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COMBINED USE AND COMPARISON OF LOCAL ANAESTHETIC AND ANALGESICS EPIDURALLY IN OPERATIVE AND POST-OPERATIVE PAIN MANAGEMENT

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ABSTRACT

With a noble intention to reduce postoperative pain of our patients in the study "Combined use and comparison of local anaesthetic and analgesicsepidurally inoperative and post-operative pain management" was carried out at the department of Anaesthesiology, KPC medical college and hospital, Kolkata, to observe potency and duration of analgesic action of these drugs when administer epidurally along with local anaestheticdrug and comparative study in between them.
One hundred twenty patients in total with physical status of ASA Grade-I and II, scheduled for lower limbs and urogenital surgery were randomly allocated to six groups with equal number-i.e. twenty (20) in each group. Group-B (n=20) received only bupivacaine (2 mg/Kg; plain (0.5%) as a single-shot epidural injection; Group-BC received bupivacaine as per Group-B plus clonidine (3 µg/Kg) as a single-shot epidural injection; Group-BN received bupivacaine plus neostigmine (5 µg/Kg); Group-BF received bupivacaine plus fentanyl (1 µg/Kg); Group-BK received bupivacaine plus ketamine (0.5 mg/Kg) and Group-BM received bupivacaine plus midazolam (0.05 mg/Kg) as a single shot epidural injection and all additives used epidurally, preservative free (in all groups). The patients were monitored intra-operatively from the beginning to end of anaesthesia and post-operatively in terms of pulse rate, blood pressure, pain VAS-score, peripheral oxygen saturation (SpO_2), capnography (E_TCO_2), peripheral and central (core) temp.(^oC), degree of motor blockade, sedation score, amnesia, post-operative nausea and vomiting(PONV) and other side effects at a frequent intervals. Post-operatively in post-anaesthesia care unit (PACU) all vitals (specially BP, HR, RR, temp.) along with pain-VAS, Sedation Score, Bromage Score, SpO_2, E_TO_2 and other effects of the individual administered drug also monitored. These assessment were done in PACU at 1st, 2nd, 4, 6, 8, 10, 12, 16, 18, 24th post-operative hour. Fasteronset, better operative relaxation and good post-operative analgesia are achieved by clonidine-bupivacaine group. Prolonged post-operative sedation and analgesia is achieved by midazolam-bupivacaine group.

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INTRODUCTION

Epidural narcotics have been widely used to relieve pain and provide post-operative analgesia following initial reports of their clinical efficacy in 1979.Intrathecal and Epidural narcotics have the appeal of ease of administration, either at the time of spinal and, or epidural local anaesthetic injection for Surgical anaesthesia or as a separate technique of providing analgesia when general anaesthesia is administered. Although this method of pain relief has shown good results in clinical practice, the most serious of which appears to be delayed respiratory depression, the other major problems with neuraxial opioids is developments of tolerance and inefficiency against certain types of pain. Hence, some newer drugs of different chemical structures and different mode of actions are being tried and introduced either intrathecally or epidurally.

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Few such drugs are Fentanyl (Eisenach *et al*., 1994; Kizilarslan and Kuvaki, 2000), Midazolam (Rigoli, 1983; Gülec *et al*., 1998), Ketamine (Ravat, 1987; Johnston *et al*., 1999), Clonidine (Eisenach *et al*., 1993; Eisenach *et al*., 1994; Kizilarslan and Kuvaki, 2000), Neostigmine5, (Abdulalif and El-Sanabary, 2002).

MATERIALS AND METHODS

Sample Size

As per the study by Sawhneyet. al[11]68% subjects did not require any rescue analgesic in Group-I (epidural infusion of ropivacaine 0.2 %) which was higher than that of Group II (epidural infusion of a solution of ropivacaine 0.1 % with fentanyl 2μg/ml) which was 48.0% in Group-II.Thus there was a need of a total 120 patients with 89% power at 95% confidence level. 120 patients were assigned in total to 6 groups[i.e. group-B(20), group-BC(20),group-BK(20),group-BN(20),group-BF(20)and group-BM(20)] in the ratio 1:1:1:1:1:1 randomly. Thus the required sample size for each group was 20 and total sample size was 120 patients with 89% power at 95% confidence level.

