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Evaluation of Pre-Operative Oral Clonidine and Oral Diazepam as Pre-Medication on Extend and Duration of Sensory Blockage after Spinal Anaesthesia.

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Abstract

Background: Spinal anesthesia is the most common technique used for lower abdominal surgeries. Clonidine has been used as oral or intramuscular premedication to prolong the effects of spinal anesthesia with local anesthetics. Diazepam is a long acting benzodiazepine. The anxiolytic, amnesic and hypnotic effects of diazepam are the basis for the use of this drug in the pre-operative medication which is preferably accomplished with oral administration. Hence in our study we evaluated the efficacy of oral clonidine and oral diazepam as pre-medication on the extent and duration of sensory blockade in patients receiving spinal anesthesia with 0.5% bupivacaine for lower abdominal surgeries.

Material And Method: In a randomized, double – blinded, control study, three groups of fourty patients each were selected. Group C received 100µg clonidine tablets, Group D received 5 mg diazepam, and group P received multivitamin tablet 90 minutes before anesthesia. Onset of sensory block, duration of sensory block, and duration of postoperative analgesia were observed along with sedation score and dryness score.

Result: Postoperative analgesia was significantly longer in the clonidine group compared to the diazepam and placebo group. The mean onset time of the sensory block and the mean time to attain the maximum sensory level were significantly faster ($P<0.01$) in the clonidine group as compared to the diazepam and placebo group. Duration of analgesia was also significantly longer in the clonidine group compared to the diazepam and placebo group.

Conclusion: We conclude that oral clonidine premedication in patients with hyperbaric bupivacaine hastens the onset of sensory block and prolongs the duration of sensory block and duration of postoperative analgesia.

Keywords: Oral Clonidine, Oral Diazepam, Spinal Anaesthesia

Introduction

Pain is derived from the word “poena” meaning punishment. Pain is an unpleasant sensation that originates from on-going and impending tissue damage. Acute pain accompanies almost all surgical procedures. Adequate pain relief provides a quick return to normal physiological function and prevents the development of chronic pain. Traditional analgesia in the post-operative

period is based on opioids, non-steroidal anti-inflammatory drugs (NSAIDS) and regional techniques.[1]

Administration of high doses of opioids during the post-operative period can result in higher incidence of complications such as respiratory depression, sedation, vomiting, constipation, pruritus, immune dysfunction and urinary retention.[2] NSAIDS may lead to gastrointestinal bleeding, renal toxicity and thromboembolic complications.

Regional analgesia techniques require additional intervention and have the potential risk of complications such as hypotension, bradycardia and toxicity of the administered drug. Hence, the search for an ideal drug continues. A drug, which has anxiolytic property without the adverse effects of traditional analgesics mentioned, may be an attractive choice for post-operative analgesia.[1]

First benzodiazepine was released for oral use in 1960[3]. In the 40 years since the introduction of the first benzodiazepine, the original molecule has undergone major modifications resulting in a completely new group of drugs with potential for use as premedicants. Flunitrazepam was introduced in 1979, chloralhydrate and trichoroethanol were tried in 1980s for sedation in paediatric patients as syrups and found to be effective[4].

Diazepam was synthesized by Sternbarch in 1959. [3] Diazepam is a long acting benzodiazepine. The anxiolytic, amnesic and hypnotic effects of diazepam are the basis for the use of this drug in the pre-operative medication which is preferably accomplished with oral administration.

Clonidine was first introduced in 1966 and used as nasal decongestant[5], its hypotensive action in human was recognized by Wolf in 1966[5]. This stimulated studies to identify the mechanism by which an alpha adrenoreceptor agonist lowered blood pressure. Stark in 1977 found clonidine to be more effective at blocking transmitted release. Within a short time the central site of action of clonidine on alpha receptors in the brainstem was identified by Walland in 1987. [6]

Oral clonidine premedication in the dose of 4-5 mcg/kg body weight has been used with both general and regional anesthesia as it decreases plasma catecholamine concentration and intraoperative liability of blood pressure and heart rate.[7] It blunts reflex tachycardia associated with direct laryngoscopy, dramatically decreases the anesthetic requirements of inhaled and injected drugs, decreases the vasoconstriction and shivering thresholds and it also enhances post-operative analgesia.[8] Clonidine has been used to prolong the effects of spinal anesthesia with local anesthetics like tetracaine, lignocaine and bupivucaine.[9, 10] It has been used as oral or intramuscular premedication or as rectal suppository in children.[11]

Considering all the pharmacological actions of these drugs, we evaluated the efficacy of oral clonidine and oral diazepam as pre-medication on the extent and duration of sensory blockade in patients receiving spinal anesthesia with 0.5% bupivacaine for lower abdominal surgeries in this study in a double blinded randomized manner to find the better drug amongst them.

Material and Methods

Methods

This study was conducted in the Department of Anaesthesiology, Acharya Vinoba Bhave Rural Hospital, affiliated to Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, from August 2015 to August 2017.

After approval from institutional ethical committee, 120 patients of either gender posted for elective lower abdominal surgeries and giving written consent were included in this study.

Inclusion Criteria

1. Age between 20 to 60 years.
2. ASA physical status I & II.

3. Height between 150 to 180 centimetres.
4. Weight between 40 to 70 Kilograms.

Exclusion Criteria

1. ASA physical status III and above.
2. Diabetics & Patients on Beta Blockers.
3. Mentally retarded patients.
4. Pregnant and lactating women.
5. Patients having allergy to local anaesthetic and study drug.
6. Patients with spinal deformity.
7. Any contraindication to spinal anaesthesia such as infection at local site, bleeding disorder or shock.

Type of Study: Prospective, Randomized, Double Blinded Study.

A pre-anaesthetic evaluation of all patients was done one day prior to surgery in which proper history was taken, general examination and systemic examination was done along with relevant laboratory investigations such as CBC, LFT, KFT, RBS, Blood coagulation profile etc. The procedure, its complications and alternative methods were explained to the patients in a language which was well understood by them. Patients were given information sheet regarding the study written in the same language and written informed consent was taken.

On the day of surgery in the pre-operative room, baseline parameters such as Pulse rate (PR), blood pressure(SBP,DBP and MAP), saturation at room air (SpO_2) were noted in addition to sedation score and dryness score.

The patients were randomly allocated into one of the two groups of 40 each according to drug they received. All the drugs were given 90 minutes prior to surgery.

Group- P (PLACEBO) : Multivitamin tab.

Group-C (CLONIDINE): 100 mcg oral Clonidine.

Group-D (DIAZEPAM): 5 mg oral Diazepam.

Randomisation was done by computer generated random number table followed by allocation of these numbers in sealed enveloped technique.

All the tablets were pre-wrapped in silver foil and were given to the patients by anaesthesiologist according to the group they belonged to. Both the patient and the anaesthesiologist, who conducted the case, were blinded to the group identities.

Patients were monitored for any side effects of these drugs such as excessive sedation in the preoperative room and were treated accordingly. Inside the operation theatre intravenous access was achieved with an 18 gauge cannula and patients were preloaded with ringer's lactate 10ml/kg. Routine monitors were attached including pulse-oxymeter (SpO_2), ECG and NIBP (SBP, DBP & MAP) and values were recorded. Lumbar puncture was performed in left lateral position with 25 gauge Quincke needle at L3 -L4 interspace. Spinal anaesthesia was induced with 3.5 ml hyperbaric inj bupivacaine hydrochloride (15mg). All patients had Foley's urinary catheter inserted for monitoring urine output.

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial blood pressure (MAP) , SpO_2 were monitored and recorded after the block for every 5 min till 30 min then every 15 minutes till one hour and at 30 min interval till end of the study period. Sedation score and dryness score were monitored and recorded just before induction (as we have given study drug 90 min before induction) then at interval of 30 min till 1 hour and then at 1 hour interval till end of study.

The sensory block level was assessed using loss of pin prick sensation. Onset of sensory block defined as time from injection of spinal drug to L_1 sensory level achieved and duration of sensory bock defined as time for 2 segment regression from highest sensory block achieved. The motor block was assessed by using Bromage grade

scale. Onset of motor block defined as time from injection of spinal drug to achievement of Bromage grade III. Duration of motor block was defined as time taken for regression from Bromage grade III to grade I.

Bromage Grade[12]:

I. The patient able to move the hip, knee and ankle
II. Patient unable to move hip but able to move knee and ankle
III. Patient unable to move hip and knee but able to move ankle.
IV. Patient unable to move hip, knee and ankle

Hypotension, defined as a decrease in systolic blood pressure >30% of the baseline value or systolic blood pressure < 90 mm Hg was treated with intravenous boluses of 6 mg inj.mephentermine. Bradycardia, defined as a pulse rate of < 50 beat/ min was treated with boluses of 0.6 mg atropine IV.

After surgery patients were shifted to the recovery room. When patients first complained of pain, they were given inj diclofenac 75 mg intramuscularly as a rescue analgesic. Duration of Post-operative analgesia was defined as time from administration of spinal drug till requirement of first rescue analgesic and this was considered as end point of the study.

Sedation score monitored according to Ramsay Sedation scale[13]:

1. Anxious and agitated or restless, or both.
2. Co-operative, oriented and tranquil.
3. Responding to commands only.
4. Brisk response to light glabellar tap.
5. Sluggish response to light glabellar tap.
6. No response to light glabellar tap.

Dryness Score taken as:

Wet : Frank saliva seen on the tongue on opening the mouth.

Moist : Droplets of saliva seen on the tongue on opening the mouth.

Dry : No saliva seen on the tongue on opening the mouth.

Adverse effects of study drugs like nausea, vomiting, respiratory depression and neurological deficit were recorded.

Statistical analysis

Statistical analysis was done by using descriptive and inferential statistics using Chi-square test, one way ANOVA and Multiple Comparison: Tukey Test. Softwares used in the analysis were SPSS 20.0 version, GraphPad Prism 6.0 version. $p<0.05$ was considered as level of significance.

Observation and Results

During the study period 120 patients of either gender posted for elective lower abdominal surgeries and fulfilling the inclusion and exclusion criteria were analysed.

