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Original Research Article

A Comparative Evaluation of Clonidine, Dexmedetomidine and Neostigmine Used as Adjuvants to 0.5% Bupivacaine in Epidural Anaesthesia for Lower Limb and Lower Abdominal Surgery

Iram Shokat[1], Mubashar Akram[2], Anumeha Jain[1], Abhinav Mani[2]

[1]Department of Anaesthesia, National Institute of Medical Sciences, Jaipur
[2]Department of Surgery, Government Medical College Jammu

Corresponding Author: Mubashar Akram

ABSTRACT

Background:- Bupivacaine is the standard local anaesthetic agent for intrathecal/epidural analgesia. Adjuvants are often added to improve analgesia and reduce the dose of bupivacaine thereby decreasing the cost of the drug used and minimize side effects.
Aim:- A comparative evaluation of clonidine, dexmedetomidine and neostigmine used as adjuvants to 0. 5% bupivacaine in epidural anaesthesia for lower limb and lower abdominal surgery.
Design and Place:- This is a comparative study which was carried out in 80(eighty) patients admitted in National Institute Of Medical Sciences & Research, Jaipur over a period of one year *w.e.f.* November 2017 to November 2018.
Method:- 80 patients of either sex ranging in age from 18-60 years, scheduled for lower limb and lower abdominal surgeries were divided into four study groups randomly by an investigator not directly linked to the study. All patients were given epidural anaesthesia for undergoing the proposed surgery. Epidural Neostigmine, Clonidine or Dexmedetomidine was added to bupivacaine depending upon the patient group and results in terms of efficacy, safety and prolongation of analgesic effect were noted.
Result: - The use of these adjuvants prolonged the post operative analgesia and the prolongation was maximum in Dexmedetomidine group followed by Clonidine and then the Neostigmine group.Conclusion: When these non opioid adjuvants are added to 0.5% Bupivacaine in epidural anaesthesia, they prolong the analgesic effect with added advantage of opioid sparing effect as the use of epidural opioids is always associated with increased incidence of unwanted side effects.
Key words: Neostigmine, Clonidine, Dexmedetomidine, Bupivacaine, Epidural Anaesthesia.

INTRODUCTION

Pain is not just a sensory modality but is an experience. The International Association for the study of pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".
Both the peripheral and the central nervous systems (CNS) are involved in the perception of pain, with the spinal and supraspinal components of the CNS playing key roles.(Fields ML)

Epidural anaesthesia is a central neuraxial block with many applications ranging from analgesia with minimal motor block to dense anaesthesia with full motor block. It offers efficacy and safety with minimal chances of side effects combined with the potential of improving an inadequate block level and prolongation of effect in the post operative period as well.

Typically, local anaesthetics and opioids, alone or in combination, are administered through the epidural injection as an infusion or a bolus to provide analgesia. Although opioids can provide profound peri-operative analgesia with fewer central or systemic side effects, their use, however, has always been surrounded by controversy because of the associated adverse affects notably pruritus and respiratory depression. (Gustafsson LL et. al.)

Bupivacaine is the standard local anaesthetic agent for intrathecal/epidural analgesia. Adjuvants are often added to improve analgesia and reduce the dose of bupivacaine thereby decreasing the cost of the drug used and minimize side effects.

Attempt to find a more suitable alternative to epidural opioids, a wide variety of non-opioid additives like ketamine, midazolam, magnesium, clonidine among many others have been tried time and again to achieve an equivalent/ better pain relief without attendant adverse reactions that are commonly seen with opioids. (Kumar D et. al.)

Clonidine, an alpha 2 agonist, is a useful adjuvant. It has analgesic properties when administered alone and acts synergistically with neuraxial opioids and local anaesthetics. (Carbine UA et. al.)

Dexmedetomidine is a superselective alpha-2 adrenergic agonist prototype. Dexmedetomidine has sedative, analgesic, sympatholytic and anxiolytic effects that blunt many of the cardiovascular responses in the perioprerative period. It reduces the volatile anesthetic, sedative and analgesic requirements of the patient without causing respiratory depression. (Paris A et. al.)

Neostigmine, an anticholinesterase drug, which is used to antagonize non depolarizing muscle relaxants, has been tried for post operative analgesia as an off label use. Being a quaternary amine, it does not cross the blood brain barrier and by epidural route provides analgesia via Ml and M2 receptors in the spinal cord, inhibiting the breakdown of acetylcholine. (Lauretti GR et. al.)

The absolute supremacy of one epidural adjuvant over the other has not yet been established equivocally

We undertook the present study in order to assess whether alpha agonists and neostigmine when administered as adjuvants in epidural anaesthesia are helpful or not in augmentation of local anaesthetic block without the unavoidable side effects commonly encountered with use of opioids.

This study was undertaken to assess the effect of combination of clonidine or dexmedetomidine or neostigmine with bupivacaine in terms of quality and duration of post operative analgesia.

MATERIALS AND METHODS

AIM: A comparative evaluation of clonidine, dexmedetomidine and neostigmine used as adjuvants to 0. 5% bupivacaine in epidural anaesthesia for lower limb and lower abdominal surgery in terms of efficacy, safety and prolongation of analgesic effect.

Objectives

- To compare onset and duration of motor and sensory blockade
- To compare side effects.

80 patients of either sex ranging in age from 18-60 years, belonging to ASA grades I and II, scheduled for lower limb and lower abdominal surgeries were included in the study. Allocation to the four study groups was done randomly by an investigator not directly linked to the study.