Sampling Technique

The patients were selected randomly and assigned into six groups with the help of random numbers. The random numbers were taken from Kevin Conroy: 5120 Random Numbers (<5k, 2002) [Call the JavaScript pseudo-random number generator.] Website: RandomNumber.org, 2004. After the study protocol was approved by the Ethical Clearance Committee of the KPC Med. Coll. and Hosp, 120 total patients undergoing lower limbs and Uro-genital surgery were studied. Every patient was fully explained about the anaesthesia and surgical procedure and they gave signed consent before inclusion in the study. The patients were in the 25-65 years age group and belonged to the American Society of Anesthesiologists (ASA) physical status Class-I or II. Study design was prospective, randomized, and double blind technique. All the postoperative variables were assessed by the same post-anaesthesia care unit person, who was unaware about the anaesthesia technique and drugs used for the patients, to avoid individual variation in the assessment.

The patients were randomly allocated to six groups by (Group B, BC, BN, BK, BM and BF) with equal numbers (n=20).The randomization of all samples was putting the names of six groups in a basket, and then drawing one ticket without replacement for each patient. Patients were excluded from the study if they have a history of allergy or contraindication to any of the study drugs, pregnant or nursing mother, any evidence of major cardiovascular, pulmonary, hepatic, renal, endocrinal or metabolic disorder, suffering from bleeding diathesis and neurological disorders would be excluded from surgery, patient with gross spinal abnormality and on chronic analgesic therapy and under sedation were excluded.

Preparation

After fasting for at least 6-8 hours all the patients did not receive any sedatives, anxiolytics or analgesics oral or parenteral on the day of surgery. Those patients, who were very much anxious, received low doses of anxiolytics and on intravenous maintenance fluid during fasting hours.

Anaesthesia Techniques

In pre-operative holding area, a large bore (18G) intravenous (IV) line was inserted in the dorsum of hand and all the patients were hydrated with Lactated Ringer's Solution calculated on the basis of body weight of the patients and hours of pre-anaesthetic fasting. Monitors like pulse oximeter, non-invasive blood pressure (NIBP), Electrocardiogram (ECG), Temperature probe (^oC) and Capnography (E_TCO_2) were attached before induction of anaesthesia (epidural blockade) to see the baseline parameters. All epidural punctures were performed in the lateral (left or right) position with an (18G) Tuohy-needle, using the midline approach at the L_{2-3} intervertebral space. Then all the patients received epidural drugs [either local anaesthetic and, or additives (analgesics)] according to their groups.

Group-B: This was the control group. After noting the baseline parameters, this group of patients received only Bupivacaine (0.5%) plain solution with a 2 mg/Kg body weight as a single-shot injection epidurally. Then turned back to supine position, after onset of block patient positioned according to type of surgery.

Group-BC: In this group of patients received bupivacaine (0.5%) plus preservative free epidural clonidine (3 μg/Kg) mixture as a single-shot epidural injection.

Group-BF: All patients in this group received bupivacaine (0.5%) plus preservative free fentanyl (1 μg/Kg) mixture as a single-shot epidural injection.

Group-BK: All patients in this group received bupivacaine (0.5%) plus preservative free Ketamine (0.5 mg/Kg) mixture as a single-shot epidural injection.

Group-BM: In this group of patients received bupivacaine (0.5%) plus preservative free midazolam (0.05 mg/Kg) mixture as a single-shot epidural injection).

Group-BN: All patients in this group received bupivacaine (0.5%) plus preservative free neostigmine (5 μg/Kg) mixture as a single-shot epidural injection.

Intraoperative Monitoring: Monitoring of blood pressure, oxygen saturation (SpO_2), end tidal carbon dioxide (E_TCO_2), respiratory rate (RR), heart rate (HR), electrocardiography (ECG), visual analogue scale (VAS) score, sedation score, Bromage score, onset of analgesia, temperature (^oC) and other adverse effects eg. nausea-vomiting, amnesia, salivation, shivering, sweating, nystagmus, pruritus and dryness of mouth looked for and treated accordingly (vesopressors, ionotropes, anticholinergics, antiemetics and benzodiazepines used accordingly).

Every parameter was assessed before giving block and was considered as the baseline value ('O' min measurement) then measure at 5 mins interval for first 30 mins then 15 mins interval upto end of surgical procedures. After that patient was send to post-anaesthesia care unit (PACU) for further assessment and treatment (based on aforementioned parameters).

Monitoring in Post-anaesthesia Care Unit

In PACU, all vital parameters monitoring and side by side special monitoring sedation score, pain visual analogue scale

score, Bromage score, any other adverse effects and retention of urine were assessed by trained anaesthesia personnel and other trained paramedical personnel. All scoring systems were assessed and calculated by trained personnel in the PACU, at 1st, 2nd, 4, 6, 8, 10, 12, 14, 16, 18, 24th post-operative hour. Whenever the patient required analgesia in post-operative period was given according to patient demand or pain-VAS (rescue analgesia).