Table 1: Distribution of Patients According To Age

Age (years)	Group P	Group C	Group D
20-30 yrs	6(15%)	7(17.5%)	8(20%)
31-40 yrs	11(27.5%)	9(22.5%)	7(17.5%)
41-50 yrs	5(12.5%)	16(40%)	10(25%)
51-60 yrs	7(17.5%)	3(7.5%)	6(15%)
61-70 yrs	11(27.5%)	5(12.5%)	5(12.5%)
Total	40(100%)	40(100%)	40(100%)
Mean ±SD	47.75±15.33	44.45±12.38	43.65±13.25
Range	20-67	23-65	21-68
p-value	$\chi 2$-value =11.54,p=0.17,NS		

Above table shows distribution of patients according to age in all groups. Mean age of the patients in group P was 47.75 ± 15.33 years, that in group C was 44.45 ± 12.38 years and in group D was 43.65 ± 13.25 years. The difference was not statistically significant ($p>0.05$) among

the groups. The patients were comparable with respect to age.

Graph 1: Distribution of Patients According To Age

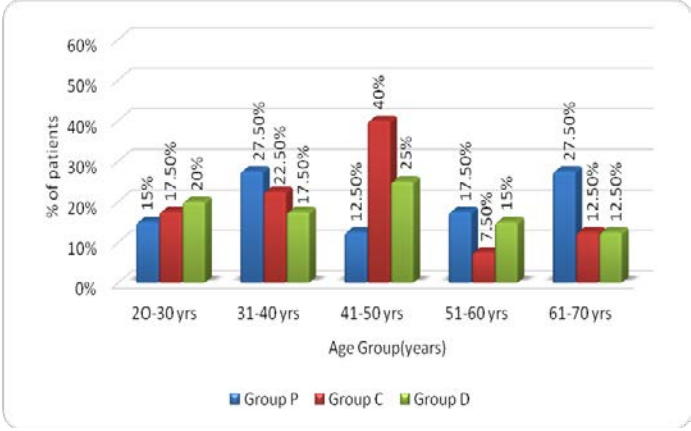


Table 2: Distribution of Patients According To Gender

Gender	Group P	Group C	Group D	p-value
Male	14(35%)	14(35%)	17(42.5%)	$\chi 2$=0.64 p=0.72,NS
Female	26(65%)	26(65%)	23(57.5%)	
TOTAL	40(100%)	40(100%)	40(100%)	

Above table shows distribution of patients according to gender. The groups were comparable regarding gender distribution among the cases as 'p' value was non-significant (p>0.05).

Graph 2: Distribution of Patients According To Gender

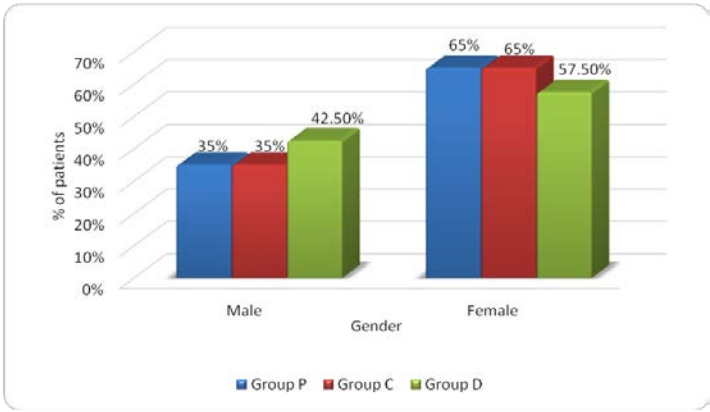


Table 3: Distribution of Patients According To ASA Grading

ASA Grading	Group P	Group C	Group D	p-value
Grade I	26(65%)	30(75%)	25(62.5%)	$\chi 2$=1.59 p=0.45,NS
Grade II	14(35%)	10(25%)	15(37.5%)	
Total	40(100%)	40(100%)	40(100%)	

Above table provides the distribution of patients according to ASA criteria in each group. In group P, there were 26(65%) patients in ASA I status, followed by 14(35%) patients in ASA II criterion. In group C, there were 30(75%) patients in ASA I criterion, followed by 10(25%) patients in ASA II status. In group D, there were 25(62.5%) patients in ASA criterion I, and 15(37.5%) patients in ASA criterion II. There is no significant difference in the comparison between the study groups (p>0.05).

Graph 3: Distribution of Patients According To ASA Grading

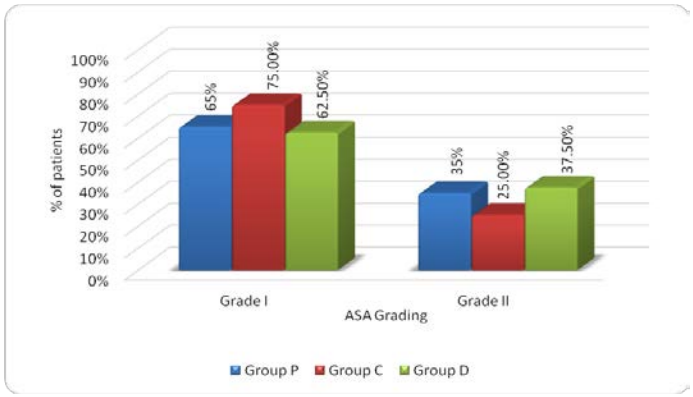


Table 4: Distribution of Patients According To Weight

Weight (kgs)	Group P	Group C	Group D
40-50 kg	23(57.5%)	25(62.5%)	22(55%)
51-60 kg	5(12.5%)	8(20%)	10(25%)
61-70 kg	12(30%)	7(17.5%)	8(20%)
Total	40(100%)	40(100%)	40(100%)
Average	58	52	54
SD	6.7	7	7.1
p-value	$\chi 2$=3.40,p=0.49,NS		

Above table shows distribution of patients according to weight. Maximum patients in all groups were in the range of 40-50 kilograms. Mean weight of the patients in group P was 58 ± 6.7 kilograms, in group C was 52 ± 7 kilograms and in group D was 54 ± 7.10 kilograms. The patients were comparable with respect to weight as the difference was not statistically significant (p>0.05).

Graph 4: Distribution of Patients According To Weigh

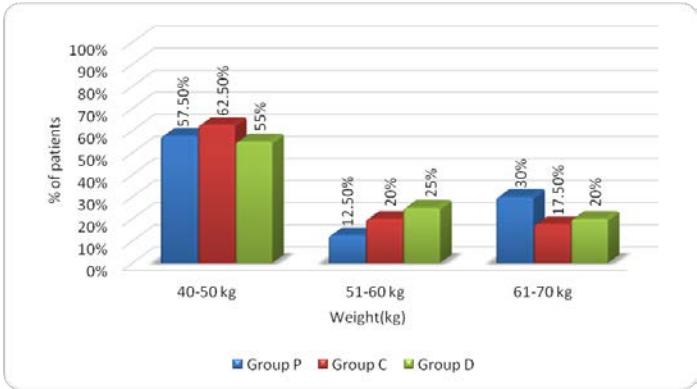


Table 5: Distribution of Patients According To Height

Height (cms)	Group P	Group C	Group D
150-160	12(30%)	17(42.5%)	13(32.5%)
161-170	18(45%)	16(40%)	19(47.5%)
171-180	10(25%)	7(17.5%)	8(20%)
Total	40(100%)	40(100%)	40(100%)
Average	168.65	162.92	166.15
Mean ±SD	4.1	7.1	7.2
p-value	χ2=1.82,p=0.16,NS		

Above table shows distribution of patients according to height in each group. Mean height of the patients in group P was 168.65 ± 4.1 cms, in group C was 162.92 ± 7.1 cms and in group D was 166.15 ± 7.2 cms. The difference was not statistically significant (p>0.05). The patients were comparable with respect to height.

Graph 5: Distribution of Patients According To Height

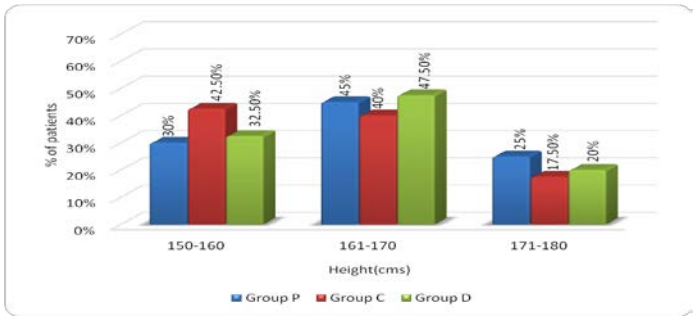


Table 6: Distribution of Patients According To Duration of Surgery

Duration(min)	Group P	Group C	Group D
50-61	5(12.5%)	7(17.5%)	8(20%)
61-70	16(40%)	8(20%)	10(25%)
71-80	19(47.5%)	25(62.5%)	22(55%)
Total	40(100%)	40(100%)	40(100%)
Average	74.12	72.16	70.23
SD	2.4	2.46	2.4
p-value	χ2=3.40,p=0.49,NS		

Above table shows distribution of patients according to duration of surgery. Maximum patients in all groups were in the range of 60-80 minutes. Mean duration of surgery in group P was 74.12 ± 2.4 minutes, in group C was 72.16 ± 2.4 minutes and in group D was 70.23 ± 2.4 minutes. The patients were comparable with respect to duration of surgery as the difference was not statistically significant (p>0.05).

