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ORIGINAL ARTICLE

A COMPARATIVE STUDY OF EPIDURAL BUPIVACAINE WITH CLONIDINE AND EPIDURAL BUPIVACAINE FOR POST OPERATIVE ANALGESIA

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ABSTRACT: BACKGROUND: Clonidine, an α_2-adrenoreceptor agonist, administered epidurally, is gaining popularity for its analgesic, sympatholytic, hemodynamic stabilizing and sedative properties without significant side effects. **METHODS:** This present study "A Comparative Study of Epidural Bupivacaine with Clonidine and Epidural Bupivacaine for Post-operative Analgesia" was conducted in 70 cases of ASA grade I and II, between the age groups of 30-75yrs undergoing abdominal, gynecological and orthopedic surgeries under epidural anaesthesia. At the end of surgery, patients were shifted to recovery room. When patients complained of pain with VAS >4/10, they were allocated to receive either of B: Plain Bupivacaine 0.125% 10ml (n = 35). B+C: Clonidine 150 mcg (1ml) + 0.125% Bupivacaine 9ml (n=35). The following parameters were monitored: A. Onset of analgesia. B. Duration of analgesia. C. VAS and Quality of analgesia. D. ardio-respiratory effects: Pulse rate, blood pressure, respiratory rate. E. Side effects like: nausea, vomiting, pruritus, hypotension, sedation and respiratory depression were studied. **ONSET OF ANALGESIA:** The time of onset of analgesia in group (B+C) was significantly less (12.7±0.87 (S.D) min) when compared to group (B) (16±3.34 (S.D) min). **DURATION OF ANALGESIA:** The duration of analgesia in group (B+C) (225.2±45.74 (SD) min) was significantly more when compared to group (B) (119±29.29 (SD) min). **VISUAL ANALOGUE SCORE:** In comparison of group B and group B+C, highly significant difference in VAS was seen from 15min till 3.5hrs in between the groups. The quality of analgesia in Group B+C was VAS 3-4 (good to excellent pain relief), as compared to Group B, where VAS was 2-3 (fair to good pain relief). **SEDATION:** In Group B+C from 30min till 2hrs, 100% of patients were asleep (sedation score 3). Even in patients with sedation score 3, patients were calm, quiet and asleep but when questions were asked, they answered with clear consciousness. In the Group B, most of the patients were awake, alert (sedation score 1) and no patient was found asleep (sedation score 3). **SIDE-EFFECTS:** No incidence of hypotension, bradycardia or respiratory depression was seen in either group. The incidence of nausea vomiting, urinary retention was similar in either groups. In Group (B+C), higher incidence of dry mouth was noticed as compared to Group (B). **CONCLUSION:** Epidural Clonidine with Bupivacaine provides, a rapid, excellent and long duration of analgesia, with significantly shorter time of onset of analgesia with good sedation, when compared to epidural Bupivacaine group with no significant adverse effects.

KEYWORDS: α_{2-} adrenoreceptor, Clonidine, Epidural, Post-operative analgesia.

INTRODUCTION: Pain has been a major concern since our beginning and it has been the object of ubiquitous efforts to understand and to control it.

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In 1979, the International Association for Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". This definition recognizes the interplay between the objective, physiologic, sensory aspects of pain and its subjective, emotional and psychological components.

Today, as then, proper management of pain remains one of the most important and most pressing issues of society in general, the scientific community and the health care professionals in particular.

Postoperative pain is an acute pain which starts with surgical trauma and ends with tissue healing. Despite advances in the knowledge, skill and sophisticated technology that characteristics most aspects of modern surgical treatment, many patients continue to experience considerable discomfort during postoperative period. There appears to have been little improvement in this aspect of care of such patients over the past several decades.

Modern day anaesthesia is not just concerned with relieving pain during surgeries but also during postoperative period. Postoperative analgesia not only improves quality of life of the patient but also results in fast recovery and hence reduces the medical costs.

The use of conventional local anesthesia like bupivacaine and lignocaine has been unable to provide anaesthesia for longer surgery or analgesia for longer duration. Continuous epidural analgesia with a catheter has been implemented for these purposes.

Various modalities have been tried for the management of postoperative pain, out of which epidural opioids is an established and accepted technique. They provide excellent, prolonged and segmental analgesia without causing autonomic or motor blockade but are associated with undesirable side effects like respiratory depression, pruritus, sedation, nausea and vomiting.

Clonidine, is an imidazoline alpha-2 adrenergic receptor agonist mainly used as an anti-hypertensive agent. Alpha-2 receptors mediate sedation, analgesia, and sympatholysis. Clonidine is known to produce anti-nociception and enhance the effect of local anaesthetics when given intrathecally, epidurally and in peripheral nerve blocks.

Clonidine produces analgesia without any respiratory depression. Furthermore, in low to moderate doses it cause no hemodynamic instability. The largest reported experience with clonidine for regional anaesthesia is with epidural administration either alone or in combination with opioids like Morphine, Fentanyl and Butorphanol. Most of the controlled, double blind perioperative period studies demonstrate efficacy and specific advantages of Clonidine over traditional agents and these studies do not demonstrate hemodynamic instability with epidural Clonidine.

Hence, the present study was undertaken to determine the effect of Clonidine, administered epidurally, as an adjuvant to Bupivacaine, to assess the efficacy and safety as post-operative analgesic.

AIMS AND OBJECTIVES:

AIMS: To assess the efficacy and safety of epidural Clonidine, as an adjuvant to Bupivacaine, with regard to onset of sensory blockade, duration of effective analgesia, sedation and adverse

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effects, in 70 cases of ASA grade I and II, between the age group 30-75 yrs., undergoing abdominal, gynecological and orthopedic surgeries under epidural anaesthesia.

OBJECTIVES:

1. To determine the effect of Clonidine as an adjuvant to Bupivacaine, on the onset of sensory blockade after epidural injection.
2. To determine the duration of effective analgesia, when Clonidine is added to epidural Bupivacaine and thereby to study its efficacy for post-operative analgesia.
3. Study the occurrence of adverse effects like hypotension, bradycardia, respiratory depression, sedation, nausea, vomiting, dry mouth, urinary retention and pruritus with epidural Clonidine.

