. All were kept fasting overnight after 10:00pm and received tab. Ranitidine 150mg and tab. Alprazolam 0.5mg orally as premedication at night before surgery and at 6:00am in the morning on the day of surgery. An intravenous line with 18G cannula was secured and all were preloaded with Ringer lactate 5ml/kg. All patients were monitored with electrocardiography, oxygen saturation, noninvasive blood pressure, end-tidal carbon-di-oxide.

Under all aseptic precautions after putting patient in left lateral position, using 23G quincke spinal needle, spinal block was performed at level of L3-L4 through a midline approach and patient put to supine position. Patients in group D received 3ml of 0.5% hyperbaric bupivacaine with 10mcg dexmedetomidine in 0.5ml of normal saline. Patients in group F received 3ml of 0.5% hyperbaric bupivacaine with 25mcg fentanyl in 0.5ml of normal saline. Patients in group C received 3ml of 0.5% hyperbaric bupivacaine with 0.5ml of normal saline. The time at intrathecal injection was considered as 0 and the following parameters were observed, time of onset of sensory blockade, the height of sensory blockade, motor blockade as per Bromage Scale, total duration of sensory blockade, quality of analgesia, two segment sensory regression time, need for rescue analgesia when patient complains of pain and incidence of side effects.

Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, Spo2 and respiratory rate was recorded every 5 min for 15 min and then every 10mins throughout the intra operative period and also at the completion of surgery. Post-operatively monitoring of pulse rate, Spo2, systolic and diastolic blood pressure, mean arterial pressure was recorded hourly.

Quality of motor block was assessed using modified Bromage scale5.

Bromage 0 - patient able to move hip, knee and ankle.

Bromage 1 – patient unable to move the hip but is able to move the knee.

Bromage 2 – patient unable to move the hip and knee but is able to move the ankle.

Bromage 3 – patient is unable to move the hip, knee and ankle.

Quality of analgesia was assessed by visual analogue scale.

Visual analogue scale for pain:

0	No pain
1-3	mild pain
4-6	moderate pain
7-10	severe pain

Hypotension: Defined as reduction of systolic blood pressure more than 30% below baseline value and it will be treated with increased rate of intravenous fluids and if needed injection mephentermine 6mg increments IV.

Bradycardia: Defined as heart rate less than 60/minute and will be treated with injection atropine 0.6mg IV.

Adverse effects: patients will be monitored for any cardiovascular side effects like changes in blood pressure, heart rate and rhythm, central nervous system depression, respiratory depression and any hypersensitivity reactions for drugs.

Statistical analysis:

To calculate the sample size, a power analysis of $\alpha = 0.05$ and $\beta = 0.80$, showed that 30 patients were needed for the study. Univariate analysis was used to estimate mean and standard deviation. Analysis of variance was used to test the significance of effects between the subjects. Post Hoc analysis using the Turkey HSD statistical test was used to test multiple comparison of means and the statistical significance between all the groups. Statistical calculations were done through SPSS 16.0 (2007) for windows

III. Results

There was no significant difference in the patient characteristics in terms of age, sex, weight or height distribution.

Onset of sensory and motor block:

The mean time taken for onset of sensory blockade in group C is 343.33±53.52 seconds, 244.0±70.31 seconds in group D and 283.17±47.60 seconds in group F. Group C is statistically different from group D and F with p-value 0.0, which is less than 0.05 at 5% significance level. Also group D and F are statistically different with p-value 0.028, which is less than 0.05 at 5% significance level.

The mean time for onset of motor blockade in group C is 400.67±55.64 seconds, 300.67±61.40 seconds in group D and 370.33±64.67 seconds in group F. Group C is statistically different from group D with p-value 0.0. Group C is statistically same as group F with p-value 0.135, which is higher than 0.05 at 5% significance level. Also group D and group F are statistically different with p-value 0.0.

Two segment sensory regression time:

The mean time for regression of sensory block by two segments in group C is 87.37±5.88 mins, 168.5±20.68 mins in group D and 103.23±8.82 mins in group F. All the three groups are statistically different. Group C (control group) is statistically different from group D and group F with p-value 0.0. Group D and group F are statistically different with p-value 0.0.