Exclusion criterion:

1. Patients with any contraindication for epidural anaesthesia
   - Patient refusal
   - Bleeding diathesis
   - Local skin infection at spinal lumbar region
   - Raised intracranial pressure
   - Hypovolemia
2. Patients with systemic disorders like respiratory, cardiac, renal or hepatic insufficiency.

3. Patients allergic to any of the used drugs

Pre-anaesthetic evaluation:

Informed written consent was taken from all patients to be enrolled in the study. They were subjected to a detailed general physical as well as systemic examination. Baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and respiratory rate (RR) were recorded. Routine investigations like Hemoglobin (Hb), Bleeding time (BT), Clotting time (CT), Renal function tests, Complete urine examination, ECG and Chest radiograph were also done.

Patient groups:

Patients will be randomly allocated to one of the four study groups as:

Group 1: CONTROL (B) group- received 20 ml of 0.5% bupivacaine and l ml of normal saline.

Group 2: BUPIVACAINE-NEOSTIGMINE (BN) group- received 1 ml of saline containing 4µg/kg Neostigmine in addition to 20 ml of 0.5% bupivacaine.

Group 3: BUPIVACAINE-CLONIDINE (BC) group- received 1 ml of normal saline containing 2µg/kg Clonidine in addition to 20 ml of 0.5% bupivacaine.

Group 4: BUPIVACAINE-DEXMEDETOMIDINE (BD) group- received 1 ml of normal saline containing 2µg/kg of Dexmedetomidine in addition to 20 ml of 0.5% bupivacaine.

Pre-anaesthetic preparation:

All patients were kept fasting for a period of 8 hours pre-operatively and received tablet Alprazolam 0.25mg orally the night before surgery and 2 hours before surgery. Linear Visual Analogue Scale will be explained to all patients.

After receiving the patient in Operation Theatre (OT), intravenous line with 18G cannula is to be established. Baseline Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Arterial Saturation (SpO_2) and Respiratory Rate (RR) was recorded. All patients were preloaded with 10 ml/kg infusion of Ringer's lactate solution 15 minutes prior to establishment of epidural block.

Anaesthetic Technique:

All patients will be given epidural anaesthesia for undergoing the proposed surgery. Epidural Neostigmine, Clonidine or Dexmedetomidine will be added to bupivacaine depending upon the patient group. Each group is first administered a test dose of 3ml of same solution and we waited for a period of 2-3 minutes to exclude intravascular/intrathecal injection of the drug. The drug combination depending upon the group will then be injected slowly. Surgical incision is allowed at least 20 minutes after delivery of the complete drug solution.

Sensory block is assessed after 5, 10, 15, 20, 25 and 30 minutes by pin prick method and time to reach the maximum block height i.e. the time taken for complete fixation of the block will be also recorded. An upper level of T 10 will be considered satisfactory.

Motor block will be assessed using Modified Bromage scale after 5, 10, 15, 20, 25 and 30 minutes.

0 No motor block
1 Inability to raise extended legs
2 Inability to flex legs
3 Inability to flex ankle joints

Parameters:

The following parameters will be recorded

1. Hemodynamic variables: HR, SBP, DBF, SPO_2 and RR will be recorded at 0,2,4,6,10,20,30,40,50,60,70,90 minutes depending upon duration of surgery.
2. Onset and highest level of sensory block at 5, 10, 15 and 20 minutes.
3. Degree of motor block according to Modified Bromage scale at 5, 10, 15 and 20 minutes.
4. Incidence of side effects-

> Hypotension (SBP ≤ 90mmhg) {treated by incremental doses of ephedrine 5mg intravenous bolus}.

> Bradycardia (HR ≤ 60) {treated with iv atropine 0.6 mg}.

> Respiratory depression (Absence of respiration ≥ 30 seconds/manual ventilation to maintain SpO2 ≥ 95%)
> Sedation: Assessed by a 5 point sedation scoring given by Yeager in 1987 along with other variables throughout the study period.

Score	
0	Alert conversant
1	Mildly sedated
2	Moderately sedated and drowsy
3	Asleep but arousable
4	Asleep not arousable

6. Duration of analgesia: Pain intensity was assessed with the help of Linear Visual Analogue Scale (VAS) using a 10 centimeter line; 0 denoting 'No Pain' while 10 denoting 'worst possible pain' (Stolting RK 1999). Duration of analgesia was taken as time period till VAS of 4 was recorded.
7. Post operative parameters: SBP, DBP, MAP, SpO_2, RR and Sedation score will be recorded 15, 30, 60 and 120 minutes post operatively.
8. Incidence of other side effects seen with epidural drug administration like pruritus, nausea, vomiting, urinary retention, respiratory depression and any other symptom was also recorded throughout the study period and appropriate treatment provided.

OBSERVATIONS

The present study was conducted with an aim to evaluate the analgesic efficacy and safety of neostigmine, clonidine and dexmedetomidine when used epidurally as adjuvants to 0.5% bupivacaine. 80 patients of either sex ranging in age from 18-60 years, belonging to ASA I and II grades, undergoing lower limb and lower abdominal surgeries were included in study. The various parameters like age, weight, height, sex and type of surgery in the patients of all the groups were comparable. No statistical difference was observed in any of these characteristics. The hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded in the preoperative period (baseline) and then at start of procedure & every 2 minutes for the first 10 minutes followed by every 10 minutes thereafter. The four groups were found to be statistically comparable as regards the distribution of baseline hemodynamic characteristics.