Rescue analgesia was provided by injection Diclofenac Sodium (75 mg) intramuscularly (if pain on VAS was 40-50) and in severe breakthrough (VAS > 50) pain then Pentazocine (30 mg) was given intramuscularly (i.m.). The following scoring systems were used for assessment of potency and duration of analgesic action of epidurally administered drugs.

Table 1. Comparison of demographic parameters of the patients of the six groups

Demographic Parameters	Group-B (n=20)	Group-BC (n=20)	Group-BF (n=20)	Group-BN (n=20)	Group-BK (n=20)	Group-BM (n=20)	Test Statistic	p-value
Age (Years)	48.55±11.00	47.10±9.83	46.10±10.69	51.90±11.71	46.35±11.32	46.45±11.18	$F_{5,114}$=0.819	0.538
Weight (Kg)	57.15±7.10	55.10±9.94	59.05±7.23	62.85±6.08	62.65±6.73	62.65±6.55	$F_{5,114}$=0.746	0.617
Height (Cm)	156.75±4.71	154.25±5.33	159.40±7.70	159.84±7.10	158.80±7.92	160.10±7.16	$F_{5,114}$=0.655	0.703
Duration of Surgery (Hrs)	1.57±0.23	1.69±0.26	1.66±0.28	1.75±0.30	1.66±0.37	1.72±0.35	$F_{5,114}$=0.766	0.576
ASA-Class (I/II)	15/5	12/8	17/3	13/7	16/4	14/6	χ^2 = 1.38	0.781

Table 2. Comparison of Onset of Sensory Block of the patients of the six groups

Group	Onset of Sensory Block (minute)
Group-B (n=20)	12.0 ± 2.5
Group-BC (n=20)	6.0 ± 1.0
Group-BN (n=20)	7.0 ± 1.5
Group-BF (n=20)	8.0 ± 2.7
Group-BK (n=20)	11.0 ± 1.2
Group-BM (n=20)	13.0 ± 1.5
Test Statistic	$F_{2,87}$=4.053;p=0.002

Table 3. Comparison of Pulse Rate of the patients of the six groups

Pulse Rate (per minute) at time interval	Group-B (n=20)	Group-BC (n=20)	Group-BF (n=20)	Group-BN (n=20)	Group-BK (n=20)	Group-BM (n=20)	$F_{5,114}$ value	p-value
Baseline	79.95±3.97	79.30±6.87	81.65±5.69	80.20±6.41	78.95±7.53	80.50±6.69	0.460	0.805 NS
At 15 minute	84.15±4.77	86.60±6.63	86.80±4.26	90.70±7.11	88.25±7.16	91.15±6.76	3.664	0.004*
At 30 minute	95.75±6.35	95.65±6.82	97.50±5.77	103.05±6.39	100.05±6.42	106.35±7.69	8.489	0.0001*
At 45 minute	84.25±4.02	84.05±4.67	84.65±6.01	93.65±4.21	88.95±5.52	92.45±5.07	12.962	0.0001*
At 1 – 2 hour	77.70±3.45	89.20±6.06	82.90±4.22	87.80±3.89	83.80±5.28	87.80±4.49	15.27	0.0001*
At 4 hour	74.20±5.40	77.55±7.73	80.25±3.93	84.15±3.12	82.80±5.82	88.85±4.13	25.869	0.0001*
At 8 hour	76.00±4.90	75.70±3.29	76.15±4.02	81.15±3.42	84.50±6.90	90.80±5.44	31.625	0.0001*
At 12 hour	77.80±4.63	72.45±3.82	74.40±4.42	79.15±3.80	82.00±5.01	90.35±5.71	38.076	0.0001*
At 16 hour	NA	74.00±2.75	73.75±5.24	79.10±4.73	NA	89.80±6.07	47.793	0.0001*