Duration of motor blockade:

The mean duration of motor blockade in group C is 180.83±24.95 mins, 424±36.32 mins in group D and 221.83±27.14 mins in group F. All the three groups are statistically different. Group C is statistically different from group D and F with p-value 0.0. Group D and F are statistically different with p-value 0.0.

Duration of Analgesia:

The mean duration of Analgesia in group C is 236.17±20.37 mins, 470.5±59.89 mins in group D and 299.5±47.98 mins in group F. All the three groups are statistically different. Group C is statistically different from group D and group F with p-value 0.0. Group D and F are statistically different with p-value 0.0.

Heart rate:

Basal mean heart rate is 87.7 ± 14.22 bpm in group C. The mean heart rate has decreased by 18.73 bpm compared to basal mean heart rate at 40th min. Basal mean heart rate is 84.63 ± 10.89 bpm in group D. The mean heart rate has decreased by 13.03 bpm compared to Basal mean heart rate at 60th min. Basal mean heart rate is 81 ± 8.53 bpm in group F. The mean heart rate has decreased by 9.03 bpm compared to Basal mean heart rate at 50th min. The mean heart rate from basal to 120th minute recording is statistically insignificant between the groups.

Mean arterial pressure:

Basal mean arterial pressure is 94.47±11.10 mm hg in group C. The mean arterial pressure (MAP) has decreased by 21.14 mm hg compared to basal MAP at 40th min. Basal mean arterial pressure is 96 ± 9.69 mm hg in group D. The MAP has decreased by 20.63 mm hg compared to Basal MAP at 40th min. Basal MAP is 97.03±9.90 mm hg in group F. The MAP has decreased by 21.00 mm hg compared to Basal MAP at 50th min. The mean MAP from basal to 120th minute recording is statistically insignificant between group c, group D and group F.

The mean MAP of group C is statistically different from group D and group F (Fentanyl group) at 110th minute recording with p-value of 0.021 and 0.024 respectively at 5% significance level. But MAP of the group D and group F are statistically insignificant with p-value of 0.999 at 5% significance level. It indicates that Control group MAP is different from Dexmedetomidine group and Fentanyl group MAP. Whereas Dexmedetomidine group and Fentanyl group MAP are statistically same.

IV. Discussion

Subarachnoid block has been most extensively used for lower abdominal and lower limb surgeries because of its simplicity, speed, reliability and minimal exposure to depressant drugs. The aim of good post-operative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects.

Adding, an intrathecal additive to local anaesthetics forms a reliable and reproducible method to prolong the duration of anaesthesia and to prolong post-operative analgesia. A number of adjuvants to local anesthetics for spinal anaesthesia like opioids (fentanyl and buprenorphine), benzodiazepines (midazolam), ketamine and neostigmine have been used. The most common agents used are opioids and they have formed a cornerstone option for the treatment of post-operative pain.[5]

Fentanyl, a highly lipophilic μ-receptor agonist opioid, has rapid onset of action following intrathecal injection. Fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action.

Spinal opiates prolong the duration of analgesia, but they do have drawbacks of late and unpredictable respiratory depression, pruritus, nausea, vomiting and urinary retention[7,8] , which requires constant postoperative monitoring and urinary catheterization. Hence there is a requirement of an adjuvant to be used along with local anesthetics which can produce prolonged analgesia without the above said side effects of opioids.

Intrathecal alpha 2 agonists are found to have antinociceptive action for both somatic and visceral pain. So in this context alpha 2 agonists may be a very useful drug along with the local anesthetic Bupivacaine 0.5%

heavy for spinal anaesthesia[5]. While clonidine has been used as an adjuvant to local anaesthetic agents for intrathecal purposes with successful results, there are only a few studies available for dexmedetomidine as adjuvant to local anesthetic agents for intrathecal purpose. We have undertaken this study to evaluate and compare the effect of adding dexmedetomidine or fentanyl as adjuvants to hyperbaric bupivacaine with a control group.