Intra-operative characteristics:

Hemodynamic variables are depicted in tables given below.

TABLE 1: INTRAOPERATIVE SYSTOLIC BLOOD PRESSURE (SBP) MEASUREMENTS

Time (Minutes)	SYSTOLIC BLOOD PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
0	128 +10.00	123.15 +9.59	124.55 +8.60	126.45 +8.45	0.36 NS
2	127.85 +9.32	122.95 +10.14	121.6 +11.89	126.15 +12.45	0.26 NS
4	125.3 +10.54	122.15 +9.58	119 +14.32	124 +10.24	0.32NS
6	120.3 +10.39	121 +7.71	113.7 +13.46	119.75 +10.48	0.12 NS
8	116.5 +12.49	117.15 +10.02	112.85 +12.09	117.2 +7.46	0.52 NS
10	114.45 +11.29	116.85 +11.29	109.9 +9.71	114.1 +10.89	0.24 NS
20	119.75 +10.93	118.4 +8.31	112.35 +8.69	114.65 +12.44	0.09NS
30	121.9 +8.54	119.45 +7.96	111.8 +8.61	111.8 +12.27	0.0009 S
40	123 +9.76	119.8 +8.16	109.95 +9.13	108.65 +10.99	0.0001 H/S
50	123.8 +9.33	119 +8.15	109.2 +10.93	106.95 +10.77	0.0001 H/S
60	124.6 +8.80	119.45 +7.78	111.2 +10.62	107.3 +11.25	0.0001 H/S
70	125.6 +10.35	108.7 +9.20	113.66 +8.93	121.05 +7.09	0.0001 H/S
80	125.3 +9.15	121.94 +6.97	111.5 +10.04	107.68 +11.24	0.0001 H/S
90	125.05 +9.64	129.94 +8.01	111 +7.84	109.44 +13.26	0.0001 H/S
100	122 +9.79	123 +7.79	109.27 +7.08	113.18 +13.53	0.001 S
110	120.9 +8.82	121.21 +6.65	110.66 +6.96	114.71 +10.40	0.01 S
120	117.88 +9.22	120.18 +6.25	111.44 +7.63	113 +4.35	0.16 NS

P > 0.05 – Not Significant,
NS: Not Significant,
S: Significant,
H/S: Highly Significant

The above table shows that there was a significant difference in the SBP starting at 30 minutes and upto 110 minutes of surgery among the four groups. In intergroup comparison, there was no

statistically significant difference between the groups B and BN (p> 0.05), while there was significant difference between groups B and BC; and groups B and BD. There was no statistically significant difference between BC and BD in regards to the intra operative SBP measurements.

TABLE 2: INTRAOPERATIVE DIASYSTOLIC BLOOD PRESSURE (DBP) MEASUREMENTS

Time (Minutes)	DIASYSTOLIC BLOOD PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
0	81.2 +7.2	79.8 +6.25	78.6 +9.01	77.35 +7.47	0.47 NS
2	82 +7.58	80.2 +8.27	75.35 +11.11	77 +7.58	0.07 NS
4	79.8 +8.1	75.55 +9.08	73.25 +9.18	74.85 +8.83	0.04 NS
6	77.75 +8.5	76.1 +9.14	71.8 +7.50	73.7 +7.90	0.121 NS
8	75.15 +11.46	76.1 +8.49	70.95 +9.42	70.75 +6.78	0.14 NS
10	76.55 +8.49	74.75 +8.45	67.1 +8.89	69.55 +7.63	0.001 S
20	78.9 +7.5	73.45 +8.58	68.15 +8.56	69.45 +8.58	0.004 S
30	79.9 +7.34	74.35 +7.92	67.1 +9.10	69 +8.75	0.0001 H/S
40	79.9 +7.15	76.8 +7.99	68.1 +7.52	68.9 +8.56	0.0001 H/S
50	81.45 +6.33	76.45 +8.08	68.15 +10.66	67.4 +9.49	0.0001 H/S
60	81.05 +6.59	77.35 +7.86	68.21 +8.24	66.7 +11.94	0.0001 H/S
70	82.15 +6.96	77.45 +7.39	69.42 +8.39	70.3 +7.87	0.0001 H/S
80	81.7 +6.75	78.2 +7.83	70.52 +9.42	67.78 +10.96	0.0001 H/S
90	81.41 +6.27	77.42 +7.95	69.93 +9.08	66.57 +11.98	0.0001 H/S
100	80.46 +7.3	77.52 +8.8	68.92 +8.76	68.36 +11.01	0.001 S
110	77.81 +8.26	76.58 +7.65	70 +11.93	70.66 +8.35	0.135 NS
120	77.7 +8.3	75.91 +7.15	70.37 +7.22	76.66 +10.42	0.27 NS

P > 0.05 – Not Significant,
NS: Not Significant,
S: Significant,
H/S: Highly Significant

The above table shows that there was no significant difference in the DBP AT 0 to 10 minutes intraoperatively. After 10 minutes, there was a statistically significant difference between the groups in the DBP measurements upto 100 minutes of the surgery. Among intergroup comparison, there was no difference between groups B and BN; and groups BC and BD, whereas there was statistically significant difference between B & BC; and groups B and BD.