NS- Statistically not significant
*- Statistically significant

Table 4. Comparison of SBP of the patients of the six groups

SBP (mmHg) at time interval	Group-B (n=20)	Group-BC (n=20)	Group-BF (n=20)	Group-BN (n=20)	Group-BK (n=20)	Group-BM (n=20)	$F_{2,87}$-value	p-value
Baseline	128.10±7.72	123.30±7.90	125.60±8.62	124.30±8.49	129.60±5.34	123.80±8.00	2.146	0.065 NS
At 15 minute	116.60±7.92	116.30±8.06	114.60±9.52	115.30±8.47	115.30±5.28	108.10±6.10	3.365	0.007*
At 30 minute	103.90±7.88	102.55±6.15	103.70±8.44	104.00±9.69	99.80±6.61	88.50±2.09	6.153	0.0001*
At 45 minute	115.40±7.43	109.60±4.97	108.10±6.54	116.20±5.46	112.00±3.31	102.40±4.66	16.963	0.0001*
At 1 hour	117.40±5.51	106.00±5.19	110.90±5.45	122.70±6.13	118.60±3.12	102.60±6.16	42.692	0.0001*
At 2 hour	121.10±6.10	104.30±3.85	113.10±5.45	129.70±3.54	123.60±3.02	104.70±7.26	39.969	0.0001*
At 4 hour	122.90±6.17	102.90±4.28	116.10±4.96	127.80±5.98	126.20±3.49	109.10±7.33	65.269	0.0001*
At 8 hour	175.00±2.20	106.05±3.71	118.70±4.78	127.00±6.60	126.15±4.59	114.40±26.43	9.686	0.0001*

* Statistically Significant

Table 5. Comparison of pain score (VAS) of the patients of the Six groups

Pain Score (VAS)	Group-B (n=20)	Group-BC (n=20)	Group-BF (n=20)	Group-BN (n=20)	Group-BK (n=20)	Group-BM (n=20)	$F_{2,87}$-value	p-value
Baseline	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	NA	NA
At 15 minute	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	NA	NA
At 45 minute	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	NA	NA
At 1 hour	3.25±4.06	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	12.659	0.0001*
At 2 hour	13.25±4.67	0.00±0.00	10.25±3.43	2.11±3.03	3.25±4.06	0.00±0.00	63.318	0.0001*
At 4 hour	27.00±5.23	7.00±2.51	17.25±4.72	13.16±5.33	11.50±4.32	4.00±4.76	63.746	0.0001*
At 6 hour	49.00±7.18	15.00±4.29	25.50±6.26	27.11±6.52	20.00±6.49	12.75±5.25	92.844	0.0001*
At 8 hour	NA	22.50±5.96	48.50±7.45	49.47±6.21	47.00±8.01	21.50±5.64	91.605	0.0001*
At 10 hour	NA	35.00±6.88	NA	NA	NA	32.00±6.96	1.879	0.178 NS
At 12 hour	NA	49.25±5.68	NA	NA	NA	48.50±8.13	0.114	0.737 NS

* Statistically Significant
NS- Statistically Not Significant

Visual Analogue Scale (VAS)

Score: 0 ⟷ 100 (mm)
(No pain) (Worst pain)

Four Point Verbal Rating Score – (0-3)

0 = No pain, pressure or tightening
1 = Aware of tightening or pressure but not painful
2 = Tolerable pain not distressing
3 = Distressing pain or pressure

Bromage Scale (Motor Blockade)

0 = Able to straight leg raise against resistance (no motor block)

1 = Unable to straight leg raise but able to flex knee

2 = Unable to flex knee but able to dorsiflex ankle

3 = Unable to move hip, knee or ankle

Sedation Score (0-3)

0 = Patient is awake and talkative
1 = Patient is awake but uncommunicative
2 = Patient is drowsy, quiet and easily arousable
3 = Patient is asleep

As the patients recovered sufficiently from the effect of anaesthesia, they were encouraged to drink and to try voiding in a standardized manner. When the patients were fully able to take oral fluid (if no contraindication for oral feeding) IV drip was omitted. 24-hours follow up made. After that the patients were shifted to general ward.

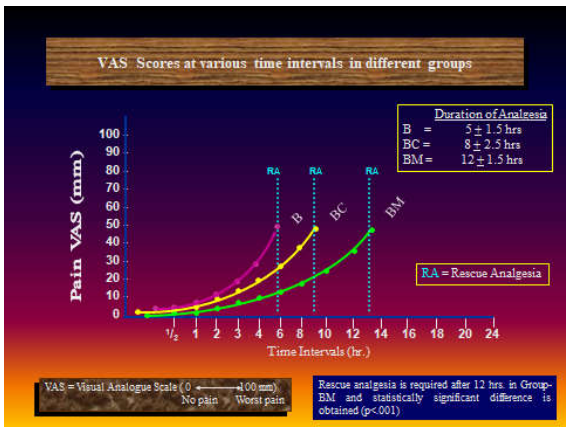
Statistical Analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.p-value ≤ 0.05 was considered for statistically significant.