Ninety patients of ASA Grade-I and Grade-II posted for elective lower abdominal and lower limb surgeries were selected and randomly divided into 3 groups (n=30). Randomization was done using simple sealed envelope technique. It was found that a sample size of 30 patients per group was required to detect an increase of 30 min in the time of two-segment sensory regression with a standard deviation of 28 min.

Demographic data: demographic data comparing age, sex, height, weight shows no statistical difference among the groups.

Harbhej singh et al[9] in 1995, Biswas et al[10] in 2002, Khanna M S et al[11] in 2002, Gupta R et al[7] in 2011 have chosen 25 mcg fentanyl as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study we have chosen 25mcg fentanyl as an additive to hyperbaric bupivacaine.

Al-Ghanem et al[12] studied the effect of addition of 5 µg dexmedetomidine or 25 µg fentanyl intrathecal to 10 mg isobaric bupivacaine in vaginal hysterectomy and concluded that 5 µg dexmedetomidine produces more prolonged motor and sensory block as compared with 25 µg fentanyl. Al-Mustafa et al[13] and Al-Ghanem et al[11] used higher doses of dexmedetoidine (5 mcg and 10 mcg), and found that its effect is dose-dependent and that the onset of sensory block to reach T10 dermatome was shorter with the use of dexmedetomidine.

Onset of sensory blockade:

In our study there is a statistically significant decrease in the onset of sensory blockade in dexmedetomidine group and in the fentanyl group compared to the control group. Al-Mustafa MM et al.[13] authors observed the onset of analgesia to be 9.5±3mins in control group and 6.3±2.7 mins and 4.7±2 mins in dexmedetomidine group (5 µg and 10 µg respectively) which concurs with our study.

The time taken for regression of sensory block by two segments:

The time taken for regression of sensory block by two segments in the present study is 87.37±5.88 mins in the group C, 103.23±9 mins in group F and 168.5±20.68 mins in group D. There is a statistically significant increase in the mean time taken for regression of sensory block by two segments in fentanyl and dexmedetomidine group compared to the control group.

Duration of effective post-operative analgesia:

The mean duration of analgesia in our study is 236.17±20.37 mins in control group, 299.5±48 mins in fentanyl group and 470.5±59 mins in dexmedetomidine group. There is a statistically significant increase in the duration of analgesia in dexmedetomidine and fentanyl group compared to the control group.

Onset of motor blockade:

In our study the mean time for onset of motor block is 6.40±0.55 mins in control group, 6.10±1.04 mins in fentanyl group and 5±1.01 mins in dexmedetomidine group. There is a statistically significant decrease in the mean time for onset of motor blockade in the dexmedetomidine group compared to fentanyl group compared to the control group. In studies conducted by Kanazi GE et al[5], Al-Mustafa MM et al[13], Gupta R et al.[6] and Shukla D et al.[14] in the dexmedetomidine group authors observed a significant decrease in the mean time for onset of motor blockade which concurs with our study.

Duration of motor blockade:

In our study the mean duration of motor blockade was 181±25 mins in control group, 222±27.14 mins in fentanyl group and 424.35±36.32 mins in dexmedetomidine group. There is a statistically significant increase in the duration of motor blockade in dexmedetomidine group and fentanyl group compared to the control group. This compares with study conducted by Kanazi GE et al.[5] where the mean duration of motor blockade is 163±47 mins in control group, 216±35 mins in clonidine group and 250±76 mins in dexmedetomidine group which is less than the value in our study. This could be due to the less doses of clonidine and dexmedetomidine used.

Mean arterial blood pressure:

In the control group we observed a maximum fall in mean MAP of 21.14 mmHg from mean basal MAP at 40th min, in the fentanyl group it was 21 mm Hg at 50th min and in the dexmedetomidine group it was 20.63 mmHg at 40th min. There was statistically no significant difference in any of the three groups regarding fall in MAP. Fifteen patients in control group, eleven patients in fentanyl group and thirteen patients in dexmedetomidine group developed hypotension and were easily managed with intravenous fluids and vasopressor. Al-Ghanem SM et al.[12] authors observed that the hypotension was mild to moderate in both

dexmedetomidine and fentanyl group. 4/38 patients in dexmedetomidine group and 9/38 patient in fentanyl group had hypotension but it did not reach a significant difference.