TABLE 3: INTRAOPERATIVE MEAN ARTERIAL PRESSURE (MAP) MEASUREMENTS

Time (Minutes)	MEAN ARTERIAL PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
0	96.95 +8.75	95 +8.29	89.2 +9.34	90 +7.85	0.01S
2	97.1 +7.22	94.8 +8.81	86.45 +10.74	91.5 +7.90	0.001 S
4	95.55 +7.84	92.7 +9.05	84.9 +10.49	89.65 +7.78	0.002 S
6	91.9 +9.74	90.4 +8.53	82.85 +8.76	89.05 +8.28	0.01 S
8	87.9 +11.45	89.4 +8.43	82.6 +9.43	85.55 +6.87	0.11 NS
10	87.59 +9.41	86.55 +10.97	80.3 +8.65	84.7 +7.84	0.06 NS
20	91.85 +7.86	88.85 +7.15	78 +9.14	84.55 +8.89	0.0001 H/S
30	92.45 +7.30	88.85 +7.15	78 +9.14	84.55 +8.89	0.0001 H/S
40	94.2 +7.06	91.5 +7.85	78.85 +9.73	81.3 +8.82	0.0001 H/S
50	94.55 +7.07	91.15 +7.56	80.1 +8.52	78.55 +10.12	0.0001 H/S
60	94.7 +6.66	92.7 +7.12	82.78 +7.53	80.4 +10.20	0.0001 H/S
70	97.2 +7.31	93.78 +6.16	79.11 +9.36	79.75 +9.45	0.0001 H/S
80	96.05 +7.29	93.05 +7.08	80.68 +8.05	77.1 +9.98	0.0001 H/S
90	96.06 +7.47	93 +8.41	83.4 +7.19	77.5 +10.42	0.0001 H/S
100	95 +7.73	93.07 +7.63	78.76 +6.74	79 +10.76	0.0001 H/S
110	93.33 +8.20	92.72 +6.73	79.88 +6.52	79.66 +7.44	0.0001 H/S
120	92.5 +7.81	92.72 +6.73	80.75 +8.22	84.2 +5.21	0.003 S

P > 0.05 – Not Significant, NS: Not Significant, S: Significant, H/S: Highly Significant

The above table shows that the MAP measurements at 0.2, 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes intra operatively. The table shows that there was significant difference in the MAP readings between the four groups from the start of surgery. The values at 8 and 10 minutes intraoperatively are insignificant. In intergroup comparison, there was no difference between groups B and Bn; and BC and BD. There was statistically significant difference between groups B and BC at all times intra operatively whereas there was no difference between group B and BD till 20 minutes of surgery after which the difference was statistically significant.

Post-operative characteristics: depicted in tables below

TABLE 4: SYSTOLIC BLOOD PRESSURE (SBP) CHANGES IN POST OPERATIVE PERIOD

Time (Minutes)	SYSTOLIC BLOOD PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
15	125.7 +8.93	122.55 +7.89	112.95 +7.27	111.7 +10.54	0.0001 H/S
30	125.6 +9.01	122.95 +7.89	115.4 +6.15	112 +8.84	0.0001 H/S
60	125.7 +9.95	123.05 +7.98	115.1 +7.92	111.9 +8.44	0.0001 H/S
120	126.15 +8.91	123.2 +8.56	117.75 +4.32	113.35 +6.77	0.0001 H/S

P > 0.05 – Not Significant, H/S: Highly Significant

The above table shows that there was statistically significant difference in the SBP measurements at 15, 30, 60 and 120 minutes post operatively among the four groups. The difference was statistically significant between groups B and BC; and B and BD. Groups B and BM; and BC and BD were comparable in their SBP readings post operatively

TABLE 5: DIASYSTOLIC BLOOD PRESSURE (DBP) CHANGES IN POST-OPERATIVE PERIOD

Time (Minutes)	DIASYSTOLIC BLOOD PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
15	81.3 +5.83	78.55 +7.91	70.6 +7.76	70 +10.25	0.0001 H/S
30	81.95 +6.42	79.05 +7.63	72.55 +7.74	68.7 +9.45	0.0001 H/S
60	81.6 +5.44	79 +7.53	73.95 +5.97	70.65 +8.34	0.0001 H/S
120	81.35 +6.87	80 +8.09	74.8 +7.18	71.3 +7.16	0.0001 H/S

P > 0.05 – Not Significant, H/S: Highly Significant

The above table shows that there was statistically significant difference in the SBP measurements at 15, 30, 60 and 120 minutes post operatively among the four groups. The difference was statistically significant between groups B and BC; and B and BD. Groups B and BN; and BC and BD were comparable in their SBP readings post operatively.

TABLE 6: MEAN ARTERIAL PRESSURE (MAP) CHANGES IN POST-OPERATIVE PERIOD

Time (Minutes)	MEAN ARTERIAL PRESSURE (mmHg) Mean + SD				P value
	Group B	Group BN	Group BC	Group BD	
15	96.65 +7.02	93 +7.60	81.45 +9.76	80.2 +8.42	0.0001 H/S
30	96.2 +6.82	93.55 +7.30	81.4 +7.71	80.45 +9.04	0.0001 H/S
60	95.75 +6.46	94 +7.13	83.5 +8.62	81.85 +10.08	0.0001 H/S
120	96.95 +6.29	94.35 +7.84	84.7 +7.31	81.35 +8.00	0.0001 H/S

P > 0.05 – Not Significant,
H/S: Highly Significant

The above table shows that there was statistically significant difference in the MAP measurements at 15, 30, 60 and 120 minutes post operatively among the four groups. The difference was statistically significant between groups B and BC; and B and BD. Groups B and BN; and BC and BD were comparable in their MAP readings post-operatively.