Graph 6: Distribution of Patients according To Duration of surgery

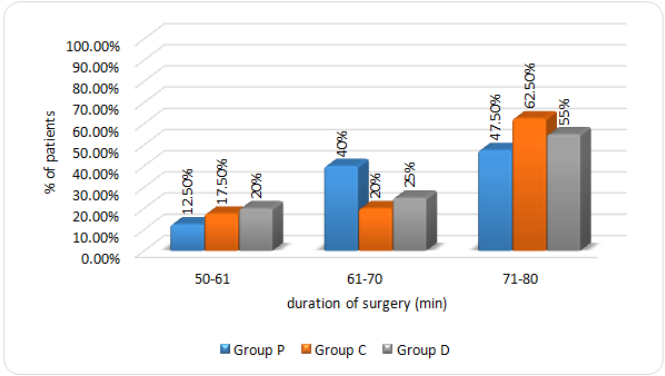


Table 7: Distribution of Patients According To Onset of Sensory Block

Duration (Mins)	Group P	Group C	Group D
1-2	4(10%)	7(17.5%)	2(5%)
3-4	6(15%)	2(5%)	6(15%)
5-6	19(47.5%)	13(32.5%)	15(37.5%)
7-8	6(15%)	13(32.5%)	12(30%)
9-10	1(2.5%)	5(12.5%)	4(10%)
11-12	0(0%	0	1(2.5%)
Total	40(100%)	40(100%)	40(100%)
Average	5.80	6.07	6.32
SD	2.23	2.32	2.05
p-value	$\chi 2$=13.56,p=0.19,NS		

Multiple Comparison: Tukey Test

Group		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Group P	Group C	-0.27	0.49	0.843,NS	-1.44	0.89
	Group D	-0.52	0.49	0.538,NS	-1.69	0.64
Group C	Group D	-0.25	0.43	0.868,NS	-1.42	0.92

Above table shows the distribution of patients according onset of sensory block. In group P, the mean duration of onset of sensory block was 5.80 $\pm$ 2.23 min. In group C it was 6.07 $\pm$ 2.32 min, in group D the mean time was 6.32 $\pm$ 2.05 min. The difference in the mean times was statistically not significant across groups as indicated by p-value > 0.05 using multiple tukey test.

Graph 7: Distribution of Patients According To Onset of Sensory Block.

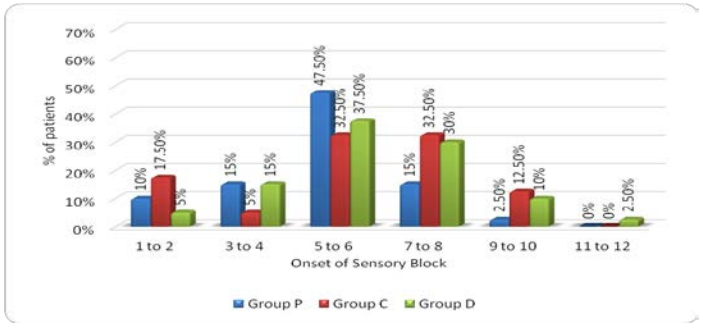


Table 8: Distribution of Patients According To Highest Level of Sensory Block Achieved

Highest level of sensory block	Group P	Group C	Group D	p-value
T4	0(0%)	3(7.5%)	1(2.5%)	
T5	2(5%)	0(0%)	5(12.5%)	
T6	28(70%)	31(77.5%)	24(60%)	$\chi 2$=14.90
T7	3(7.5%)	0(0%)	5(12.5%)	p=0.061,NS
T8	7(17.5%)	6(15%)	9(22.5%)	
Total	40(100%)	40(100%)	40(100%)	

Above table shows the number of cases with dermatome sensory level achieved in three groups. All patients achieved T_4-T_7 sensory dermatome level in our study. Most of the patients in our study achieved sensory level T_6. In group P 28(70%), in group C 31(77.5%) and in group D 24(60%) achieved T_6. Highest level T_4 was seen in 3(7.5%) in group C, 1(2.5%) in group D, 0(0%) in group P according to above data there is no significance difference in highest level of sensory block achieved in three groups (p> 0.05).

Graph 8: Distribution of Patients According To Highest Level of Sensory Block Achieved

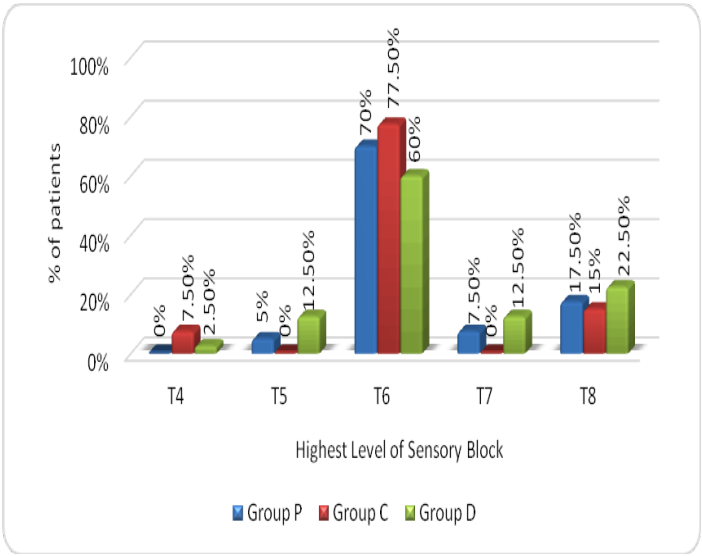


Table 9: Distribution of Patients According To Time Taken to Reach Highest Level of Sensory Block

Duration (Mins)	Group P	Group C	Group D
11-15	10(25%)	16(40%)	9(22.5%)
16-20	20(50%)	21(52.5%)	21(52.5%)
21-25	7(17.5%)	1(2.5%)	6(15%)
26-30	3(7.5%)	2(5%)	4(10%)
Total	40(100%)	40(100%)	40(100%)
Average	17.62	16.12	17.77
SD	3.92	1.91	3.51
p-value	$\chi 2$=7.58,p=0.278,NS		

Multiple Comparisons: Tukey Test

Group		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Group P	Group C	1.50	0.73	0.105,NS	-0.23	3.23
	Group D	-0.15	0.73	0.977,NS	-1.88	1.58
Group C	Group D	-1.65	0.73	0.066,NS	-3.38	0.08

Above table shows distribution of patients according to time taken to reach highest level. The mean time taken to reach highest level for group P was 17.62 $\pm$ 3.92, for group C it was 16.12 $\pm$ 1.91 and that for group D was 17.77 $\pm$ 3.51. The difference in the mean times was statistically not significant across groups as indicated by p-value > 0.05 using multiple tukey test.

Graph 9: Distribution of Patients According To Time Taken to Reach Highest Level of Sensory Block

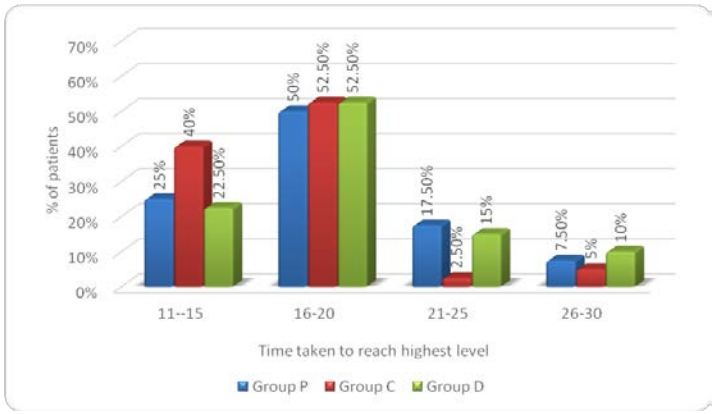


Table 10: Distribution of Patients According To Duration of Sensory Block

Duration (Mins)	Group P	Group C	Group D
40-60	0(0%)	0(0%)	10(25%)
61-80	34(85%)	4(10%)	16(40%)
81-100	6(15%)	12(30%)	11(27.5%)
101-120	0(0%)	7(17.5%)	3(7.5%)
121-140	0(0%)	16(40%)	0(0%)
141-160	0(0%)	1(2.5%)	0(0%)
Total	40(100%)	40(100%)	40(100%)
Average	73.07	110.92	81.50
SD	6.52	21.41	15.63
p-value	$\chi 2$=88.87,p=0.0001,S		

Multiple Comparisons: Tukey Test

Group		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Group P	Group C	-37.85	3.52	0.0001,S	-46.21	-29.48
	Group D	-8.42	3.52	0.048,S	-16.79	-0.05
Group C	Group D	29.42	3.52	0.0001,S	21.05	37.79

Above table shows distribution of patients according to duration of sensory block. In group P, the mean duration of sensory block was 73.07 $\pm$ 6.52 min. In group C it was

110.92 ± 21.41 min, in group D the mean time was 81.50 ± 15.63 min. The differences in the mean times is significant across groups as indicated by p-value < 0.05 using multiple tukey test.

In group C mean duration of sensory block was maximum followed by group D and group P. This clearly states that oral Clonidine and oral Diazepam are superior to placebo in this regard. While comparing between the study groups, oral clonidine is better than oral Diazepam.

Graph 10: Distribution of Patients According To Duration of Sensory Block

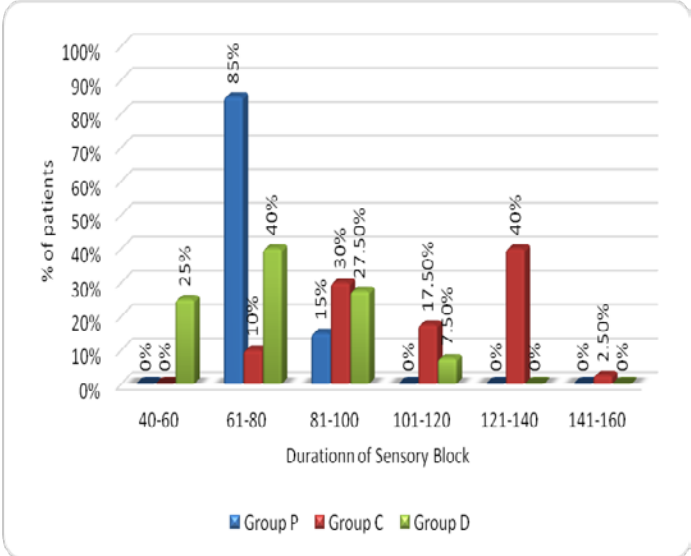


Table 11: Distribution of Patients According To Duration of Post-Operative Analgesia

Duration (Mins)	Group P	Group C	Group D
60-90	9(22.5%)	0	4(10%)
91-120	31(77.5%	14(35%)	33(82.5%)
121-150	0	17(42.5%)	3(7.5%)
151-180	0	9(22.5%)	0
181-210	0	0	0
Total	40(100%)	40(100%)	40(100%)
average	95.07	136.82	108.13
SD	5.13	18.13	11.50
p-value	$\chi 2=62.01, p=0.0001, S$		

Multiple Comparisons: Tukey Test

Group		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Group P	Group C	-41.75	2.85	0.001,S	-48.51	-34.98
	Group D	-10.32	2.85	0.001,S	-17.09	-3.55
Group C	Group D	31.42	2.85	0.0001,S	24.65	38.19

Above table shows distribution of patients according to duration of Post-operative analgesia. In group P, the mean duration of sensory block was 95.07 ± 5.13 min. In group C it was 136.82 ± 18.13 min, in group D the mean time was 108.13 ± 11.50 min. The difference in the mean times is significant across groups as indicated by p-value < 0.05. In group C mean duration of post-operative analgesia was more followed by group D and group P. Hence oral Clonidine and oral Diazepam have more postoperative analgesic effect than placebo. While comparing between the study groups, oral clonidine is better than oral Diazepam.