Heart rate:

In the control group a maximum decrease in the mean heart rate of 19 bpm from basal value occured at 40th min, in the fentanyl group it was 10 bpm at 50th min and in the dexmedetomidine group it was 13 bpm at 60th min. There was no statistically significant difference in any of the three groups regarding decrease in the mean heart rate. However it was found that there was a delay in maximum decrease in the mean heart rate in the dexmedetomidne group compared to the fentanyl group and the control group. Nine patients in dexmedetomidine group, seven patients in fentanyl group and five patient in control group had bradycardia which is statistically not significant. Bradycardia was easily reversed with 0.6mg intravenous atropine in all the patients. Our study is consistent with the studies done by Kanazi GE et al[5], Al-Ghanem SM et al[12], and Al-Mustafa MM et al[13], who observed that there was no significant difference in mean value of heart rate throughout the intraoperative and postoperative period.

V. Conclusion

we conclude Dexmedetomidine when used intrathecally along with bupivacaine significantly prolongs the duration of sensory, motor blockade and duration of effective post op analgesia and as there was no clinically significant difference between fentanyl and dexmedetomidine on spinal block characteristics, use of dexmedetomidine as adjuvant to hyperbaric bupivacaine in spinal anaesthesia is an attractive alternative especially in those surgeries requiring long duration.

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Tables And Graphs

Table 1: Sensory and motor block onset time, duration of motor blockade and effective analgesia and the time taken for two segment sensory regression.

Spinal block characteristics	Group F	Group C	Group D
Time taken for onset of sensory blockade	4.43±0.47 mins	5.43±0.53 mins	4.04±1.1 mins
The time taken for regression of sensory block by two segments	103.23±9 mins	87.37±6 mins	168.5±21mins
Duration of effective analgesia	299±48 mins	236.17±20.37mins	470±59 mins
Onset of motor blockade	6.10±1.04 mins	6.40±0.55 mins	5±1.01 mins
Duration of motor blockade	222.±27.14 mins	181±25 mins	424.35±36.32mins

Table 2: Time taken for onset of sensory blockade in seconds

Time taken for Onset of sensory blockade	Groups			P Value: GROUP C Vs GROUP D	P Value: GROUP C Vs GROUP F	P Value: GROUP D Vs GROUP F
	GROUP C	GROUP D	GROUP F			
Mean ±SD	343.33±53.52	244±70.31	283.17±47.60	0	0	0.028
Minimum	20	20	22			
Maximum	45	45	45			

Graph 1: onset of sensory blockade in seconds

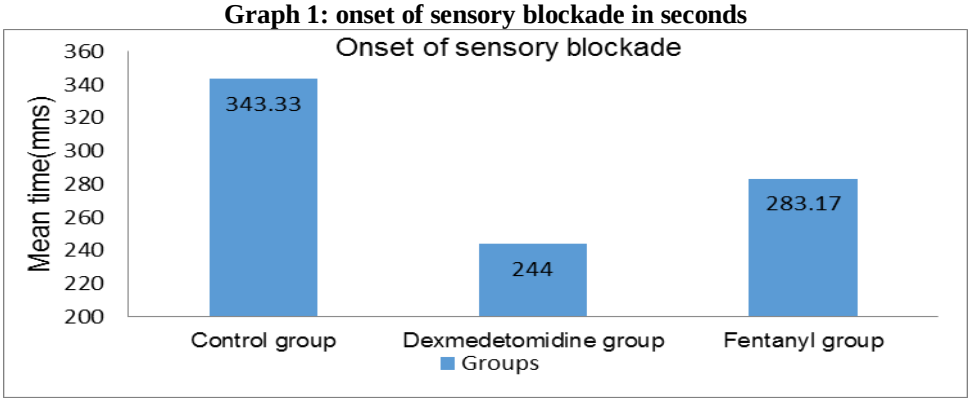

Table 3: Time taken for onset of motor blockade in seconds

Time taken for Onset of motor blockade	Groups			P Value: GROUP C vs GROUP D	P Value: GROUP C vs GROUP F	P Value: GROUP D vs GROUP F
	GROUP C	GROUP D	GROUP F			
Mean ±SD	400.67±55.64	300.67±61.40	370.33±64.67	0	0.135	0
Minimum	270	180	270			
Maximum	540	;420	600			