Analgesia:

TABLE 7: TIME TO REACH THE HIGHEST LEVEL OF SENSORY BLOCKADE (IN MINUTES)

TIME TO REACH THE HIGHEST LEVEL OF SENSORY BLOCKADE	Group B	BN	BC	BD	P value	F value
Time (Minutes)	11.52	13.6	8.2	7.35	0.0001 H/S	36.48
Mean+ SD	+1.12	+2.27	+2.06	+2.25		

H/S: Highly Significant

Time to reach the highest level of sensory blockade in group B was 11.52+1.12min.
Time to reach the highest level of sensory blockade in group BN was 13.6+2.27min.
Time to reach the highest level of sensory blockade in group BC was 8.2+2.06min.
Time to reach the highest level of sensory blockade in group BD was 7.35+2.25min.

The difference was found out to be statistically highly significant among the four groups.

TABLE 8: HIGHEST LEVEL OF SENSORY BLOCK OBTAINED IN THE FOUR GROUPS

HIGHEST LEVEL OF SENSORY BLOCK	Group B	BN	BC	BD
T11/12	2	2	0	0
T10/9	10	15	3	2
T8/7	7	3	14	14
T6/<	1	0	3	4

For the purpose of statistical analysis block level was divided as higher than T 10 and < T10.

The patients in groups B and BN showed a significantly lower level of sensory block when compared to the other two groups. The difference was found to be statistically highly significant on comparing groups BC and BD to the control group, whereas insignificant between BN and control group. On inter group comparison; there was no statistically significant difference between BC and BD, whereas the difference was statistically significant between groups BC and BN; and BD and BN.

TABLE 9: HIGHEST LEVEL OF MOTOR BLOCK (MODIFIED BROMAGE SCALE) OBTAINED IN THE FOUR GROUPS

MODIFIED BROMAGE SCALE	Group			
	B	BN	BC	BD
0	0	0	0	0
1	0	0	0	0
2	11	16	6	5
3	9	4	14	15

χ^2 =14.95; P= 0.001 S (Significant)

11 patients in group B, 16 in group BN, 6 in group BC and 5 in group BD had a motor blockade of scale 2.

The absolute numbers of patients with motor block of scale 3 were proportionately larger in group BC (14) and BD (15) as compared to groups B (9) and BN (4). On statistical analysis, there was significant in between BC and BD when compared to the control group. No significant difference was found between groups B and BN.

On intergroup comparison, the difference was statistically significant between BC and BN, BD and BN; whereas insignificant between BC and BD.

TABLE 10: DURATION OF ANALGESIA (IN MINUTES)

	Number of Patients				F Value	P Value
	GROUP B n=20	GROUP BN n=20	GROUP BC n=20	GROUP BD n=20		
Mean	188.55	252	335.3	455.5		
SD	+16.76	+43.48	+69.76	+75.08		
Range	138-210	168-330	200-450	300-580	84.94	0.0001 H/S

H/S (Highly Significant) S.D: Standard Deviation

Duration of sensory block (in minutes) was found to be statistically different between the four groups with Dexmedetomidine having the longest duration of analgesia.

The duration of analgesia in B group was 188.55 + 16.76 minutes
BN group was 252 + 43.48 minutes
BC group was 335.3 + 69.76 minutes
BD group was 455.5 + 75.08 minutes

TABLE 11: INCIDENCE OF COMMON SIDE EFFECTS AMONG THE FOUR GROUPS:

SIDE EFFECTS	Number of Patients			
	GROUP B n=20	GROUP BN n=20	GROUP BC n=20	GROUP BD n=20
Hypotension SBP< 90mm Hg	1	1	7*	6*
Bradycardia HR< 50/Min	0	0	2	2
Respiratory Depression SPO_2 < 95% OR RR < 10/ Min	0	0	0	0
Sedation Score 1 2/>	 0 0	 0 0	 8* 4	 12* 6
Nausea / Vomiting	0	0	0	0
Pruritus	0	0	0	0
Urinary retention	0	0	0	0

*P< 0.05 S: Significant

No significant side effect in the form of bradycardia, respiratory depression, nausea / vomiting, pruritus or urinary retention was observed in any of the four groups.

7 patients in group BC and 6 patients in group BD developed hypotension requiring intervention as compared to 1 patient each in groups B and BN. The difference was found to be statistically significant in groups BC and BD when compared to the control group and insignificant between group BN and the control group. On intergroup comparison, there was no statistical difference between groups BC and BD whereas there was statistically significant difference between BC and BN; and BD and BN groups

2 patients each in group BC and BD developed bradycardia requiring intervention but the overall incidence was found to be insignificant as compared to the other two groups

8 and 12 patients in groups BC and BD respectively had a mild sedation (score 1) while as 4 patients in group BC and 6 patients in group BD had a sedation score of 2. The difference was found to be statistically significant ($p < 0.050$) when compared to the other two groups in which none of the patients had sedation. There was no statistical difference between groups BC and BD

DISCUSSION

The challenge of modern anaesthesia and perioperative medicine is to create efficient treatment regimens with optimal balance between protective and unwanted effects, in order to ensure patient safety and comfort, and to facilitate recovery.