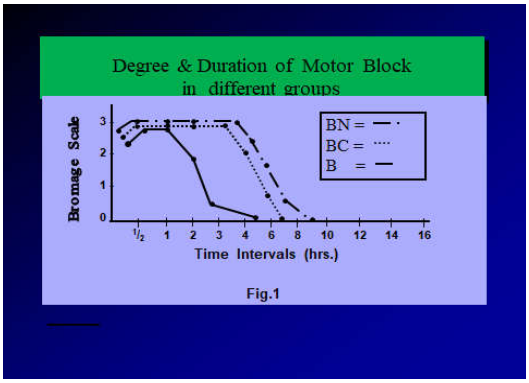
Observations

As per Table-1 ANOVA-test showed that there was no significant difference in mean age, weight, height and duration of surgery of the patients of the three groups ($p>0.05$). Also corrected Chi-square test square (x^2) test showed there was no significant association between ASA-Class and patients of the six groups ($p>0.05$). Thus the patients of the three groups were comparable for age, weight. age, weight, height, duration of surgery and ASA-Class. Onset of sensory block in different groups as following after epidural block:

Table-II showed that according to ANOVA there was significant difference between onset of sensory block of the patients ($p<0.01$). As per CD of the six groups, early onset of blockade in Group-BC, BN and Group-BF was observed than that of Group-BK and Group-BM compared with Group-B ($p<0.01$). ANOVA there was no significant difference between pulse rate of the patients of the patients of the six groups at baseline ($p>0.05$). However, significant differences were observed between pulse rates of the patients of the six groups at different time intervals other than baseline ($p<0.0001$). ANOVA there was no significant difference between SBP of the patients of the patients of the six groups at baseline ($p>0.05$). However, significant differences were observed between SBP of the patients of the six groups at different time intervals other than baseline ($p<0.0001$). There was no pain from baseline to 45 minute of all the patients of the six groups. As per ANOVA there were significant differences of pain scores of the patients of the six groups from 1 hour to 8 hour ($p<0.001$). As CD the mean pain score of Group-B was significantly higher than other groups ($p<0.0001$). At 10 hour and 12 hour there were significant differences of pain scores at 10 hour and 12 hour ($p>0.05$).



In this figure shows the VAS score, duration of analgesia and time interval to require rescue analgesic (RA). Rescue Analgesia (RA) was given to all patients in Group-Bat a mean duration of (5.5 ± 1.5 hr.) post-operatively. Rescue Analgesia was given to all patients in Group-BCat a mean duration of 10 ± 2.5 hr.) post-operatively. In Group-BN patients received rescue analgesia at a mean duration of (9 ± 1.8 hr.) post-operatively. Patients of Group-BF received rescue analgesia at a mean durationof (7 ± 1.6 hrs.) post-operatively. In Group-BK patients received rescue analgesia at a mean duration of (11±1.5 hrs.)post-operatively. Patients of Group-BM received rescue analgesia at a mean duration of (12±1.5 hrs.) post-operatively. Prolonged analgesia was obtained in Group-BM, BK, BC, BN and Group-BF, than Group-B (as per VAS / requirement of RA).



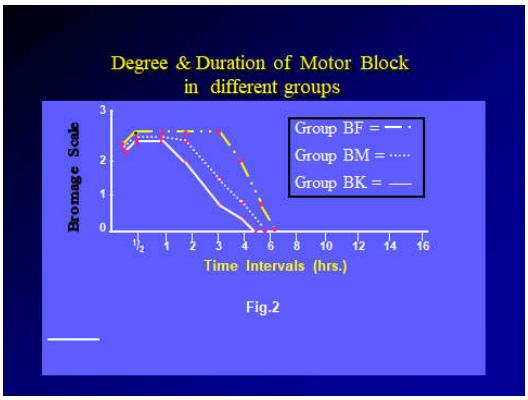
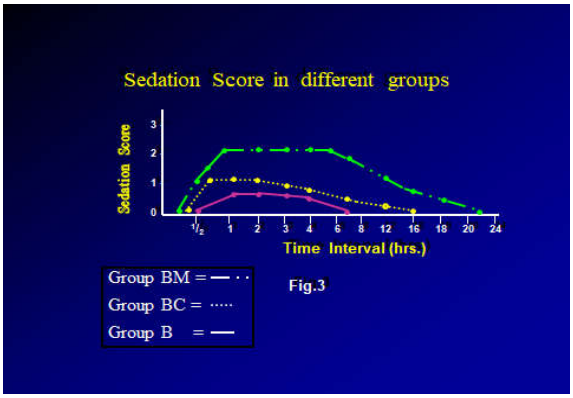