Graph 11: Distribution of Patients According To Duration of Post-Operative Analgesia

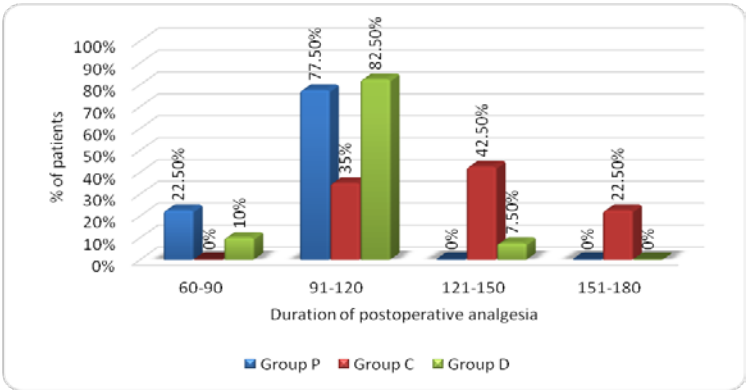


Table 12: Distribution of Patients According To Mean Pulse Rate at Various Intervals in Different Groups

	Group P		Group C		Group D		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD		
Pre OP	87.9	9.04	83.9	7.08	88.05	10.53	2.734	0.069,NS
0 min	88.67	9.93	73.77	10.84	90.22	13.68	24.523	0.0001,S
5 min	87.25	11.69	75.5	9.61	89.75	14.458	15.855	0.0001,S
10 min	87.3	10.33	73.05	9.63	88	14.28	21.162	0.0001,S
15 min	86	10.89	71.47	10.60	85.87	14.88	18.488	0.0001,S
20 min	85.8	11.05	70.52	11.43	85.4	15.31	18.649	0.0001,S
25 min	84.75	11.21	70.52	10.78	84.3	14.66	17.166	0.0001,S
30 min	84.12	12.16	70.37	10.87	83.45	14.341	15.280	0.0001,S
45 min	83	11.70	69.97	11.62	82.57	13.448	14.512	0.0001,S
60 min	82.1	11.44	69	11.66	80.85	11.79	15.445	0.0001,S
90 min	81.9	10.59	69.1	11.66	81.62	12.13	16.214	0.0001,S
120 min	81.72	10.26	69.32	11.62	81.5	11.79	15.907	0.0001,S
150 min	81.12	10.04	68.75	11.55	81.37	12.07	16.444	0.0001,S
180 min	82.15	9.87	68.4	10.04	82.8	11.84	23.441	0.0001,S

Multiple Comparisons: Tukey Test

			Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Pre- Op	Group P	Group C	4.00	2.01	0.120,NS	-0.77	8.77
		Group D	-0.15	2.01	0.997,NS	-4.92	4.62
	Group C	Group D	-4.15	2.01	0.102,NS	-8.92	0.62
0 min	Group P	Group C	14.90	2.59	0.0001,S	8.74	21.05
		Group D	-1.55	2.59	0.822,NS	-7.70	4.60
	Group C	Group D	-16.45	2.59	0.0001,S	-22.60	-10.29
5 min	Group P	Group C	11.75	2.70	0.0001,S	5.33	18.16
		Group D	-2.50	2.70	0.626,NS	-8.91	3.91
	Group C	Group D	-14.25	2.70	0.0001,S	-20.66	-7.83
10 min	Group P	Group C	14.25	2.59	0.0001,S	8.09	20.40
		Group D	-0.70	2.59	0.961,NS	-6.85	5.45
	Group C	Group D	-14.95	2.59	0.0001,S	-21.10	-8.79
15 min	Group P	Group C	14.52	2.74	0.0001,S	8.00	21.04
		Group D	0.12	2.74	0.999,NS	-6.39	6.64
	Group C	Group D	-14.40	2.74	0.0001,S	-20.91	-7.88
20 min	Group P	Group C	15.27	2.85	0.0001,S	8.50	22.00

		Group D	0.40	2.85	0.989,NS	-6.36	7.16
	Group C	Group D	-14.87	2.85	0.0001,S	-21.64	-8.10
25 min	Group P	Group C	14.22	2.76	0.0001,S	7.67	20.77
		Group D	0.45	2.76	0.985,NS	-6.10	7.00
	Group C	Group D	-13.77	2.76	0.0001,S	-20.32	-7.22
30 min	Group P	Group C	13.75	2.80	0.0001,S	7.09	20.40
		Group D	0.67	2.80	0.969,NS	-5.98	7.33
	Group C	Group D	-13.07	2.80	0.0001,S	-19.73	-6.41
45 min	Group P	Group C	13.02	2.74	0.0001,S	6.50	19.54
		Group D	0.42	2.74	0.987,NS	-6.09	6.94
	Group C	Group D	-12.60	2.74	0.0001,S	-19.12	-6.07
60 min	Group P	Group C	13.10	2.60	0.0001,S	6.92	19.27
		Group D	1.25	2.60	0.881,NS	-4.92	7.42
	Group C	Group D	-11.85	2.60	0.0001,S	-18.02	-5.67
90 min	Group P	Group C	12.80	2.56	0.0001,S	6.70	18.89
		Group D	0.27	2.56	0.994,NS	-5.82	6.37
	Group C	Group D	-12.52	2.56	0.0001,S	-18.62	-6.42
120 min	Group P	Group C	12.40	2.51	0.0001,S	6.42	18.37
		Group D	0.22	2.51	0.996,NS	-5.74	6.19
	Group C	Group D	-12.17	2.51	0.0001,S	-18.14	-6.20
150 min	Group P	Group C	12.37	2.51	0.0001,S	6.39	18.35
		Group D	-0.25	2.51	0.995,NS	-6.22	5.72
	Group C	Group D	-12.62	2.51	0.0001,S	-18.60	-6.64
180 min	Group P	Group C	13.75	2.37	0.0001,S	8.11	19.38
		Group D	-0.65	2.37	0.960,NS	-6.28	4.98
	Group C	Group D	-14.40	2.37	0.0001,S	-20.03	-8.76

Above table shows the distribution of patients according to Mean pulse rate at various intervals in different groups. Preoperative mean Pulse Rate in group P was 87.9 ± 9.04 that in group C was 83.9 ± 7.08, and in group D was 88.05 ± 10.53. The 'p' value was 0.069 and the difference was non-significant.

After induction and throughout the study period, there was a statistically significant difference in mean pulse rate across the group as shown by multiple tukey test. ($p<0.05$) When Multiple Comparisons: Tukey Test was applied we found that after induction there was a significant difference in mean pulse rate when group C was compared with group D and group P at different point of times ($p<0.05$). Throughout the study period, patients in clonidine group had low pulse rate compared to patients in diazepam and placebo group.

Graph 12: **Distribution of Patients According To Mean Pulse Rate at Various Intervals in Different Groups**

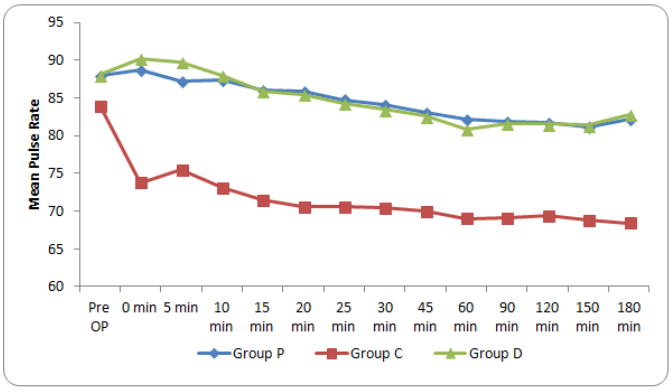


Table 13: Distribution of Patients According To Mean Respiratory Rate at Various Intervals in Different Groups

	Group P		Group C		Group D		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD		
Pre OP	14.1	1.86	14.15	1.83	14.1	1.86	0.010	0.990,NS
0 min	13.7	2.42	13.95	1.78	13.8	1.96	0.147	0.863,NS
5 min	13.65	1.49	13.85	1.45	13.4	1.64	0.863	0.425,NS
10 min	13.55	1.31	13.3	1.53	13.15	1.42	0.798	0.453,NS
15 min	13.45	1.35	13.2	1.68	12.95	1.43	1.116	0.331,NS
20 min	12.95	1.28	12.65	1.65	12.35	1.49	1.632	0.200,NS
25 min	13.3	1.32	12.8	1.41	12.5	1.55	2.174	0.055,NS
30 min	13.25	1.25	12.9	1.35	12.45	1.53	2.345	0.059,NS
45 min	13.2	1.48	12.75	1.54	12.35	1.42	2.268	0.052,NS
60 min	12.9	1.35	12.55	1.01	12.3	1.06	2.727	0.070,NS
90 min	12.85	1.27	12.45	1.31	12.45	1.15	1.365	0.259,NS
120 min	12.85	1.27	12.4	1.44	12.3	1.32	1.885	0.156,NS
150 min	12.95	1.43	12.5	1.41	12.45	1.39	1.518	0.223,NS
180 min	12.65	1.05	12.3	1.15	12.15	0.94	2.359	0.099,NS