Pre-emptive analgesia is the administration of an analgesic before a painful stimulus, such as tissue injury during surgery, in an attempt to obtain better pain relief compared with when the same analgesic intervention is used after the painful stimulus. The concept was propounded in the early 1980s when experimental studies showed that measures to antagonize the nociceptive signals before injury prevented central hyper-sensitization, thereby reducing the intensity of pain following the injury (Woolf CJ, 1983). Accordingly, the use of long acting analgesic agents before surgery can avert the establishment of a sensitized state in the peripheral nervous system, greatly diminishing the degree and persistence of postoperative pain.

Postoperative analgesia provides not only pain relief but also inhibits trauma induced nociceptive impulses to blunt autonomic reflexes. It allows the patients to breathe and move freely to enhance early restoration of function (Ready LB, 1998).Treatments are evaluated not only according to their ability to provide satisfactory analgesia but also by their ability to promote recovery and rehabilitation. Epidural analgesia has been shown: to promote early-mobilization and reduce rehabilitation time (Singleyn FJ et al, 1998; Gootschalk A et al, 1998); to limit pulmonary morbidity (Ballantyne JC et al, 1998; Rigg J et al, 2002); to promote early extubation of the trachea after major thoracic surgery (Beattie W et al, 2001; Priestley MC et al, 2002); to reduce the incidence of cardiac ischaemia and arrhythmias in high risk patients (Beattie W et al, 2001); and to reduce postoperative ileus thereby reducing hospital stay (Carli F et al, 2001).

Blood pressure-

A general trend was towards fall in the blood pressure parameters in all the groups peaking between 10 -20 minutes of epidural blockade. The blood pressure stabilized to prefall values after this time interval and remained stable throughout the observation period in the groups B and BN. The patients in group B and BN remained hemodynamically stable throughout the intra operative period and were comparable regarding the hemodynamic parameters like SBP, DBP, MAP and HR throughout the duration of surgery. Only one patient each in group B and BN developed hypotension, requiring intervention. This finding was in accordance with the finding of Hellman, 1965 who found an overall incidence of 1.3% hypotension while reviewing 26.127 epidural blocks.

Hypotension, one of the common side effects of neuraxial (spinal/epidural) blocks occurs due to the paralysis of the preganglionic sympathetic nerves with arteriolar dilatation and compensatory vasoconstriction elsewhere, a fall in venous return due to vasodilatation causing a fall in cardiac output; block of preganglionic nerve fibers to adrenal medulla and psychic influences. To these basic physiological changes must be added, the effect of operation, the patient age and preoperative circulatory volume (Morris and DDB, 1972).During epidural blockade, the hypotension is slower in onset and blood pressure reaches lower limits more gradually than spinal blockade because the local anaesthetic has more distance to travel and has more obstacles in its spread from site of injection to final area of action (Massey Dawkins, 1969; Stanton-Hicks, 1975).

The lower incidence of this side effect in our study was probably due to adequate preloading of the patients prior to the block and the fact that no patient had an excessive cervical spread of block. The findings are in accordance with those of Lauretti GR et al, 2000; Nakayama M et al, 2001; Roelants F et al, 2003; Kaya FN et al, 2004; Roelants F et al, 2004; Tekin S et al, 2006 and Vermon H et al, 2009 who found no significant hemodynamic change on addition of neostigmine as compared to their control groups while providing epidural anaesthesia.

7 patients in clonidine group and 6 in the dexmedetomidine group developed hypotension as shown by the reduction in the SBP, DBP and MAP readings intraoperatively and there was statistically significant difference in comparison to the control and the neostigmine group. The clonidine and the dexmedetomidine groups were comparable in their hemodynamic characteristics intra operatively. The hypotension responded well to fluid administration and intravenous mephentermine supplementation in all the cases. These findings are consistent with those of De Kock M et al, 1993; Eisenach JC et al, 1995; De Kock M et al, 1997; Fukushima K et al,1997; Schnaider et al, 2005; Guler G et al, 2005 and Dobrydnjov I et al, 2005; who found significant hemodynamic effect on addition of clonidine and dexmedetomidine through the epidural route when compared to their respective control groups.

Heart rate-

A total of 2 patients in both clonidine and dexmedetomidine groups developed heart rate of <50 beats per minute requiring atropine bolus. No patient in the control or neostigmine group developed bradycardia. On inter group comparison, the results were found to be insignificant statistically.

The action of alpha$_2$ -adrenergic agonists on myocardial performance is complex. Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by a vagomimetic effect. Although clonidine depresses atrioventricular nodal conduction, severe bradyarrhythmias are rare with chronic clonidine use (Ferder L, 1987). By reducing afterload, cardiac output may increase after clonidine treatment in some patients, including those with heart failure, whereas by reducing heart rate, it may reduce cardiac output in other patients (Masotti G, 1984). Clonidine may reduce myocardial oxygen demand and has been shown to reduce infarct size when administered to patients in the acute phase of myocardial infarction (Zochowski RJ, Lad a W, 1986). Delayed onset of hypotension has not been observed with use of clonidine for analgesia alone or in combination.

The sympatholytic effect of dexmedetomidine decreases heart rate and blood pressure by reducing noradrenaline release (Wong DL, 1997). A major advantage of dexmedetomidine is its higher selectivity compared with clonidine for α-2a receptors responsible for the hypnotic and analgesic effect of such drugs (Asano T,

2000; Alves TCA, 2000 and Bagatini A 2002).