Graph 2: Onset of motor blockade in seconds

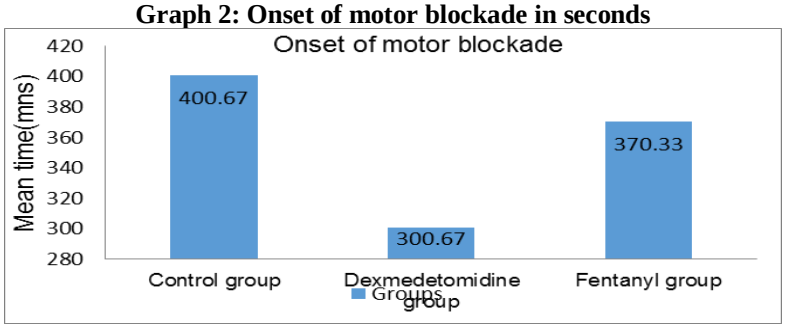

Table 4: Time taken for regression of sensory block by two segments in minutes

Duration of two segment sensory regression in mins	**GROUP C**	**GROUP D**	**Fentanyl group**	**P Value: GROUP C vs GROUP D**	**P Value: GROUP C vs GROUP F**	**P Value: GROUP D vs GROUP F**
Mean ±SD	87.37±5.88	168.5±20.68	103.23±8.82	0.0	0.0	0.0
Minimum	75	130	90			
Maximum	100	210	120			

Graph 3: Time to two segment sensory regression in minutes

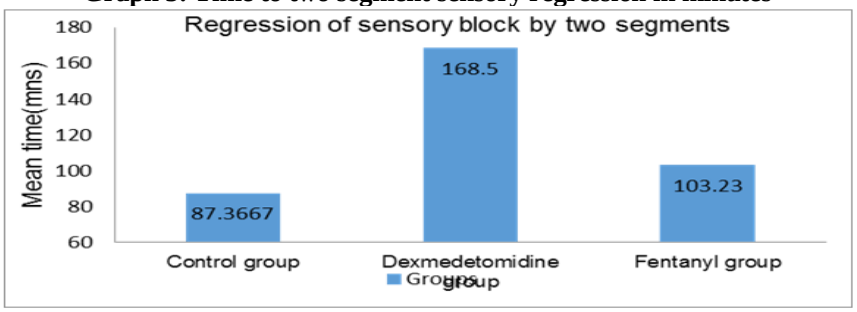

Table 5: Duration of motor blockade in minutes.

Duration of motor blockade	Group			P Value: group C Vs Group D	P Value: group C Vs group F	P Value: group D vs Group F
	Group C	Group D	Group F			
Mean ±SD	180.83±24.95	424±36.32	221.83±27.14	0	0	0
Minimum	140	380	150			
Maximum	230	540	280			