MATERIALS AND METHODS:

Patients and Methods: Source Of Data: Adult patients of age group 30-75 yrs scheduled for abdominal, gynecological and orthopedic surgery under epidural anaesthesia, admitted in S.V.S Medical College and Hospital, Mahabubnagar.

Method of Collection of Data:

Sample Size: A clinical study of 70 cases of ASA grade I and II, between the age group 30-75 yrs, undergoing abdominal, gynecological and orthopedic surgeries under epidural anaesthesia.

Inclusion Criteria:

- ASA grade I and II.
- Age between 30-75 years.
- Patients of either sex.
- Patients scheduled for elective abdominal, gynecological and orthopedic surgeries.

Exclusion Criteria:

- Poorly controlled hypertension, angina, and congestive cardiac failure.
- Atrial fibrillation, arrhythmias.
- Weight >95kg.
- Age >75 years and <30 years.
- ASA grade III and IV.
- Patients on tricyclic anti-depressants, alpha-2 adrenergic agonists or opioids.
- Any contra-indications to epidural anaesthesia.

METHOD OF STUDY: PRE-ANAESTHETIC EVALUATION: Patients were visited on the previous day of the surgery, a detailed medical history was taken and systemic examinations were carried out. Basic laboratory investigations like complete haemogram, bleeding time, clotting time, blood sugar, blood urea, serum creatinine, and urine analysis were carried out routinely on all patients. ECG was done in patients more than 40 years of age and chest X-ray when indicated. The entire procedure was explained to the patient and asked to notify after

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surgery when the patient experiences pain. Patients were also explained about Visual Analogue Scale (VAS) and were taught how to express the degree of pain on the scale.

A written consent was taken from the patient.

PREMEDICATION: Tab. alprazolam 0.5 mg was given orally on the previous night. Patients were kept nil orally for 8 hrs before surgery.

ANAESTHESIA: All patients were operated under epidural blockade using either 2 % lignocaine with adrenaline 1: 2,00,000 or 0.5% bupivacaine.

ANAESTHETIC TECHNIQUE: Drugs and equipment's necessary for resuscitation and general anaesthesia administration were kept ready. An autoclaved epidural tray was used. The patient was made to lie supine on the operation table. Routine monitors like NIBP, pulse oximetry, ECG leads connected. Baseline blood pressure, heart rate and respiratory rate were noted. An I.V. line was secured with 18 G cannula and infusion was started. The patient was placed in sitting position. With all aseptic precautions, a skin wheal was raised at L2-3 interspace with 2cc of 2% lignocaine. The epidural space was identified using a 18G TUOHY needle with loss of resistance to air technique. Then 18G PORTEX epidural catheter was passed through the epidural needle till about 2-3 cm of the catheter is in the space. The needle was withdrawn and the catheter was fixed to the back. 3cc of 2% lignocaine with adrenaline 1:2,00,000 was injected through the catheter as a test dose and observed for any intravascular or intrathecal injection. After confirming correct placement of catheter, 0.5% bupivacaine was injected as required. No narcotics were administered throughout the intra-operative period. At the end of surgery patients were shifted to recovery room. When the patient first complained of pain, they were shown VAS and were asked to express the intensity of pain on the scale. When it reached >4 mark on the scale, they were allocated to receive either of:

B: Plain Bupivacaine 0.125%, 10 ml (n = 35).

BC: Clonidine 150 mcg, (1 ml) + 0.125% Bupivacaine (9 ml).(n = 35)

RESULTS: Baseline pulse rate, respiratory rate, blood pressure (SBP/DBP) noted and intra operatively pulse rate, respiratory rate and blood pressure were recorded every.

15min. Intra operatively and post operatively, incidence of bradycardia (pulse <60/min), hypotension (fall in SBP> 30% of baseline and fall in DBP > 15% of baseline), nausea, vomiting, urinary retention, pruritus and shivering were noted.

Duration of analgesia that is the time of onset of sensory block of test dose till request of 1st analgesia was noted. Rescue analgesia with intramuscular Diclofenac was given and study stopped.

Post operatively SBP/DBP, respiratory rate and pulse rate were measured every 15min in 1st hr and at 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 24hrs or till the time when pain reappeared.

Sedation score every 15 min in 1st hr and 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 24hrs or till the time when pain reappeared.

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Sedation Score:

- SS1 –Awake.
- SS2 – Drowsy.
- SS3 – Asleep.

Visual Analog Score every 15 min interval for 1hr and 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 24 hrs or till the time when pain reappeared.

Visual Analogue Scale (VAS) was used to assess the intensity of pain and pain relief. This scale consists of a 10 cms line, marked at 1cm each, on which patient expresses the degree of pain by placing a point. Mark "0" represents no pain and mark "10" represents worst possible pain. At the time at which rescue analgesia was given, the patient was asked to give a global assessment of the overall effectiveness of the analgesic treatment.

Quality of analgesia was assessed depending on this as noted below and compared in both the groups.

PAIN SCORE	PAIN RELIEF
0	NO PAIN RELIEF
1	POOR PAIN RELIEF
2	FAIR PAIN RELIEF
3	GOOD PAIN RELIEF
4	EXCELLENT PAIN RELIEF

TABLE 1: QUALITY OF ANALGESIA

Adverse effects like hypotension (fall in systolic blood pressure by >30% or fall in diastolic blood pressure by 15%), bradycardia (pulse rate <60/min), respiratory depression (RR < 10/min), sedation, shivering, dry mouth, nausea, vomiting, drowsiness, urinary retention and pruritus were noted in post-operative period.

STATISTICAL ANALYSIS: Continuous data was analyzed by student's t-test test. Any possible significance has been determined considering it statistically significant if it's $P < 0.05$ - Significant (S); < 0.01 – Very significant; < 0.001 – Highly significant (HS); > 0.05 – Not significant (NS).

STATISTICAL TESTS: The statistical analysis of data is done using:

- Student t-test for parametric data (paired and unpaired).
- P- Value.

RESULTS:

GROUP	MALE	FEMALE	ASA I	ASA II	AGE (yrs)mean
B	18	18	14	15	50.77
B+C	17	17	21	20	50.51

TABLE 2: DEMOGRAPHIC PROFILE

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The mean age in both the groups is comparable (50.77 yrs in group B and 50.51yrs in group B+C). The maximum and minimum age in group B was 70yrs and 32yrs and in group B+C was 71yrs and 29yrs. The ASA status and the sex incidence in both group B and B+C are also similar.