Sensory block-

The mean time in minutes for establishment of highest level of sensory block was found to be 10.9 ± 1.24 minutes in group B; 12.9 ± 2.84 minutes in group BN; 8.2 ± 2.01 minutes in group BC; 7.35 ±2.19 minutes in group BD. The difference was found to be statistically significant ($p < 0.0001$). On intergroup comparisons, the time in minutes for establishment of highest level of sensory block was found to be significantly decreased in the dexmedetomidine and clonidine group when compared with neostigmine and the control group. No significant difference was found in clonidine and dexmedetomidine groups on intergroup comparison.

The difference in highest level of sensory blockade obtained between the four groups was again found to be statistically significant ($p<0.05$) and addition of clonidine and dexmedetomidine was found to have a higher levels of blockade. The number of patients reaching a sensory level of higher than T10 at 20 min was 15, 7, 17 and 18 in group B, BN, BC and BD respectively. Thus, a significant number of patients had a higher level of sensory block in clonidine and dexmedetomidine groups as compared to the control group. The patients in the neostigmine group had a significantly lower level of block as compared to the rest of the three groups and the difference between groups B and BN was statistically insignificant. The results are in accordance with those of Singelyn FJ et al, 1992; Singelyn FJ et al, 1996; Butterwort F et al, 1993; Mizobe T et al, 1995 that showed that sensory blockade effects of local anesthetics are enhanced by clonidine.

Motor block-

The highest level of motor block obtained was also found to be relatively lower in control and neostigmine groups as compared to other two groups. 11 patients had a modified Bromage scale of 3 in control group, 6 patients with a modified bromage scale of 3 in the neostigmine group as compared to 14 and 15 patients in the clonidine and dexmedetomidine groups respectively and the difference was not found to be statistically significant ($p<0.05$). The results are in accordance with those of Singelyn FJ et al, 1992; Singelyn FJ et al, 1996; Butterwort F et al, 1993; Mizobe T et al, 1995 that showed that motor and sensory blockade effects of local anesthetics are enhanced by clonidine. Sukhwinder et al, 2010 also showed that the onset of anesthesia was shorter in clonidine group as compared to ropivacaine alone. The establishment $_0$f complete motor blockade was also much earlier in the clonidine group which was again statistically significant *(P* < 0.05).

Clonidine augments the action of local anesthetics in regional blockade by interrupting the neural transmission of painful stimuli in Aδ and C fibres and by increasing the conductance of K^+ ions in nerve fibres. It also exerts a vasoconstricting effect on smooth muscles, which results in a decreased absorption of the local anesthetic drug and eventually prolongs the duration of analgesia (Butterwort et al, 1993; Mizobe T et al, 1995).

Analgesia-

The duration of analgesia, as defined by time to reach a VAS of 4, was found to be significantly different between the four groups. The mean duration of analgesia in different groups was found to be 118.15 ± 17.62 minutes in group B, 251.6±42.82 minutes in group BN; 335.3±69.09 minutes in group BC and 455.5±72.21 minutes in group BD. The duration was significantly prolonged in all the study groups as compared to the control group. On intergroup comparisons the difference in total duration of analgesia was found to be statistically significant among the groups. The maximum prolongation was seen in the BD group followed by BC group and then the group BN.

Lauretti et al., 1999 have proven that epidural neostigmine in lignocaine produces dose independent analgesia. Our results are

in accordance with Tekin S et al, 2006 who showed that 4µg/kg neostigmine with 0.125% bupivacaine delivered by the patient controlled analgesia method can be safely used in post operative analgesia, after gynaecologic surgery, without any increase in side effects. Ivani G, De Negri P, Conio A, et al, 2000 showed that addition of clonidine 2 µg/kg to ropivacaine 0.1% (1 ml/kg) resulted in better postoperative analgesia than ropivacaine 0.2% alone (1 ml/kg). This combination was not associated with significant sedation or motor block.

Our results are also in accordance with those of Antonio MV et al, 2004; Paula F et al, 2005; Salgado PF et al, 2008; Saadawy I et al, 2008; El Hennawy et al, 2009; Mason LJ et al. 2009; Mausumi N et al, 2010 that showed a similar prolongation of post operative analgesia with the use of epidural dexmedetomidine.

Our study results are in accordance with Toshio A et al, 2000 who studied the antinociceptive and hemodynamic effects of clinically available α-2 adrenoceptor agonists to their binding affinity for α-2 adrenoceptors in the spinal cord and brain in rats. The spinal antinociception caused by the epidural administration of α-2 agonists is well correlated with their binding affinity to spinal α-2 adrenoceptors. Their results showed that rank order for the antinociceptive effects of spinally administered α-2 agonists seems to be dexmedetomidine more than clonidine which can explain the longer duration of analgesia by dexmedetomidine. Our results are in contrast with those of Antonio MV et al, 2004 who concluded that the association of clonidine 150 µg or dexmedetomidine 2 µg/kg along with local anaesthetic induces analgesia and sedation and clonidine promotes prolonged analgesia than dexmedetomidine. El Hennawy et al, 2009 and Mausumi Neogi et al, 2010 had not found any statistically significant difference between dexmedetomidine and clonidine as regards analgesia time.