Multiple Comparisons: Tukey Test

			Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Pre- Op	Group P	Group C	-0.05	0.41	0.992,NS	-1.03	0.93
		Group D	0.00	0.41	1.000,NS	-0.98	0.98
	Group C	Group D	0.05	0.41	0.992,NS	-0.93	1.03
0 min	Group P	Group C	-0.25	0.46	0.852,NS	-1.35	0.85
		Group D	-0.10	0.46	0.975,NS	-1.20	1.00
	Group C	Group D	0.15	0.46	0.944,NS	-0.95	1.25
5 min	Group P	Group C	-0.20	0.34	0.830,NS	-1.01	0.61
		Group D	0.25	0.34	0.747,NS	-0.56	1.06
	Group C	Group D	0.45	0.34	0.392,NS	-0.36	1.26
10 min	Group P	Group C	0.25	0.31	0.715,NS	-0.50	1.00
		Group D	0.40	0.31	0.426,NS	-0.35	1.15
	Group C	Group D	0.15	0.31	0.886,NS	-0.60	0.90
15 min	Group P	Group C	0.25	0.33	0.736,NS	-0.54	1.04

		Group D	0.50	0.33	0.298,NS	-0.29	1.29
	Group C	Group D	0.25	0.33	0.736,NS	-0.54	1.04
20 min	Group P	Group C	0.30	0.33	0.639,NS	-0.48	1.08
		Group D	0.60	0.33	0.172,NS	-0.18	1.38
	Group C	Group D	0.30	0.33	0.639,NS	-0.48	1.08
25 min	Group P	Group C	0.50	0.32	0.268,NS	-0.26	1.26
		Group D	0.80	0.32	0.057,NS	0.03	1.56
	Group C	Group D	0.30	0.32	0.619,NS	-0.46	1.06
30 min	Group P	Group C	0.35	0.31	0.498,NS	-0.38	1.08
		Group D	0.80	0.31	0.030,NS	0.06	1.53
	Group C	Group D	0.45	0.31	0.318,NS	-0.28	1.18
45 min	Group P	Group C	0.45	0.33	0.369,NS	-0.33	1.23
		Group D	0.85	0.33	0.052,NS	0.06	1.63
	Group C	Group D	0.40	0.33	0.454,NS	-0.38	1.18
60 min	Group P	Group C	0.35	0.25	0.367,NS	-0.26	0.96
		Group D	0.60	0.25	0.056,NS	-0.01	1.21
	Group C	Group D	0.25	0.25	0.598,NS	-0.36	0.86
90 min	Group P	Group C	0.40	0.27	0.329,NS	-0.26	1.06
		Group D	0.40	0.27	0.329,NS	-0.26	1.06
	Group C	Group D	0.00	0.27	1.000,NS	-0.66	0.66
120 min	Group P	Group C	0.45	0.30	0.299,NS	-0.26	1.16
		Group D	0.550	0.30	0.167,NS	-0.16	1.26
	Group C	Group D	0.10	0.30	0.941,NS	-0.61	0.81
150 min	Group P	Group C	0.45	0.31	0.332,NS	-0.30	1.20
		Group D	0.50	0.31	0.258,NS	-0.25	1.25
	Group C	Group D	0.05	0.31	0.986,NS	-0.70	0.80
180 min	Group P	Group C	0.35	0.23	0.303,NS	-0.21	0.91
		Group D	0.50	0.23	0.091,NS	-0.06	1.06
	Group C	Group D	0.15	0.23	0.801,NS	-0.41	0.71

Above table shows the distribution of patients according to mean respiratory rate at various intervals in different groups. Preoperative mean RR in group P was 14.1 $\pm$ 1.86 that in group C was 14.15 $\pm$ 1.83, and in group D was 14.1 $\pm$ 1.86. The 'p' value was 0.010 and the difference was non-significant. Intraoperatively and throughout the study period, no statistically significant difference was noticed across the three groups. (p>0.05) This indicates that no patient in our study had respiratory depression.

Graph 13: Distribution of Patients According Mean Respiratory Rate at Various Interval in Different Groups

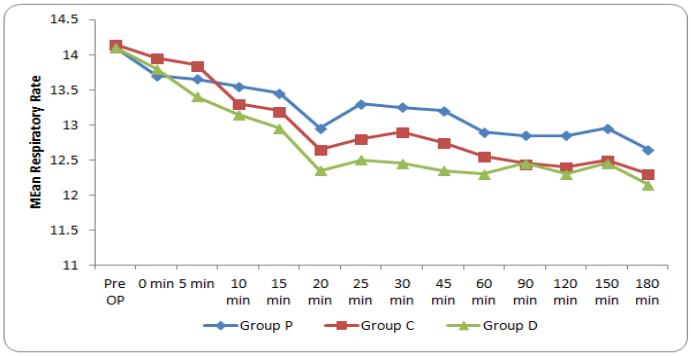


Table14: Distribution of Patients According To Mean of Mean Arterial Pressure at Various Intervals in Different Groups.

	Group P		Group C		Group D		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD		
Pre OP	97.38	3.66	96.73	15.67	98.92	6.74	0.424	0.656,NS
0 min	97.44	2.93	89.04	8.28	95.22	6.97	18.023	0.0001,S
5 min	94.79	2.92	85.43	13.74	92.41	6.54	10.658	0.0001,S
10 min	94.50	2.72	86.53	7.32	89.22	5.48	21.623	0.0001,S
15 min	94.11	2.83	86.94	7.48	88.39	5.72	17.765	0.0001,S
20 min	94.01	4.04	85.18	7.54	88.19	5.86	15.975	0.0001,S
25 min	93.52	3.57	83.95	7.52	88.11	5.43	27.946	0.0001,S
30 min	93.25	3.68	83.23	6.71	86.34	12.90	34.080	0.0001,S
45 min	92.93	3.89	81.01	12.57	87.82	5.85	32.512	0.0001,S
60 min	92.61	3.44	82.19	6.68	84.15	18.91	11.903	0.0001,S
90 min	92.70	3.41	82.28	5.90	86.74	13.70	37.535	0.0001,S
120min	92.52	3.28	78.66	14.30	89.79	6.184	34.340	0.0001,S
150 min	92.51	3.22	81.54	6.20	90.79	5.55	52.284	0.0001,S
180 min	92.38	3.12	81.6	5.98	89.80	5.61	49.306	0.0001,S

Multiple Comparisons: Tukey Test

			Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Pre- Op	Group P	Group C	0.91	2.41	0.924,NS	-4.82	6.66
		Group D	-1.29	2.41	0.853,NS	-7.04	4.44
	Group C	Group D	-2.21	2.41	0.631,NS	-7.95	3.52
0 min	Group P	Group C	8.38	1.44	0.0001,S	4.95	11.82
		Group D	2.21	1.44	0.282,NS	-1.22	5.65
	Group C	Group D	-6.17	1.44	0.0001,S	-9.61	-2.73
5 min	Group P	Group C	9.63	2.17	0.0001,S	4.47	14.79
		Group D	2.37	2.17	0.521,NS	-2.78	7.53
	Group C	Group D	-7.25	2.17	0.003,S	-12.41	-2.09
10 min	Group P	Group C	7.96	1.23	0.0001,S	5.03	10.88

		Group D	5.27	1.23	0.0001,S	2.34	8.19
	Group C	Group D	-2.69	1.23	0.078,NS	-5.61	0.23
15 min	Group P	Group C	7.15	1.26	0.0001,S	4.14	10.17
		Group D	5.70	1.26	0.0001,S	2.69	8.72
	Group C	Group D	-1.45	1.26	0.490,NS	-4.46	1.56
20 min	Group P	Group C	7.05	1.33	0.0001,S	3.89	10.22
		Group D	5.81	1.33	0.0001,S	2.65	8.98
	Group C	Group D	-1.24	1.33	0.621,NS	-4.40	1.92
25 min	Group P	Group C	9.57	1.28	0.0001,S	6.52	12.62
		Group D	5.40	1.28	0.0001,S	2.35	8.45
	Group C	Group D	-4.16	1.28	0.004,S	-7.21	-1.11
30 min	Group P	Group C	10.01	1.21	0.0001,S	7.13	12.89
		Group D	5.04	1.22	0.0001,S	2.14	7.94
	Group C	Group D	-4.97	1.22	0.0001,S	-7.86	-2.07
45 min	Group P	Group C	10.22	1.26	0.0001,S	7.21	13.23
		Group D	5.11	1.26	0.0001,S	2.10	8.12
	Group C	Group D	-5.11	1.26	0.0001,S	-8.12	-2.10
60 min	Group P	Group C	10.41	2.15	0.0001,S	5.28	15.53
		Group D	6.61	2.17	0.008,S	1.45	11.77
	Group C	Group D	-3.80	2.17	0.192,NS	-8.96	1.35
90 min	Group P	Group C	10.41	1.21	0.0001,S	7.53	13.29
		Group D	4.03	1.21	0.004,S	1.14	6.93
	Group C	Group D	-6.37	1.21	0.0001,S	-9.26	-3.47
120 min	Group P	Group C	12.21	1.54	0.0001,S	8.54	15.89
		Group D	2.72	1.54	0.187,NS	-0.94	6.40
	Group C	Group D	-9.49	1.54	0.0001,S	-13.16	-5.81
150 min	Group P	Group C	10.95	1.15	0.0001,S	8.22	13.69
		Group D	1.70	1.15	0.303,NS	-1.02	4.44
	Group C	Group D	-9.24	1.15	0.0001,S	-11.98	-6.51
180 min	Group P	Group C	10.77	1.13	0.0001,S	8.08	13.46
		Group D	2.56	1.13	0.065,NS	-0.12	5.25
	Group C	Group D	-8.20	1.13	0.0001,S	-10.89	-5.51

Above table shows the distribution of patients according to mean of Mean arterial pressure at various intervals in different groups. Preoperative mean of MAP in group P was 97.38 $\pm$ 3.66 that in group C was 96.73 $\pm$ 15.67 and in group D was 98.92 $\pm$ 6.74. The 'p' value was 0.646 and the difference was non-significant.