GROUP	WEIGHT (kg)	HEIGHT (cm)
B	46.68	152.68
B+C	45.91	153.94

TABLE 3: ANTHROPOMETRIC COMPARISON

The mean weight in group B and B+C are comparable (46.7kg and 47.9kg). The maximum and minimum weights in group B were 58 kg and 42 kg and in group B+C were 56kg and 41kg. The mean height in group B and B+C are similar (152.7cm and 153.9cm). The maximum and minimum heights in group B were 172cm and 140cm and in group B+C were 178cm and 139cm.

GROUP	AGE (yrs)			
	31-40	41-50	51-60	61-75
B	10(29%)	6(17%)	9(26%)	10(29%)
B+C	10(29%)	6(17%)	9(26%)	10(29%)

TABLE 4: DISTRIBUTION OF AGE GROUPS

The age groups are comparable in group B and B+C with the maximum patients in age groups of 31-40yrs and 61-75yrs (29% each) and minimum patients in 41-50yr (17%).

	TYPE OF SURGERY		
GROUP	GEN SURG	ORTH SURG	GYN SURG
B	5(14.3%)	19(54.3%)	11(31.4%)
B+C	7(20%)	17(48.6%)	11(31.4%)

TABLE 5: TYPE OF SURGERY

In both the groups, Orthopedic surgeries constituted maximum with 54% (group B) and 49% (group B+C) respectively. All the surgical procedures are comparable in both the groups.

	GROUP B		GROUP B+C		T	P	
	MEAN	SD	MEAN	SD	VALUE	VALUE	SIGNIFICANCE
OOA	16	3.34	12.7	0.87	5.66	0.0001	HS
RFA	135	30.19	238	30.19	14.27	0.0001	HS
DOA	119	29.3	225	29.3	11.5	0.0001	HS

TABLE 6: ONSET OF ANALGESIA (OOA); REQUEST FOR FIRST ANALGESIA (RFA); DURATION OF ANALGESIA (DOA):

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- The mean time of onset of analgesia in group-B was 16+/- 3.34(S.D) minutes.
- The mean time of onset of analgesia in group-B+C was 12.7+/-0.87 (S.D) minutes.
- The Statistical analysis by Student's unpaired t-test showed that time of onset of analgesia in group - B+C was significantly less when compared to group - B. (t = 5.66, P<0.0001).
- Duration of analgesia in group (B) was 119+/- 29.29 (SD) min.
- Duration of analgesia in group (B+C) was 225.2+/-45.74 (SD) min.

The Statistical analysis by Student's unpaired t-test showed that time of duration of analgesia in group-B+C was significantly more when compared to group-B. (t=11.5, P< 0.0001).

		VISUAL ANALOGUE SCORE					
TIME	**GROUP B**		**GROUP B+C**		**T**	**P**	**SIGNIFICANCE**
	MEAN	**SD**	**MEAN**	**SD**	**VALUE**	**VALUE**	
0 min	4	0	4	0			NS
15 min	2.89	1.16	2	0.64	3.97	0.0002	HS
30 min	1.43	0.5	1	0	5.08	0.0001	HS
45 min	1.66	0.54	1	0	7.23	0.0001	HS
60 min	2.4	0.604	1	0	13.71	0.0001	HS
90 min	2.76	0.51	1.17	0.38	14.79	0.0001	HS
2 hr	3.28	0.52	1.57	0.56	13.23	0.0001	HS
2.5 hr	3.59	0.503	1.89	0.47	14.61	0.0001	HS
3 hr	3.78	0.44	2.23	0.69	11.2	0.0001	HS
3.5 hr	4	0	2.81	0.72	9.77	0.0001	HS
4 hr			3.45	0.8			
5 hr			3.55	0.5			
6 hr			4	0			

TABLE 7: COMPARISON OF VISUAL ANALOGUE SCORE

In the plain Bupivacaine group, pain appeared as early as 60 minutes in 2 patients. At 1.5hrs 3 patients, at 2hrs 13 patients (37%), at 2.5hrs 26 patients (74%), at 3hrs 33 patients (94%) and by 3.5hrs (100%) of patients experienced pain.

In the Bupivacaine and Clonidine group, pain appeared at 3hrs in 2 patients. At 3.5hrs 6 patients (17%), at 4hrs 24 patients (69%), at 5hrs 30 patients (86%) and by 6 hrs 100% of patients experienced pain.

In comparison of group B and group B+C, by using the unpaired student t test, at the baseline VAS of two groups are similar.

Highly significant difference in VAS was seen from 15min till 3.5hrs in between the groups.

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	SEDATION SCORE						
TIME	**GROUP B**		**GROUP B+C**		T	P	**SIGNIFICANCE**
	MEAN	SD	MEAN	SD	VALUE	VALUE	
0 min	1	0	1.1	0.3	1.97	0.0527	NS
15 min	1	0	2.86	0.36	30.56	0.0001	HS
30 min	1.06	0.24	3	0	47.82	0.0001	HS
45 min	1.14	0.36	3	0	30.56	0.0001	HS
60 min	1.2	0.4	3	0	26.62	0.0001	HS
90 min	1.16	0.37	3	0	29.42	0.0001	HS
2 hr	1.09	0.296	3	0	38.17	0.0001	HS
2.5 hr	1	0	2.97	0.17	41.2	0.0001	HS
3 hr	1	0	2.63	0.49	19.7	0.0001	HS
3.5 hr	1	0	2.23	0.43	16.92	0.0001	HS
4 hr			1.03	0.18			
5 hr			1	0			
6 hr			1	0			

TABLE 8: COMPARISON OF SEDATION SCORE

In the Bupivacaine group, most of the patients were awake, alert (sedation score 1) and only 16-17% of patients were drowsy (sedation score 2) in between 45-90 minutes after epidural dose. No patient was found asleep (sedation score 3).

In the Bupivacaine + Clonidine group, after 15 min of drug administration, 29 patients (83%) were asleep (sedation score 3) and from 30min till 2hrs 100% of patients were asleep (sedation score 3) and up to 70% patients were asleep at 3hrs. By 4hrs all the patients were awake and alert (sedation score 1).

In comparison of group B and group B+C, by using the unpaired student t test, at the baseline sedation score of two groups are similar.