Respiratory depression:

In our study, we monitored respiratory rate and oxygen saturation (SpO_2) during the entire observation period. In our study, none of the patients in any of the four groups had respiratory rate of <10/ minute and SpO_2 <95%. These observations assert the absence of respiratory depression with all the four drugs. Alpha 2 -adrenergic agonists alone do not induce profound respiratory depression, even after massive overdose (Marruecos L, Roglan A, Frati ME, Artigas A, 1988) nor do they potentiate respiratory depression from opioids (Bailey PL, 1991; Ooi R, 1991).Our results are similar to that of Upadhyay K 2005 andEl Hennawy et al, 2009 who showed that there was no statistically significant respiratory depression with the use of clonidine and dexmedetomidine.

Sedation:

A total of 8 patients in group BC (40%) and 12 patients in group BD 60%) developed sedation score of 1 during the study period and 4 and 6 patients in BC (20%) and BD (30%) respectively developed a sedation score 2. The difference was found to be statistically significant ($p< 0.05$) when compared to the other two groups in which none of the patients had sedation. There was no statistical difference between groups BC and BD.

None of the patients in the neostigmine group had any sedation. This result is in contrast with the study of Kaya FN, 2004 that showed that sedation occurred with the administration of neostigmine as an epidural bolus. Vermon et al, 2009 also found out that administered as a bolus or by continuous infusion, neostigmine can lead to mild sedation.

Sedation commonly accompanies the use of clonidine for regional anesthesia, by actions in the locus coeruleus (Maze M, Tranquilli W, 1991). This brainstem nucleus is associated with a wide variety of physiologic regulatory processes, including regulation of sleep and wakefulness, and is inhibited by α-2 adrenergic agonists via a G-protein mediated mechanism that involves inhibition of adenylate cyclase

(Maze M, Tranquilli W, 1991). Hall JE et al, 2001 showed that clonidine infusions have significant pharmacologic activity that results in progressive sedation.

Sedation with dexmedetomidine is *Active sedation* which is characterized by allowing a focused and reactive patient prepared to respond lucidly to commands. Our results are in accordance with those of Mauro VA et al, 2004 and Brandao ST et al, 2005 which showed that dexmedetomidine 2µg/kg epidurally increases the duration of analgesic quality and causes sedation without respiratory depression. SA Oriol Lopez et al, 2008 similarly showed that dexmedetomidine given epidurally at 1 µg/kg plus local anaesthetic is an alternative to achieve an anaesthetic quality that enables us to keep the patient in a state of *active sedation,* which reduces the likelihood of respiratory depression, which can arise when other adjuvants drugs are administered intravenously.

None of the patients included in our study developed any complaints in form of pruritus, urinary retention or nausea/vomiting in the observation period of the study which are some of the common side effects expected with use of neuraxial opioids. Thus, significant prolongation of epidural block duration by addition of adjuvants like neostigmine, clonidine and dexmedetomidine without addition of unwanted side effects as compared to control group is a potential advantage for the patient and the care takers as well, that can be successfully exploited in day to day anaesthetic practice. This long duration of analgesia allowed better patient satisfaction and decreased use of postoperative analgesics. The uses of these non opioid adjuvants prolonged the post operative analgesia and hence, have a opioid sparing effect as the use of epidural opioids is always associated with increased incidence of unwanted side effects.

CONCLUSION

While comparing Control group with Clonidine, Neostigmine and Dexmedetomidine groups, it was found that addition of Clonidine and Dexmedetomidine to epidural bupivacaine led to faster onset of higher sensory level with overall higher levels of sensory and motor blocks. The control and Neostigmine groups remain comparable in the above parameters with each other and so were the Clonidine and Dexmedetomidine groups. The addition of neostigmine, clonidine and dexmedetomidine was associated with a significant prolongation of duration of analgesia as compared to epidural bupivacaine alone. The prolongation was maximum in Dexmedetomidine group followed by Clonidine and then the Neostigmine group.

The Neostigmine and the control group remained hemodynamically stable throughout the study period and were also comparable to each other. 7 patients in clonidine group and 6 patients in Dexmedetomidine developed hypotension requiring intervention. The difference was found to be statistically significant in groups BC and BD when compared to the control group. On intergroup comparison, there was no statistical difference between groups BC and BD whereas there was statistically significant difference: between BC and BN; and BD and BN groups. 2 patients each in group BC and BD developed bradycardia requiring intervention but the overall incidence was found to be insignificant as compared to the other two groups. No patient in either control or Neostigmine group developed bradycardia.

8 and 12 patients in Clonidine and Dexmedetomidine group respectively had a mild sedation (score 1) while as 4 patient in group Clonidine and 6 patients in group Dexmedetomidine had a sedation score of 2. The difference was found to be statistically significant when compared to the other two groups in which none of the patients had sedation. There was no statistical difference between Clonidine and Dexmedetomidine groups. This sedation can be considered as a beneficial effect as it leads to better patient satisfaction and comfort during anaesthesia.

From our study, it can be concluded that for lower limb and lower abdominal surgeries, addition of neostigmine, clonidine and dexmedetomidine to epidural bupivacaine significantly prolongs its duration of analgesia as compared to bupivacaine alone. The addition of neostigmine has the least prolongation of analgesia with no side effects like hypotension, sedation and respiratory depression. Clonidine has better analgesia than neostigmine with the side effect of hypotension and sedation. Dexmedetomidine leads to maximum prolongation of analgesia with active sedation with the side effect of hypotension.

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