After induction and throughout the study period, there was a statistically significant difference in mean of MAP across the group as shown by one way ANOVA ($p<0.05$). When Multiple Comparisons: Tukey Test was applied we found that after induction there was a significant difference in mean of MAP when group C was compared with group D and group P at different point of times.($p<0.05$) Throughout the study period, patients in

clonidine group had low MAP compared to patients in diazepam and placebo group.

Graph 14: Distribution of Patients According To Mean of Mean Arterial Pressure at Various Intervals in Different Groups.

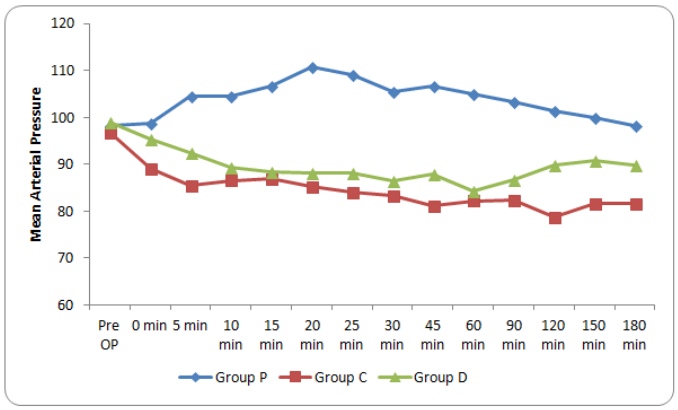


Table15: Comparison of Mean Sedation Score in Three Groups at Various Intervals in Different Groups.

	Group P		Group C		Group D		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD		
Pre OP	1.00	0.00	1.03	0.16	1.70	0.91	22.15	0.0001,S
0 min	1.00	0.00	1.13	0.33	2.05	0.88	44.91	0.0001,S
30 min	1.00	0.00	2.53	0.72	3.43	0.75	168.44	0.0001,S
60 min	1.00	0.00	2.90	0.81	3.68	0.57	231.02	0.0001,S
120 min	1.00	0.00	3.05	0.71	3.65	0.53	294.49	0.0001,S
180 min	1.00	0.00	3.10	0.67	3.98	0.66	316.42	0.0001,S

Multiple Comparisons: Tukey Test

			Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Pre- Op	Group P	Group C	-0.02	0.11	0.976,NS	-0.30	0.25
		Group D	-0.70	0.11	0.0001,S	-0.98	-0.41
	Group C	Group D	-0.67	0.11	0.0001,S	-0.95	-0.39
0 min	Group P	Group C	-0.12	0.12	0.558,NS	-0.41	0.16
		Group D	-1.05	0.12	0.0001,S	-1.33	-0.76
	Group C	Group D	-0.92	0.12	0.0001,S	-1.21	-0.63
30 min	Group P	Group C	-1.52	0.13	0.0001,S	-1.84	-1.20
		Group D	-2.42	0.13	0.0001,S	-2.74	-2.10
	Group C	Group D	-0.90	0.13	0.0001,S	-1.21	-0.58
60 min	Group P	Group C	-1.90	0.12	0.0001,S	-2.20	-1.59
		Group D	-2.67	0.12	0.0001,S	-2.97	-2.37
	Group C	Group D	-0.77	0.12	0.0001,S	-1.07	-0.47
120 min	Group P	Group C	-2.05	0.11	0.0001,S	-2.32	-1.77
		Group D	-2.65	0.11	0.0001,S	-2.92	-2.37
	Group C	Group D	-0.60	0.11	0.0001,S	-0.87	-0.32
180 min	Group P	Group C	-2.10	0.12	0.0001,S	-2.38	-1.81
		Group D	-2.97	0.12	0.0001,S	-3.26	-2.68
	Group C	Group D	-0.87	0.12	0.0001,S	-1.16	-0.58

Above table shows comparison of mean sedation score at various intervals in three groups. The difference in mean sedation score preoperatively was significant across the groups due to the study drugs clonidine and diazepam, which were given to patients 90 minutes before induction. This significance in mean sedation score across the three groups continued throughout the study period as indicated by one way ANOVA. ($p<0.05$)

When Multiple Comparisons: Tukey Test was applied for comparison in individual groups, we found that throughout the study period, patients in diazepam group were more sedated compared to patients in clonidine and placebo group, as indicated by p value <0.05.

Graph 15: Comparison of Sedation Score in Three Groups at Various Intervals in Different Groups.

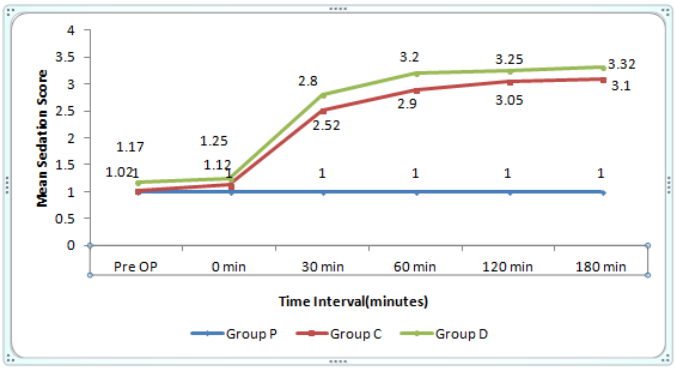


Table16: Comparison of Dryness Score in Three Groups at Various Intervals in Different Groups

Dryness Score at-	Group	Wet		Moist		Dry		Significance	
		No.	%	No.	%	No.	%	χ2-value	p-value
Pre-Op	Placebo	0	0	39	97.5%	1	2.5%	4.65	0.32,NS
	Clonidine	2	5%	36	90%	2	5%		
	Diazepam	0	0	39	97.5%	1	2.5%		
0 min	Placebo	0	0	34	15%	6	15%	9.01	0.06,NS
	Clonidine	2	5%	36	90%	2	5%		
	Diazepam	0	0	39	97.5%	1	2.5%		
30 min	Placebo	0	0	14	35%	26	65%	4.95	0.29,NS
	Clonidine	1	2.5%	21	52.5%	18	45%		
	Diazepam	0	0	19	47.5%	21	52.5%		
60 min	Placebo	0	0	6	15%	34	85%	0.93	0.62,NS
	Clonidine	0	0	9	22.5%	31	77.5%		
	Diazepam	0	0	9	22.5%	31	77.5%		
120 min	Placebo	0	0	11	27.5%	29	72.5%	3.45	0.17,NS
	Clonidine	0	0	6	15%	34	85%		
	Diazepam	0	0	5	12.5%	35	87.5%		
180 min	Placebo	0	0	8	20%	32	80%	7.22	0.057,NS
	Clonidine	0	0	3	7.5%	37	92.5%		
	Diazepam	0	0	1	2.5%	39	97.5%		

Above table shows the distribution of patients according to the mean dryness score at various intervals in different groups. According to the above table it is evident that there was no statistically significant difference across the groups when mean dryness scores were compared. (p>0.05)

Graph16: Comparison of Dryness Score in Three Groups at Various Intervals in Different Groups.

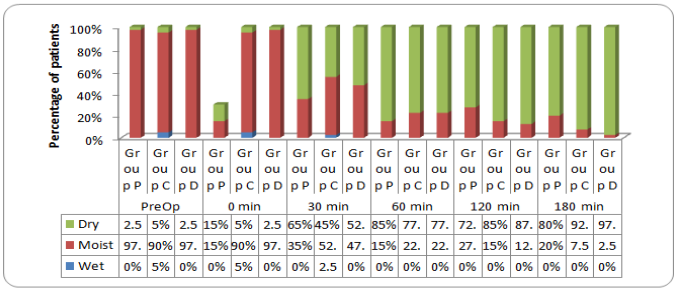


Table 17: Comparison of Incidence of Hypotension in Three Groups

Hypotension	Group P	Group C	Group D	p-value
No of patients	0	4	0	χ2=8.27
Percentage (%)	100	10	100	p=0.016 ,S

From the above table it is evident that no patient in group P as well as group D had any episode of hypotension throughout the study period, while 4 (10%) patients in clonidine group had hypotension which was immediately after induction of spinal anesthesia. Statistical analysis revealed that this hypotension in clonidine group was statistically significant compared to the other groups. (p<0.05)

Graph17: Comparison of Incidence of Hypotension in Three Groups.

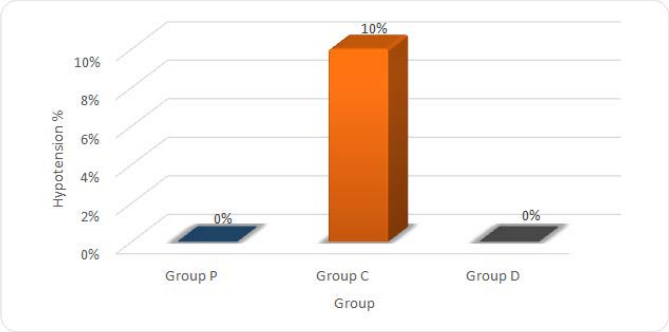
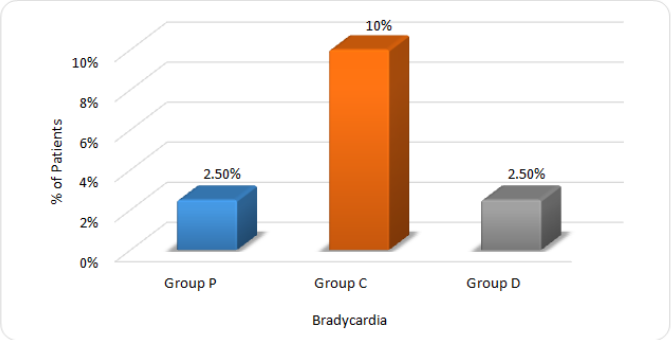


Table 18: Comparison of Incidence of Bradycardia in Three Groups.