Highly significant difference in sedation score is seen from 15min till 3.5hrs in between the groups.

	SYSTOLIC BLOOD PRESSURE						
TIME	**GROUP B**		**GROUP B+C**		**T**	**P**	**SIGNIFICANCE**
	MEAN	**SD**	**MEAN**	**SD**	**VALUE**	**VALUE**	
0 min	116.2	6.94	117.2	6.51	0.62	0.5362	NS
15 min	110.7	6.78	107.2	4.63	3.97	0.0140	S
30 min	107.1	6.22	102.06	4.67	3.83	0.0003	HS
45 min	108.2	5.98	103.37	4.31	3.88	0.0002	HS
60 min	109.5	5.93	104.17	4.35	4.29	0.0001	HS
90 min	110.1	6.24	105.2	4.15	3.87	0.0002	HS
2 hr	112.8	7	105.89	4.28	4.98	0.0001	HS

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2.5 hr	116.1	8.05	106.8	4.18	6.06	0.0001	HS
3 hr	114.3	6.71	108.17	4.29	4.55	0.0001	HS
3.5 hr	118	9	109.39	4.7	5.01	0.0001	HS
4 hr			111.21	4.73			
5 hr			112.2	4.57			
6 hr			113.2	4.15			

TABLE 9: COMPARISON OF SYSTOLIC BLOOD PRESSURE

In Bupivacaine group, by using independent t test for comparison with the baseline SBP, significant decrease in systolic blood pressure was observed at 15min, 30min and 45 min. Also no incidence of hypotension (fall of SBP by >30% of baseline) was observed. Maximum decrease in SBP was noticed in between 30-45min.

In Bupivacaine and Clonidine group, by using independent t test for comparison with the baseline SBP, significant decrease in systolic blood pressure was observed from 15 min till 6hrs. Also no incidence of hypotension (fall of SBP by >30% of baseline) was observed. Maximum decrease in SBP was observed in between 30min to 60min.

In comparison of group B and group B+C, by using the unpaired student t test, at the baseline SBP of two groups are similar.

Significant decrease in the SBP was observed at 15min and highly significant decrease in SBP was seen from 30min till 3.5hrs in between the two groups.

However, no incidence of hypotension was noticed in either group.

	SYSTOLIC BLOOD PRESSURE						
TIME	**GROUP B**		**GROUP B+C**		**T**	**P**	**SIGNIFICANCE**
	MEAN	**SD**	**MEAN**	**SD**	**VALUE**	**VALUE**	
0 min	116.2	6.94	117.2	6.51	0.62	0.5362	NS
15 min	110.7	6.78	107.2	4.63	3.97	0.0140	S
30 min	107.1	6.22	102.06	4.67	3.83	0.0003	HS
45 min	108.2	5.98	103.37	4.31	3.88	0.0002	HS
60 min	109.5	5.93	104.17	4.35	4.29	0.0001	HS
90 min	110.1	6.24	105.2	4.15	3.87	0.0002	HS
2 hr	112.8	7	105.89	4.28	4.98	0.0001	HS
2.5 hr	116.1	8.05	106.8	4.18	6.06	0.0001	HS
3 hr	114.3	6.71	108.17	4.29	4.55	0.0001	HS
3.5 hr	118	9	109.39	4.7	5.01	0.0001	HS
4 hr			111.21	4.73			
5 hr			112.2	4.57			
6 hr			113.2	4.15			

TABLE 10: COMPARISON OF DIASTOLIC BLOOD PRESSURE

In Bupivacaine group, by using independent t test for comparison with the baseline DBP, significant decrease in diastolic blood pressure was observed in between 30-45min. Also no

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incidence of hypotension (fall of DBP by >15% of baseline) was observed. Maximum decrease in DBP was observed in between 30min to 60min.

In Bupivacaine and Clonidine group, by using independent t test for comparison with the baseline DBP, significant decrease in diastolic blood pressure was observed from 15min till 3hrs. Also no incidence of hypotension (fall of DBP by >15% of baseline) was observed. Maximum decrease in DBP was observed in between 30min to 90min.

In comparison of group B and group B+C, by using the unpaired student t test, at the baseline DBP of two groups are similar.

At 15min no significant difference is noticed between the two groups.

Highly significant decrease in the DBP was observed at 30min and significant decrease in DBP was seen from 45min till 2hrs in between the two groups.

	PULSE RATE						
TIME	**GROUP B**		**GROUP B+C**		**T**	**P**	**SIGNIFICANCE**
	MEAN	**SD**	**MEAN**	**SD**	**VALUE**	**VALUE**	
0 min	76.39	10.67	78.02	9.59	0.67	0.5038	NS
15 min	71.43	7.78	70.57	9.38	0.4	0.6910	NS
30 min	69.09	6.22	65.26	8.24	1.99	0.0496	NS
45 min	69.12	7.35	66	8.28	1.67	0.1001	NS
60 min	70.11	8.61	66.54	8.12	1.78	0.0788	NS
90 min	68.76	7.5	67.14	8.1	0.87	0.3883	NS
2 hr	71.38	7.32	68.03	8.06	1.82	0.0731	NS
2.5 hr	73	8.42	68.4	8.06	2.36	0.0209	S
3 hr	71.42	9.12	68.71	8.2	1.31	0.1955	NS
3.5 hr	71.5	9.89	69.42	8.52	0.94	0.3492	NS
4 hr			70.63	7.63			
5 hr			74.5	8.31			
6 hr			80.8	7.96			

TABLE 11: COMPARISON OF PULSE RATE

In Bupivacaine group, by using independent t test for comparison with the baseline pulse rate, significant decrease in pulse rate was observed in between 15-90min. Also no incidence of bradycardia (pulse rate<60/min) was observed. Maximum decrease in pulse rate was observed in between 30-45min.

In Bupivacaine and Clonidine group, by using independent t test for comparison with the baseline pulse rate, significant decrease in pulse rate was observed in between 15min to 3.5hrs. Also no incidence of bradycardia (pulse rate<60/min) was observed. Maximum decrease in pulse rate was observed in between 30-90min.

In comparison of group B and group B+C, by using the unpaired student t test, at the baseline pulse rate of two groups are similar.