Graph 4: Duration of motor blockade in minutes

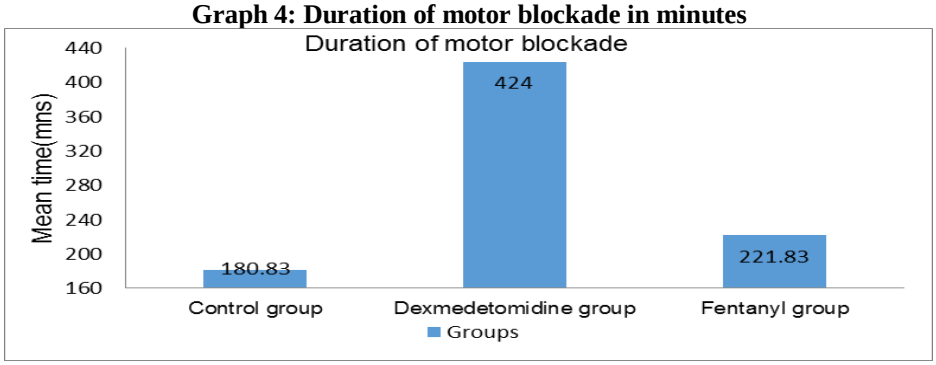

Table 6: Duration of Analgesia in minutes

Duration of Analgesia	Group			P Value: Group C vs Group D	P Value: Group C vs Group F	P Value: Group D vs Group F
	Group C	Group D	Group F			
Mean ±SD	236.17±20.37	470.5±59.89	299.5±47.98	0	0	0
Minimum	200	410	180			
Maximum	300	720	435			

Graph 5: Mean duration of Analgesia in minutes

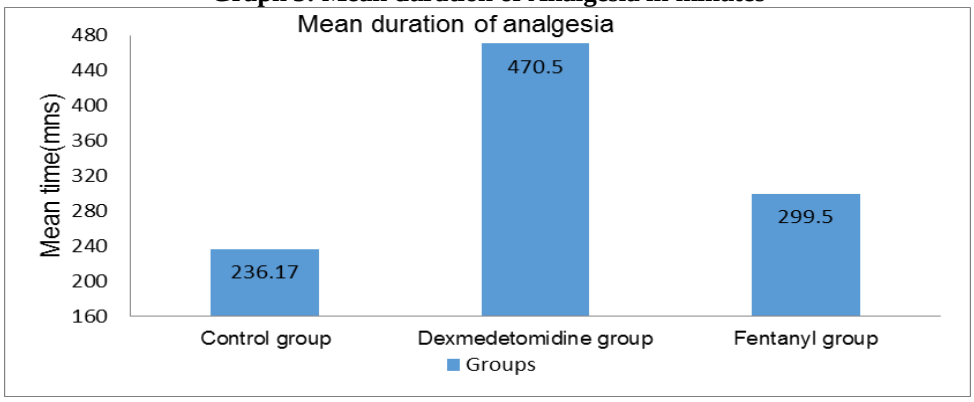

Table 7: Heart rate in bpm at various intervals

Heart rate	Groups			P Value: Control vs	P Value: Control vs	P Value: Dexmedetomidine
	Control group	Dexmedetomidine group	Fentanyl group			
BASAL_HR	87.7±14.22	84.63±10.89	81±8.53	0.556	0.066	0.44
HR_0_MIN	90.07±11.84	89.7±12.69	88.4±9.49	0.977	0.8	0.9
HR_2_MIN	91.3±10.31	91.2±11.78	89.06±9.92	0.99	0.647	0.721
HR_5_MIN	87.03±12.27	89.63±11.73	86.43±10.99	0.721	0.962	0.544
HR_10_MIN	81.73±11.77	84.53±13.15	80.13±11.29	0.688	0.846	0.345
HR_20_MIN	78.7±10.43	77.36±10.19	75.7±11.60	0.861	0.513	0.824
HR_30_MIN	72.66±8.41	73.8±10.18	75.73±12.07	0.922	0.523	0.753
HR_40_MIN	68.97±9.93	72.13±10.20	71.97±12.53	0.528	0.564	0.998
HR_50_MIN	69.93±10.50	72.53±11.58	71.93±11.90	0.6	0.725	0.977
HR_60_MIN	71.1±9.78	71.6±11.35	72.8±11.099	0.979	0.809	0.903
HR_70_MIN	74.6±9.25	73.73±11.48	76.43±10.90	0.984	0.709	0.591
HR_80_MIN	79.73±8.51	77±10.27	78.63±10.67	0.667	0.972	0.796
HR_90_MIN	82.57±8.02	79.43±9.44	82.87±8.14	0.484	0.928	0.273
HR_100_MIN	84.37±7.85	82.43±7.86	84.23±8.71	0.861	0.942	0.662
HR_110_MIN	84.2±7.56	83.5±7.03	84.73±8.49	0.867	0.995	0.812
HR_120_MIN	86.5±8.12	84.97±7.21	86.33±7.10	0.589	0.956	0.758