Bradycardia	Group P(n=40)	Group C(n=40)	Group D(n=40)	p-value
No of patients	1	4	1	χ2=3.15
Percentage	2.5	10	2.5	p=0.25,NS

Above table shows the distribution of patients according to incidence of bradycardia in different groups. The incidence of bradycardia was more in patients receiving clonidine (4 patients) while 1 patient each in placebo group as well as diazepam group had bradycardia. The statistical analysis done across the group was found to be insignificant. (p>0.05)

Graph 18: Comparison of Incidence of Bradycardia in Three Groups



Discussion

Regional anesthesia has been known to be the best technique for lower limb and lower abdominal surgeries especially in patients with impaired ventilatory performances. It causes minimal intervention of airways, reduces the stress response during surgery and at the same time provides post-operative pain relief. Spinal anesthesia is the most common form of regional anaesthetic procedure being practiced today due to its safety, reliability, rapid onset of neural blockade and the ease with which it is performed.[14]

The main limitations of spinal anaesthesia are its short duration of action and that it does not provide prolonged postoperative analgesia when it is performed only with local anaesthetics.[15]

Pain is generally considered an important postsurgical complication, which may result in serious morbidities if left unaddressed.[16] Furthermore, pain-induced reflex responses may adversely influence respiratory function, increase cardiac demands, decrease intestinal motility and initiate skeletal muscle spasm. Therefore, there is a common belief that alleviation of acute pain may also reduce the surgical stress response and improve outcome.[17]Acute postoperative pain management is challenging and also a major concern.[18]

Various agents (opioid and non-opioid), routes (oral, intravenous, neuraxial, regional) and modes (patient controlled and "as needed") for the treatment of postoperative pain exist.[19]

Diazepam is a long acting benzodiazepine. The anxiolytic, amnesic and hypnotic effects of diazepam are the basis for the use of this drug in the pre-operative medication which is preferably accomplished with oral administration.

Clonidine is a centrally acting selective partial alpha-2 adrenergic agonist (220:1 α2 toα1) that acts by depressing the sympathetic nervous system output from the central nervous system. It also has sedative and analgesic properties. Oral clonidine premedication has been used with both general and regional aesthesia as it decreases plasma catecholamine concentration, along with reduction of intraoperative liability of blood pressure and heart rate. Clonidine has been used to prolong the effects of spinal anaesthesia with local anaesthetics like tetracaine, lignocaine and bupivacaine.[9, 10, 20]

To find out the better agent amongst them, we conducted a double blinded randomised study to compare the effects of oral clonidine and oral diazepam as pre-medication on the extent and duration of sensory blockade in patients receiving spinal anaesthesia with 0.5% bupivacaine for lower abdominal surgeries.

120 ASA grade I and II patients scheduled for lower abdominal surgeries were included in this study after obtaining their informed valid written consent.

Patients were divided in three groups group P, group C and group D of 40 each according to computer generated random number followed by allocation of these numbers in sealed enveloped technique.

Patients in **group P** received oral multivitamin tablet, **group C** received 100 mcg Oral Clonidine, patients in **group D** received Diazepam 5 mg oral premedication 90 minutes before spinal anaesthesia.

The dose of oral clonidine 100 mcg, oral diazepam 5 mg and time interval (90 minutes before spinal anaesthesia)

were decided according to previous studies [21, 22] in which these doses were safely used without any adverse effects like nausea, vomiting, respiratory depression with clonidine and sedation with diazepam.

We compared oral premedication of clonidine 100 mcg and Diazepam 5 mg with placebo to make double blinding of the study more effective. All the tablets were pre-wrapped in silver foil and were given to the patients by anaesthesiologist according to the group they belonged to. Both patient and anaesthesiologist who conducted the case were blinded to the group identities.

Statistical analysis was done by using descriptive and inferential statistics using Chi-square test, one way ANOVA and Multiple Comparison: Tukey Test. Softwares used in the analysis were SPSS 20.0 version, GraphPad Prism 6.0 version. $p<0.05$ was considered as level of significance.

Demographic variables

Table 1, Graph 1 shows distribution of patients according to age in all groups. Mean age of the patients in group P was 47.75±15.33 years, in group C was 44.45±12.38 years, in group D was 43.65±13.25 years. The difference was not statistically significant (p=0.17) among the groups.

Table 2, Graph 2 shows distribution of patients according to their gender. The groups were comparable regarding gender distribution amongst the cases as 'p' value was non-significant. (P=0.72)

Table 4, Graph 4 shows distribution of patients according to weight. Maximum patients in all groups were in the range of 40-50 kilograms. Mean weight of the patients in group P was 58±6.7 kilograms, in group C was 52±7 kilograms and in group D was 54±7.10 kilograms. The patients were comparable with respect to weight as the difference was not statistically significant (p=0.49).

Table 5, Graph 5 shows distribution of patients according to height in each group. Mean height of the patients in group P was 168.65±4.1 cms, in group C was 162.92±7.1 cms and in group D was 166.15±7.2 cms. The difference was not statistically significant (p=0.16). The patients were comparable with respect to height.

Table 6, graph 6 shows distribution of patients according to duration of surgery. Maximum patients in all groups were in the range of 60-80 minutes. Mean duration of surgery in group P was 74.12±2.4 minutes, in group C was 72.16±2.4 minutes and in group D was 70.23±2.4 minutes. The patients were comparable with respect to duration of surgery as the difference was not statistically significant ($p>0.05$).

Collective similar demographic variables were compared in previous studies.[14, 23, 24].

Onset of sensory block, time taken to reach highest level and highest level of sensory block achieved:

Onset of sensory block was defined as time from injection of spinal drug to L_1 sensory level achieved.

Table 7, Graph 7 shows distribution of patients according to onset of sensory block. The mean time for onset of sensory block in group P was 5.80±22.23 min, 6.07±2.32 min in group C and 6.32±2.05 min in group D. There was no significant difference in time of onset of sensory block in group P compared to group C (p=0.83), between group P and group D (p=0.53) and between group C and group D (p=0.86).

Table 8, Graph 8 shows distribution of patients according to highestlevel of sensory block achieved.

There was no significance difference in highest level of sensory block achieved in the three groups (p=0.061). T_4-T_7 sensory dermatome level was achieved in all patients. Most of the patients in our study achieved sensory level T_6, 28(70%) in group P, 31(77.5%) in group C and

24(60%) in group D. Highest level T_4 was seen in 3(7.5%) in group C, 1(2.5%) in group D, 0(0%) in group P.

Table 9, Graph 9 shows distribution of patients according to time taken to reach highest level of sensory block. The mean time taken to reach highest sensory level for group P was 17.62±3.92 min, for group C was 16.12±1.91 min and that for D group was 17.77±3.51 min. Therefore, no significant difference was observed in time taken to reach highest sensory level between group P and group C (p=0.10), between group P and group D (p=0.97), and between group C and group D (p=0.06).

Our results are consistent with the study conducted by Dziubdziela et al[10] in 2003, on the effects of oral and intramuscular clonidine in prolongation of bupivacaine spinal anesthesia. They observed no statistical difference in onset of sensory and motor blockade and in level of sensory analgesia.

In 2014, Kumari et al[24], compared the effects of two different doses of oral clonidine on prolongation of spinal analgesia. They also obtained no difference in onset of sensory block, maximum level achieved and time to achieve the maximum level of analgesia. In their study, initial onset of analgesia at T-10 level was 3.9±13.33 (min) in group 1(placebo), 3.85±1.22 (min) in group 2(clonidine 0.15mg) and 3.80±1.23 (min) in group 3(clonidine 0.3mg). Maximum level of analgesia in all three groups was T6-7 and time to achieve maximum level in group 1 was 5.75±1.91 (min), in group 2 was 5.6±1.93 (min) and in group 3 was 5.65±2.03 (min).

Our results are contrary to the study done by Toshniwal[21] et al, in 2008, who compared the effect of oral clonidine and oral diazepam on the extent and duration of sensory blockade. In their study, they observed significant difference in time of onset of anesthesia and time taken to reach highest sensory level. The mean time for onset of anesthesia for Group C was 6.73±2.39 min and that for Group D was 8.50±2.43 min (p value 0.006). The mean time taken to reach highest level for Group C was 18.9±6.23 min and that for Group D was 24.40±6.026 min (p value 0.001).

Duration of sensory block

Duration of sensory bock was defined as time for 2 segment regression from highest sensory block achieved.

Table 10, Graph 10 shows distribution of patients according to duration of sensory block. Mean duration of sensory block in group P was 73.07±6.52 min, in group C was 110.92±21.41 min and that in group D was 81.50±15.63 min. Our results showed that oral premedication with 100 mcg clonidine prolongs the duration of sensory blockade by bupivacaine as compared to that of 5 mg Diazepam oral premedication and Placebo.

Our results agree with the study done by Koichi Ota et al[20] who studied dose related prolongation of tetracaine spinal anaesthesia by oral clonidine. In their study, time for two-segment regression in group 1(0.25mg trizolam) was 78.5±15 (min), in group 2 (75 mcg clonidine) was 125±29 (min), in group 3 (150mcg clonidine) was 169±24 (min) and in group 4 (300mcg clonidine) was 154±32 (min). Hence they concluded that the optimal dose of oral clonidine produces a clinically useful prolongation of tetracaine spinal anaesthesia.

Toshniwal et al[21] also found similar increase in duration of sensory block with oral clonidine in their study. The mean duration analgesia was 286.67±79.01 min in clonidine group and 114.30±15.23 min in diazepam group (p=0.001).

Kumari et al[24] also noted statistically significant increase in duration of sensory block with oral clonidine 0.15 mg and 0.30 mg (150.2±23.07 min and 149.3±18.33 min respectively) as compared to placebo (78.3±10.44 min).

Our results are also consistent with the study conducted by Kulkarni et al[14] in 2014, who observed similar increase

in duration of sensory block with oral clonidine (121.10±19.71 min) as compared to placebo (76.26±13.66 min).