At 15min no significant difference is noticed between the two groups. Significant difference in pulse rate was seen at 2.5hrs in between the groups.

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At all other time, there was no significant difference between the two groups.

TIME	RESPIRATORY RATE				T	P	SIGNIFICANCE
	GROUP B		GROUP B+C				
	MEAN	SD	MEAN	SD	VALUE	VALUE	
0 min	16.46	1.04	16.71	0.99	1.03	0.3066	NS
15 min	13.01	0.81	12.83	0.57	1.07	0.2861	NS
30 min	13.06	0.8	12.86	0.49	1.26	0.2115	NS
45 min	13.03	0.66	12.83	0.62	1.31	0.1957	NS
60 min	13.6	0.73	13.14	0.79	2.53	0.0137	S
90 min	13.3	0.77	13.01	0.69	1.66	0.1016	NS
2 hr	13.53	0.88	13.11	0.72	2.18	0.0323	S
2.5 hr	14.41	0.94	13.31	0.63	5.75	0.0001	HS
3 hr	14.41	0.64	13.57	0.61	5.62	0.0001	HS
3.5 hr	14.5	1.41	13.54	0.78	3.88	0.0002	HS
4 hr			13.71	0.7			
5 hr			13.8	0.8			
6 hr			14.4	0.8			

TABLE 12: COMPARISON OF RESPIRATORY RATE

In Bupivacaine group, by using independent t test for comparison with the baseline respiratory rate, significant decrease in respiratory rate was observed in between 15min to 2hrs. Also no incidence of respiratory depression (respiratory rate <10/min) was observed. Maximum decrease in pulse rate was observed in between 15-45min.

In Bupivacaine and Clonidine group, by using independent t test for comparison with the baseline respiratory rate, significant decrease in respiratory rate was observed in between 15min to 3.5hrs. Also no incidence of respiratory depression (respiratory rate <10/min) was observed. Maximum decrease in respiratory rate was observed in between 15- 90 min.

	QOA 1	QOA 2	QOA 3	QOA 4
Group B	5(14%)	14(40%)	16(46)	0
Group B+C	0	4(11%)	19(54%)	12(35%)

TABLE 13: COMPARISON OF QUALITY OF ANALGESIA

The patients in Group B had fair (QOA 2 -40%) to good pain relief (QOA 3 - 46%) and the patients in Group B+C had good (QOA 3 -54%) to excellent pain relief (QOA 4 - 35%).

SIDE EFFECT	GROUP B	GROUP B+C
Nausea/Vomiting	5(14%)	4(11%)
Shivering	3(9%)	0
Dry Mouth	0	7(20%)

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Urinary Retention	2(6%)	2(6%)
Hypotension	0	0
Bradycardia	0	0
Respiratory Depression	0	0
Pruritus	0	0

TABLE 14: COMPARISON OF SIDE EFFECTS

From the Table 27, it is observed that the incidence of nausea and vomiting was similar in both groups (14% in Group B as compared to 11% in Group B+C).

3 patients in Group B out of 35 had incidence of shivering (9%) while no shivering was observed in Group B+C.

Dry mouth was observed in 7 patients (20%) and was significantly higher in

Group B+C than Group B.

Incidence of urinary retention was similar in both groups.

No incidence of bradycardia, hypotension or respiratory depression was observed in either group.

DISCUSSION: The incidence of postoperative pain varies with individual patients. The state of pain following a surgical procedure is a combination of pain as a specific sensation due to nociceptive response to tissue damage and pain as a suffering. Uncontrolled postoperative pain can result in several negative physiological effects that include disturbances of respiratory, cardiac, gastrointestinal, coagulation, renal, autonomic nervous system, endocrine and central nervous system function.

1. Pain can greatly impede the return of normal pulmonary function. Splinting, inability to cough, bronchospasm all lead to atelectasis and hypoxemia especially in upper abdominal and thoracic surgeries.
2. Pain promotes increased sympathetic activity resulting in peripheral vasoconstriction and production of a hypercoaguable state. These changes, associated with post-operative inactivity lead to a significant reduction of blood flow in the lower limbs and can increase the risk of deep vein thrombosis.
3. Pain produces an accelerated catecholamine response and increased concentrations of epinephrine and norepinephrine. The resultant increase in systemic vascular resistance, cardiac work and myocardial oxygen consumption may be particularly harmful in patients with cardiac disease and decreased cardiac reserve. Inadequately treated pain may result in cardiac arrhythmias, hypertension and myocardial ischemia.
4. Increased catabolic response to surgical trauma and impaired immune mechanisms cause delayed wound healing.
5. A decrease in the gastro intestinal motility and splanchnic circulation due to pain induced catecholamine response. Peri-operative starvation of the patient also has important implications for fatigue, recovery of gastro intestinal function and impairment of postoperative rehabilitation.

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Keeping in mind the above detrimental effects of pain, post-operative pain relief is very important. After any surgery, the pain following the tissue damage is rather self-limited, that is it persists at the most for the first twenty four hours, subsides in four days-time. The postoperative pain is dull in nature, aggravated by mobility, relieved by rest to that part. The acute pain of surgery is strongly accompanied by emotional elements of fear, anxiety and depression due to previous experience of pain.

In recent times, the role of epidural clonidine for the relief of postoperative pain promises a new platform in this field. Clonidine is a selective partial alpha-2 adrenergic agonist with a selectivity ratio of 200:1 in favor of alpha-2 receptors. It is lipid soluble and easily penetrates BBB to reach the hypothalamus and medulla, when injected epidurally. It stimulates alpha-2 adrenoreceptors to reduce central neural transmission in the spinal neurons. Inhibition of substance-P release is also believed to be involved in analgesic effect. Cholinergic mechanism may also be involved, atleast in part, in analgesia due to neuraxially administered clonidine. The alpha-2 adrenoreceptors are located on the afferent terminals of both peripheral and spinal neurons, on neurons in the superficial laminae of spinal cord and within several brainstem nuclei. The superficial laminae of dorsal horn contain 3 groups of neurons: tonic, adapting and single-spike-firing; all of which are important neuronal structures for pain transmission, receiving most of their primary sensory input from A delta and C fibers. The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action and favours neuraxial administration.