Graph 6: Mean heart rate at various interval in bpm

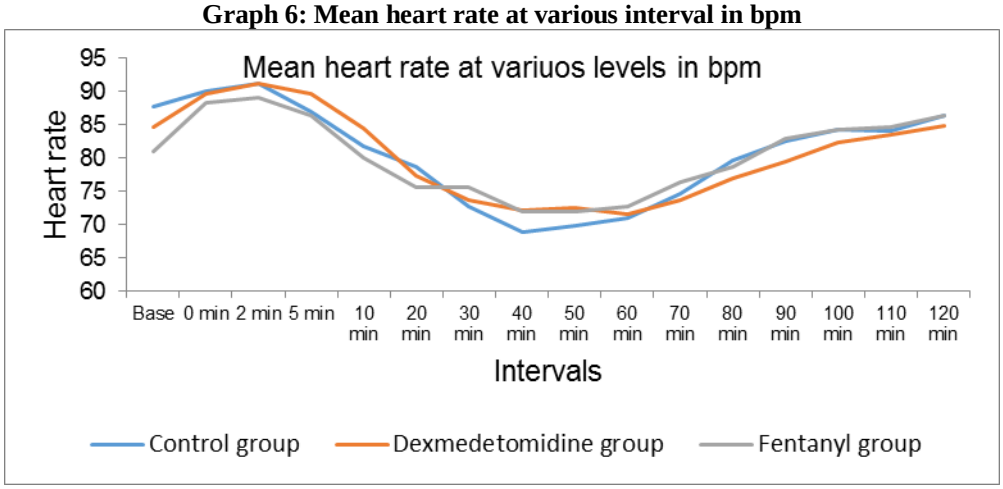

Table 7: Mean MAP at various intervals in mm Hg

MAP	Groups			P Value: Control vs Dexmedetomidine	P Value: Control vs Fentanyl group	P Value: Dexmedetomidine vs Fentanyl group
	Control group	Dexmedetomidine group	Fentanyl group			
BASAL_MAP	94.47±11.10	96±9.69	97.03±9.90	0.81	0.579	0.92
MAP_0_MIN	96±8.73	100.23±8.46	95.3±9.71	0.189	0.949	0.095
MAP_2_MIN	95.4±9.92	97.63±7.69	94.9±7.96	0.507	0.995	0.44
MAP_5_MIN	88.3±9.10	90.6±8.70	88±8.39	0.387	0.984	0.475
MAP_10_MIN	83.2±9.27	83.93±8.33	83.0667±8.54	0.831	0.978	0.921
MAP_20_MIN	77.73±9.24	80.8±8.74	79.9±9.12	0.254	0.449	0.92
MAP_30_MIN	74.47±9.53	76.87±9.39	78.03±9.97	0.481	0.244	0.886
MAP_40_MIN	73.33±10.22	75.37±8.91	77.5±9.34	0.625	0.184	0.665
MAP_50_MIN	76.13±9.77	76.5±7.97	76.03±8.73	0.985	0.999	0.978
MAP_60_MIN	79.3±7.64	78.7±6.66	80±8.99	0.928	0.964	0.8
MAP_70_MIN	82±6.74	80.6±5.49	81.43±6.31	0.618	0.903	0.864
MAP_80_MIN	84.37±7.19	81.6±6.10	83.43±7.02	0.238	0.814	0.556
MAP_90_MIN	86.37±6.63	83.23±5.04	83.6±6.18	0.112	0.179	0.969
MAP_100_MIN	87.3±6.52	84.77±6.29	84.2±5.91	0.264	0.138	0.934
MAP_110_MIN	89.17±6.07	84.7±6.82	84.77±6.16	0.021	0.024	0.999
MAP_120_MIN	89.9±5.66	86.43±7.4	84.6±5.19	0.081	0.004	0.485

Graph 7: Mean MAP at various intervals in mm Hg