The antinociceptive effect produced by the orally administered α2- adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.[21] Action of orally administered diazepam to prolong the duration of sensory block is mediated through $GABA_A$ receptors. Benzodiazepines bind nonspecifically to benzodiazepine receptors which mediate sleep, affect muscle relaxation, anticonvulsant activity, motor coordination, and memory. As benzodiazepine receptors are thought to be coupled to gamma-aminobutyric acid-A ($GABA_A$) receptors, this enhances the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site opens the chloride channel, resulting in a hyperpolarized cell membrane that prevents further excitation of the cell. Orally administrated diazepam acts on $GABA_A$ receptors in lamina II of dorsal horn in human spinal cord suggesting the possible role in pain modulation.[13, 25, 26]

Duration of Post-operative analgesia

Duration of Post-operative analgesia was defined as time from administration of spinal drug till requirement of first rescue analgesic.

Table 11, Graph 11 shows distribution of patients according to duration of post-operative analgesia. The mean duration of Post-operative analgesia in group P was 95.07±5.13 min, in group C was 136.82±18.33 min and that in group D was 108.13± 11.50 min. Thus, mean duration of postoperative analgesia was significantly more in group C (p=0.001) and group D (p=0.0001) as compared to group P. Also, the mean duration of postoperative analgesia was significantly more in group C as compared to group D (p=0.001).

Our results demonstrated that 100 mcg oral clonidine premedication prolongs the duration of analgesia from Bupivacaine spinal anaesthesia as compared to that of 5 mg Diazepam oral premedication.

Dobrydnjoy et al[27] et al in 2002, studied the postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. They found that Oral and subarachnoid clonidine both increase the time until first request of analgesia (313±29 min respectively) as compared to 236±27 min in patients who received only intrathecal bupivacaine, consistent with our study.

Our observations also coincide with the study done by Prasadet al[1] in 2014, who compared preoperative oral clonidine and pregabalin on postoperative analgesia after spinal anesthesia. In their study, mean duration of analgesia in clonidine group was 238.41±7.32 (min), in pregabalin group was 255.14±5.02 (min) and in placebo group was 178.24±7.43 (min). They found that time to first demand of a rescue analgesic was more with clonidine than with placebo, similar to our study.

Toshniwal et al[21] also observed significant increase in duration of analgesia with oral clonidine (286.67±79.01 min) as compared to diazepam (114.30±15.23 min) (p value 0.001).

However Bonnet[9] et al in 1990, in their study to determine effects of oral and subarachnoid clonidine on spinal anaesthesia with bupivacaine observed no significant prolongation of duration of spinal anaesthesia with oral clonidine and concluded that only subarachnoid clonidine achieves adequate concentration to significantly increase the duration of spinal anaesthesia. The study population

used in their study was relatively small as compared to the study population used in our study which might have affected the results.

There are also previous studies [20, 28] which have shown that oral clonidine premedication prolongs the sensory and motor blockade from lignocaine and tetracaine spinal anaesthesia. The antinonciceptive effect produced by the orally administered alpha-2 adrenergic agonist is mainly caused by direct spinal activation due to the spread of the drug via the systemic circulation into the spinal cord.[21].

Haemodynamic variables

Table 12, Graph 12 shows the distribution of patients according to Mean pulse rate at various intervals in different groups. Preoperative mean Pulse Rate in group P was 87.9±9.04 that in group C was 83.9±7.08, and in group D was 88.05±10.53. The 'p' value was 0.069 and the difference was non-significant.

After induction and throughout the study period, there was a statistically significant difference in mean pulse rate across the groups. ($p<0.05$)

During inter group comparison we found that after induction there was a significant difference in mean pulse rate when group C was compared with group D and group P at different point of times.($p<0.05$) Throughout the study period, patients in clonidine group had low pulse rate as compared to patients in diazepam and placebo group.

Table 14, Graph 14 shows the distribution of patients according to mean of mean arterial pressure at various intervals in different groups. Preoperative mean of MAP in group P was 97.38±3.66 mmHg that in group C was 96.73±15.67 mmHg, and in group D was 98.92±6.74 mmHg. The 'p' value was 0.646 and the difference was non-significant.

After induction and throughout the study period, there was a statistically significant difference in mean of MAP across the group. ($p<0.05$)

During inter group comparison we found that after induction there was a significant difference in mean of MAP when group C was compared with group D and group P at different point of times ($p<0.05$). Throughout the study period, patients in clonidine group had low MAP compared to patients in diazepam and placebo group.

Our results are consistent with the study done by Dobrydjnjov et al. [27] They found that Mean arterial pressure decreased in 14% of intrathecal clonidine group in 1st hour and in 14-19% of oral clonidine group in first 5 hours.

Our results also agree with the study done by Harjai[29] et al in 2014, on the effect of different doses of oral clonidine on subarachnoid block. Intraoperative MAP was 92.57±1.72 mmHg in placebo group and 85.1±2.24 mmHg, 82.67±2.34 mmHg, 80.53±2.22 mmHg in clonidine group at 3 mcg/kg, 4 mcg/kg and 5 mcg/kg respectively. Similarly pulse rate was 72.67±2.31 bpm in placebo group and 68.03±2.33 bpm, 60.1±1.99 bpm and 58.1±2.26 bpm in clonidine group at 3 mcg/kg, 4 mcg/kg and 5 mcg/kg respectively. They stated that clonidine groups showed significant decrease in MAP and pulse rate from baseline both intraoperatively and postoperatively.

Toshniwal[21] et al also observed that the mean arterial pressure was significantly lower in clonidine group as compared to diazepam group.

Table 13, Graph 13 shows the distribution of patients according mean respiratory rate at various intervals in different groups. Preoperative mean RR in group P was 14.1±1.86 that in group C was 14.15±1.83, and in group D was 14.1±1.86. The 'p' value was 0.010 and the difference was non-significant. Intraoperative and

throughout the study period, no statistically significant difference was noticed across the three groups. (p>0.05) This indicates that no patient in our study had respiratory depression.

Previous studies conducted by Harjai et al[29] and Prasad et al[1] also observed no significant respiratory depression with oral clonidine.

Sedation Score and Dryness Score

Table 15, Graph 15 shows comparison of mean sedation score at various intervals in three groups. The mean sedation score preoperatively was significant across the group because we had given the study drugs that are clonidine and diazepam 90 min before induction. This significance in mean sedation score across the three groups continued throughout the study period. (p<0.05)

Table 16, Graph 16 shows the distribution of patients according to the mean dryness scores at various intervals in different groups. It is evident that there was no statistically significant difference across the groups when mean dryness scores were compared. (p>0.05)

Clonidine premedication causes sedation and xerostomia. In our study degree of sedation was significantly more in Diazepam group as compared to Clonidine and Placebo group.

Adverse Drug Reactions

Table 17, Graph 17 shows that, no patient in group P as well as group D had any episode of hypotension throughout the study period, while 4 (10%) patients in clonidine group had hypotension which was immediately after induction of spinal anesthesia. Statistical analysis revealed that this hypotension in clonidine group was statistically significant compared to the other groups. (p<0.05).

All patients responded to single dose of inj mephentermine 6 mg I.V. Previous studies[30, 31] have shown that there is an increase in serum epinephrine and nor-epinephrine levels after clonidine induced hypotension, which suggests preserved sympathetic response to hypotension. Another study[32] demonstrated that oral clonidine premedication enhances pressor response to sympathomimetic drug during spinal anaesthesia.

Table 18, Graph 18 shows the distribution of patients according to incidence of bradycardia in different groups. The incidence of bradycardia was more in patients receiving clonidine (4 patients) while 1 patient each in placebo group and diazepam group had bradycardia. When statistical analysis was done across the group, it was found to be non-significant. (p>0.05)

All patients responded to single dose of inj Atropine 0.6 mg I.V. In literature[66] the incidence of bradycardia after clonidine premedication is 5-10% which responds to 0.6 mg Atropine I.V. Clonidine causes resetting of baroreflexes which results in increased vagal tone at any given blood pressure. Increased vagal tone has been implicated in the anti-arrhythmic effect of Alpha-2 adrenergic agonists which is beneficial intraoperatively to protect against dysrhythmias from bupivacaine or halothane.[33]

The observations are consistent with dose response studies of oral clonidine that responded to dose dependent reduction of tonic sympathetic outflow and depression of blood pressure and heart rate. [34]

In a previous study done by Dobreydnjov et al [27], hypotension was more pronounced after oral than subarachnoid clonidine. In another study done by Dziubdziela [10], side effects like hypotension and bradycardia were more pronounced after intramuscular clonidine than after oral administration.

Our results also coincide with the study done by Kumari et al[24] who found more incidences of hypotension and bradycardia with oral clonidine.

However, Regmi et al[22] in 2010, who studied the effect of oral clonidine and diazepam on hemodynamic response during surgery observed no significance difference in incidence of hypotension and bradycardia between the two groups.

Thus our study demonstrates that oral clonidine premedication in a dose of 100 mcg increases duration of sensory block by spinal anaesthesia with bupivacaine compared to oral diazepam 5 mg and oral placebo with minimal side effects.

Conclusion

- Oral premedication with clonidine prolongs the duration of sensory blockade followed by oral diazepam followed by placebo, though they have no effect on onset of sensory blockade.
- Diazepam was associated with higher incidences of sedation than clonidine and placebo.
- Clonidine was associated with more incidences of bradycardia and hypotension as compared to diazepam and placebo.

Duration of post-operative analgesia was more with premedication by orally administrated clonidine 100 mcg followed by diazepam 5 mg followed by placebo after spinal anaesthesia.

Abbreviations

CSF: Cerebrospinal fluid

V/Q: Ventilation/Perfusion

CNS: Central nervous system

NMD: N-methyl-D-aspartate

VAS: Visual analogue scale

SD: Standard deviation

µg: microgram

Kg: kilogram

MAC: Minimum alveolar concentration

GPCRs: G-protein coupled receptors

MAP: Mean arterial pressure

ED: Effective dose

ASA: American Society of Anaesthesiologists

HR: Heart rate

RR: Respiratory rate

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

SS: Sedation Score

DS: Dryness Score

SpO2: Peripheral Oxygen saturation

IV: Intravenous

Hrs: hours

Min: minute

cms: Centimetres

S: Significant

NS: Non significant

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