Sedation is due to its action on locus ceruleus. Sedation after epidural clonidine is due to its systemic absorption and vascular redistribution to higher centers. Clonidine causes a decrease in peripheral resistance, renal vascular resistance, heart rate and blood pressure. Clonidine alone does not produce profound respiratory depression even after massive overdose nor does it potentiate respiratory depression from opioids.

The current clinical study was undertaken in surgical patients to evaluate the analgesic, hemodynamic, respiratory and sedative effects of epidural Clonidine as an adjuvant to Bupivacaine in the management of postoperative pain. Hence, a clinical study of 70 cases of ASA grade I and II, between the age group 30-75yrs undergoing abdominal, gynecological and orthopedic surgeries under epidural anaesthesia was undertaken for achieving our objectives.

The mean age in both the groups is comparable (50.77 yrs in group B and 50.51yrs in group B+C, (Table 2). The maximum and minimum age in group B is 70yrs and 32yrs and in group B+C is 71yrs and 29yrs (Table 3). The age groups (Table 4) are comparable in group B and B+C with the maximum patients in age groups of 31-40yrs and 61-75yrs (29%) and minimum patients in 41-50yr (17%). The ASA status and the sex incidence in Group B and B+C are also similar (Table 2). The mean weight and height in Group B and B+C are also comparable (Table 3). All the surgical procedures are comparable in both the groups. In both the groups, Orthopedic surgeries constituted maximum with 54% (group B) and 49% (group B+C) respectively (Table 3).

In Operation theatre a peripheral vein was cannulated with 18G intravenous catheter. Under aseptic conditions 18G epidural catheter was put in L2-L3 space with 2% Lignocaine with Adrenaline (1:200000) 3ml of test dose was administered to exclude intrathecal placement and

surgery was done under epidural anaesthesia. At the end of surgery, patients were shifted to recovery room. When patients complained of pain with VAS > 4/10 they were allocated to receive either of:

B: Plain Bupivacaine 0.125% 10ml (n = 35).

B+C: 0.125% Bupivacaine (9ml) + Clonidine 150mcg (1ml) (n = 35)

It was found that all patients experienced pain relief. However onset, duration and quality of analgesia was found to be variable because of difference in drug used, severity of pain, pain threshold and the type of surgery, etc.

ONSET OF ANALGESIA: In present study, the mean time of onset of analgesia (TABLE 7) in group-B was 16+/- 3.34(S.D) minutes and in group-B+C was 12.7+/-0.87 (S.D) minutes. The

Statistical analysis by Student's unpaired t-test showed that time of onset of analgesia in group-B+C was significantly less when compared to group-B (t = 5.66).

Results of the present study coincided with study done by Bonnet, Boica, et al,[1] who compared epidural clonidine 150 mcg with epidural saline injection. In their study onset of analgesia was within 15 min and they suggested high lipid solubility of clonidine to be responsible for its rapid action.

Results of the present study coincided with study done by Bonnet, et al,[1] who in their study compared epidural and intramuscular clonidine (2mcg/kg). In their study, onset of analgesia in both clonidine groups was found to be within 15min.

Results of the present study coincided with study done by Shobhana Gupta, et al,[2] In their study, patients received either an epidural Clonidine (1mcg/kg) with Bupivacaine (1.5mg/kg) group CL (n=30) or Bupivacaine alone group CT (n=30). The onset of sensory anesthesia was faster (493.8±31.66 in sec.) in Bupivacaine + Clonidine group compared to plain Bupivacaine.

VAS (VISUAL ANALOGUE SCORE): In present study, when the patient first complained of pain, they were shown VAS and were asked to express the intensity of pain on the scale. When it reached >4 mark on the scale, they were allocated to receive the drug. Visual Analogue Scale (VAS) was used to assess the intensity of pain and pain relief. This scale consisted of a 10 cm line, marked at 1cm each, on which patient expresses the degree of pain by placing a point. Mark "0" represents no pain and mark "10" represents worst possible pain. The time at which rescue analgesia (reappearance of pain with VAS >4/10) given was noted and the patient was asked to give a global assessment of the overall effectiveness of the analgesic treatment (quality of analgesia).

In the Group B (Table 8), pain appeared as early as 60 minutes in 2 patients. At 1.5hrs 3 patients, at 2hrs 13 patients (35%), at 2.5hrs 26 patients (75%), at 3hrs 33 patients (95%) and by 3.5hrs 100% of patients experienced pain.

In the Group B+C (Table 9), pain appeared at 3hrs in 2 patients. At 3.5hrs 6 patients (16%), at 4hrs 24 patients (65%), at 5hrs 30 patients (86%) and by 6 hrs 100% of patients experienced pain.

In comparison of group B and group B+C (Table 10), by using the unpaired student t test, the baseline VAS of two groups is similar. Highly significant difference in VAS was noted from 15min till 3.5hrs.

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QOA (QUALITY OF ANALGESIA): From the table 26, the patients in Group B had fair (QOA 2 - 40%) to good pain relief (QOA 3 - 46%) and the patients in Group B+C had good (QOA 3 - 54%) to excellent pain relief (QOA 4 - 35%). Patients in group Bupivacaine with Clonidine had better pain relief than in plain Bupivacaine group.

Nishikawa T, Dohi S et al,[3] in their double blind study of 20 ASA1/2 patients undergoing Perineal or Orthopedical surgeries, evaluated the efficacy of 150 mcg of epidural clonidine in normal saline (15mcg/ml) with that of normal saline. They found that maximum pain relief was noted in 68.2% of pre injection levels in epidural clonidine patients whereas it was only 14.7% in epidural saline group. Better pain relief (satisfactory analgesia) was noted in epidural clonidine group.

DURATION OF ANALGESIA: In present study, duration of analgesia in Group-B was 119+/-29.29 (SD) min and range of analgesic duration was 41-198 min. Duration of analgesia in Group-B+C was 225.2+/-45.74 min and the range of analgesic duration was 77-346 min. The Statistical analysis by Student's unpaired t-test showed that time of duration of analgesia in group-B+C was significantly more, when compared to group-B ($t = 11.5$, $P < 0.0001$).

Results of the present study coincided with study done by Bonnet, Boica et al,[4] a double blind study of 20 ASA1/2 patients undergoing Perineal or Orthopedic surgeries, which evaluated the efficacy of 150 mcg of epidural Clonidine in normal saline (15mcg/ml) with that of normal saline. They found that mean duration of analgesia in epidural clonidine was significantly longer (210min vs 45min) than epidural plain Bupivacaine.

Bonnet et al,[1] who in their study compared epidural and intramuscular Clonidine (2mcg/kg) and concluded that duration of action in epidural Clonidine group was 208+/-87min and the range of analgesic duration was 45-360min.

Mendez et al,[5] conducted a double blind, placebo controlled study to assess the efficacy, safety and appropriate dose of epidural Clonidine for post cesarean section analgesia. 60 women were randomly assigned to three groups and received bolus saline, 400 mcg (5mcg/kg) Clonidine bolus or 800 mcg (10mcg/kg) bolus Clonidine. The duration of analgesia was similar in 400 mcg and 800 mcg group (4.5hrs vs 5hrs) which was significantly longer than saline group (2hrs).

In the present study, Duration of analgesia of epidural Bupivacaine is prolonged when Clonidine is added compared to epidural plain Bupivacaine, which is also similar to the studies done by Rostaing S. et al,[6] Jamali S et al,[7] Capogna G et al,[8] KK Upadhyay et al,[9] Archna Koul et al,[10] Ghatak T et al,[11] Shobhana Gupta et al[2] and Parameswari A et al.[12]

SEDATION: In the present study, in Group B (Table11) most of the patients were awake, alert (sedation score 1) and only 16-17% of patients were drowsy (sedation score 2) in between 45-90 minutes after epidural dose. No patient was found asleep (sedation score 3).

In the Group B+C (Table 12), after 15 min of drug administration, 29 patients (85%) were asleep (sedation score 3). From 30min till 2hrs, 100% of patients were asleep (sedation score 3). Upto 70% patients were asleep, at 3hrs. By 4hrs, all the patients were awake and alert (sedation score 1). In patients with sedation score 3, patients were calm, quiet and asleep but when questions were asked they answered with clear consciousness.

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In comparison of group B and group B+C (Table 13), by using the unpaired student t test, at the baseline sedation score of two groups are similar. Highly significant difference in sedation score is seen from 15min till 3.5hrs in between the groups.

Results of the present study coincided with study done by Bonnet et al,[4] who in their study compared epidural and intramuscular clonidine (2mcg/kg). In their study, it was observed that following Clonidine administration, all patients experienced drowsiness. Patients rested quietly in beds with eyes closed but were able to respond immediately and accurately. In their study, duration of drowsiness ranged from 141+/-38min and the duration of drowsiness corresponded with duration of analgesia. They also concluded that presence of drowsiness neither compromised nor complicated VAS measurement, as patients were able to measure their VAS whenever required.

Eisenach et al,[13] in their study of epidural Clonidine analgesia following surgery compared 3 doses of Clonidine. They studied 100-300 mcg; 400-700 mcg and 700-900 mcg epidural Clonidine. They concluded that sedation following any dose of Clonidine was variable and lasted for 1-3hrs and was not dose dependent.

Mendez et al,[5] conducted a double blind, placebo controlled study to assess the efficacy, safety and appropriate dose of epidural clonidine for post cesarean section analgesia. 60 women were randomly assigned to three groups and received either bolus saline, 400mcg (5mcg/kg) Clonidine bolus or 800mcg (10mcg/kg) bolus Clonidine. They concluded that clonidine produced dose dependent sedation lasting for 3-4hrs.

SYSTOLIC BLOOD PRESSURE: In present study, in Group B (Table 14), by using independent t test for comparison with the baseline SBP, significant decrease in systolic blood pressure was observed at 15min, 30min and 45 min. Maximum decrease in SBP was noticed in between 30-45min.

In Group B+C (Table 15), by using independent t test for comparison with the baseline SBP, significant decrease in systolic blood pressure was observed from 15min till 6hrs. Maximum decrease in SBP was observed in between 30min to 60min.

In comparison of group B and group B+C (Table 16), by using the unpaired student t test, the baseline SBP of two groups is similar. Significant decrease in the SBP was observed at 15min and highly significant decrease in SBP was seen from 30min till 3.5hrs in between the two groups. No incidence of hypotension (fall of SBP by >30% of baseline) was observed in both the groups.

Results of the present study coincided with study done by Bonnet Boica et al,[4] who compared epidural clonidine 150mcg with epidural saline injection. They concluded that maximum decrease in MAP is at 30 min of epidural clonidine injection and significant decrease in MAP is seen till 180min.

Eisenach et al,[13] in their study of epidural Clonidine analgesia following surgery compared 3 doses of Clonidine. They studied 100-300 mcg; 400-700 mcg and 700-900 mcg epidural clonidine. They observed that with epidural clonidine 100-300 mcg dose, MAP decreased maximally at around 47±4min (range 15-90min) and decrease was 21±4% from baseline.

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DIASTOLIC BLOOD PRESSURE: In present study, in Group B (Table 17), by using independent t test for comparison with the baseline DBP, significant decrease in diastolic blood pressure was observed in between 30-45min. Also no incidence of hypotension (fall of DBP by >15% of baseline) was observed. Maximum decrease in DBP was observed in between 30min to 60min.

In Group B+C (Table 18) by using independent t test for comparison with the baseline DBP, significant decrease in diastolic blood pressure was observed from 15min till 3hrs. No incidence of hypotension (fall of DBP by >15% of baseline) was observed. Maximum decrease in DBP was observed in between 30min to 90min.

In comparison of Group B and Group B+C (Table 19), by using the unpaired student t test, at the baseline DBP of two groups are similar. At 15min no significant difference is noticed between the two groups. Highly significant decrease in the DBP was observed at 30min and significant decrease in DBP was seen from 45min till 2hrs in between the two groups.

Results of the present study coincided with study done by Bonnet et al,[4] who in their study compared epidural and intramuscular Clonidine (2mcg/kg). In their study, mean arterial pressure (MAP) decreased in epidural Clonidine and was significantly lower than baseline value until 360min. Maximum decrease in MAP was in between 30-60min and 29.5+/-11.5% from baseline and no patient experienced hypotension.

Mendez et al,[5] conducted a double blind, placebo controlled study to assess the efficacy, safety and appropriate dose of epidural clonidine for post cesarean section analgesia. 60 women were randomly assigned to three groups and received either bolus saline, 400mcg (5mcg/kg) clonidine bolus or 800mcg (10mcg/kg) bolus Clonidine. They showed that both Clonidine groups had lower blood pressures than the saline group from 2-12hrs, no patient required treatment for hypotension and there were no reports of delayed hypotension or bradycardia from cephalad spread of epidural Clonidine.

PULSE RATE: In present study, in the Group B (Table 20) by using independent t test for comparison with the baseline pulse rate, significant decrease in pulse rate was observed in between 15-90min. Also, no incidence of bradycardia (pulse rate<60/min) was observed. Maximum decrease in pulse rate was observed in between 30-45min.

In Group B+C (Table 21), by using independent t test for comparison with the baseline pulse rate, significant decrease in pulse rate was observed in between 15min to 3.5hrs. Also, no incidence of bradycardia (pulse rate<60/min) was observed. Maximum decrease in pulse rate was observed in between 30-90min.

In comparison of Group B and Group B+C (Table 22), by using the unpaired student t test, at the baseline pulse rate of two groups are similar. Significant difference in pulse rate was seen at 2.5hrs in between the groups. At all other times, there was no significant difference between the two groups.

Results of the present study coincided with study done by Bonnet et al[1], who in their study compared epidural and intramuscular Clonidine (2mcg/kg). In their study, heart rate decreased significantly but transiently (15-180min) as compared to baseline in epidural Clonidine group with 2 patients experiencing bradycardia (PR<50/min) and the maximum decrease was observed at 60-90min.

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Eisenach et al,[13] in their study of epidural Clonidine analgesia following surgery compared 3 doses of Clonidine. They studied 100-300mcg; 400-700mcg and 700-900mcg epidural Clonidine. They observed that with epidural clonidine 100-300mcg dose, maximal decrease in heart rate occurred later than maximal decrease in MAP, was more variable in timing and occurred around 113+/-18min (range 20-300min) and decrease was 19+/-2% from baseline.

Mendez et al,[5] conducted a double blind, placebo controlled study to assess the efficacy, safety and appropriate dose of epidural Clonidine for post cesarean section analgesia. 60 women were randomly assigned to three groups and received either bolus saline, 400mcg (5mcg/kg) Clonidine bolus or 800mcg (10mcg/kg) bolus Clonidine. They suggested that maximum decrease in heart rate after epidural Clonidine occurs 1-2hrs of injection, at times of peak plasma concentration. They showed that both Clonidine groups differ from saline group from 15min to 6hrs. There have been no reports of delayed hypotension or bradycardia from cephalad spread of epidural Clonidine.

RESPIRATORY RATE: In present study, in Group B (Table 23), by using independent t test for comparison with the baseline respiratory rate, significant decrease in respiratory rate was observed in between 15min to 2hrs. Also, no incidence of respiratory depression (respiratory rate <10/min) was observed. Maximum decrease in pulse rate was observed in between 15-45min.

In Group B+C (Table 24), by using independent t test for comparison with the baseline respiratory rate, significant decrease in respiratory rate was observed in between 15min to 3.5hrs. Also no incidence of respiratory depression (respiratory rate <10/min) was observed. Maximum decrease in respiratory rate was observed in between 15-90min.

In comparison of group B and group B+C (Table 25), by using the unpaired student t test, at the baseline respiratory rate of two groups are similar. In between 2.5-3.5hrs highly significant difference is noticed between the two groups. Significant difference in respiratory rate was seen at 60min and 2hrs in between the groups. At all other time, there was no significant difference between the two groups.

SIDE EFFECTS: From the Table 27, it is observed that the incidence of nausea and vomiting was similar in both groups (14% in Group B as compared to 11% in Group B+C). 3 patients in Group B out of 35 had incidence of shivering (9%) while no shivering was observed in Group B+C. Dry mouth was observed in 7 patients (20%) and was significantly higher in Group B+C than Group B. Incidence of urinary retention was similar in both groups. No incidence of bradycardia, hypotension or respiratory depression was observed in either group.

Mendez et al,[5] conducted a double blinded, placebo controlled study to assess the efficacy, safety and appropriate dose of epidural Clonidine for post cesarean section analgesia. 60 women were randomly assigned to three groups and received either bolus saline, 400mcg (5mcg/kg) Clonidine bolus or 800mcg (10mcg/kg) bolus Clonidine. They concluded that groups did not differ in respiratory rate at any time, and no patient had a respiratory rate of <12 breaths per min. there was no hypotension observed also there were no reports of delayed hypotension or bradycardia from cephalad spread of epidural Clonidine.

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Shobhana Gupta et al,[2] conducted a randomized double-blind design, and 60 adult patients (40-60 years) of ASA grade I and II, scheduled for post-operative pain relief in total knee replacement surgeries by epidural Clonidine were studied. Patients received either an epidural Clonidine (1mcg/kg) with Bupivacaine (1.5mg/kg) group CL (n=30) or Bupivacaine alone group CT (n=30).

Incidence of significant hypotension was higher in (26%) patients in Clonidine group compared to patient in control group (6%). Incidence of dryness of mouth was higher, (48%) patients in Clonidine group, compared to patients in control group (18%).

LIMITATIONS OF THE STUDY: Since pain is a subjective phenomenon associated with a wide variability of responses among the individuals, it is difficult to standardize the variable. What may be tolerable for one person may be intolerable for another person. Under these circumstances it is difficult to assess and grade the pain the same manner leading to a lot of unwanted bias in the present study, patients also varied with respect to the type of surgery, in the present study.

CONCLUSIONS: Epidural Clonidine with Bupivacaine provides a rapid, excellent and longer duration of analgesia when compared to epidural Bupivacaine. Significantly shorter time for onset of analgesia and longer duration of analgesia with good sedation was seen in epidural Bupivacaine with Clonidine group, when compared to epidural Bupivacaine group. No incidence of hypotension, bradycardia and respiratory depression was seen in epidural Bupivacaine with Clonidine group. Dry mouth was the only side effect observed. However, the duration of action of single epidural Clonidine dose is too short for most of the patients (3-4hrs). Because of its relatively brief duration of analgesia, it may be necessary to infuse epidural Clonidine continuously in order to provide analgesia for prolonged duration. Refinement of Clonidine therapy and its ultimate usefulness compared to current therapies (patient controlled analgesia and epidural Opioids) has to be determined in future studies.

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