Fig. 1. shows early onset of motor blockade in Group-BN (7±2.5 mins) and the Group-BC (9±1.2 mins) than in Group-B (15±3.5 mins). Bromage score is also higher in Group-BN and Group-BC than Group-B. Duration of motor blockade is also prolonged in Group-BN and Group-BC than Group-B

Fig. 2 shows onset of motor blockade in Group-BF (10±2.5 mins.), in Group-BM (11±2.6 mins.) and in Group-BK (13±3.4 mins.). Degree and duration of motor blockade is higher in Group-BF than Group-BM and Group-BK. Degree and duration of motor blockade, in different groups clearly shown, higher and prolonged in Group-BN > Group-BC > Group-BF than other groups (Group-B; BK and BM).



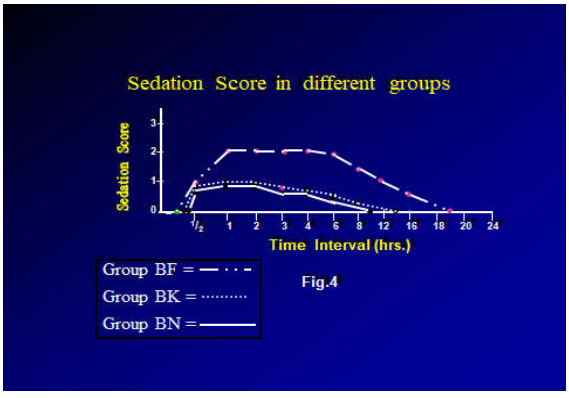
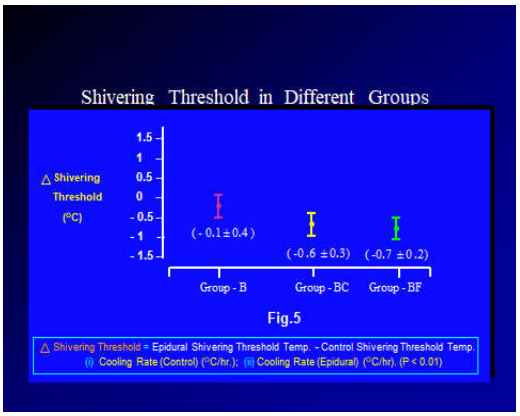


Fig. 3. shows sedation score is higher in Group-BM > and in Group-BC than Group-B (no sedation). Prolonged sedation is observed in Group-BM and Group-BC than Group-B.

Fig. 4 shows sedation score is higher in Group-BF than Group-BK and Group-BN. Moderate sedation was found in Group-BM, Group-BF and mild sedation in Group-BC. Prolonged and better sedation was found in Group-BM > Group-BF > Group-BC than other groups.



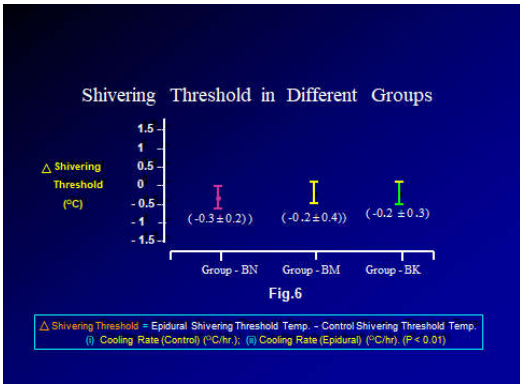
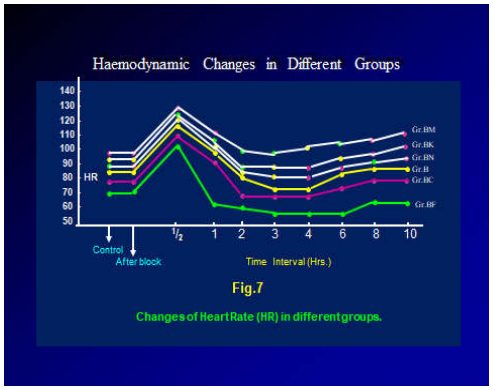


Fig. 5 and 6 show in Group-BC and Group-BF decrease body core temperature (oC) thereby decreases shivering threshold but not in the other groups (as core temperature in other groups not decrease so much that causing shivering threshold to alter)



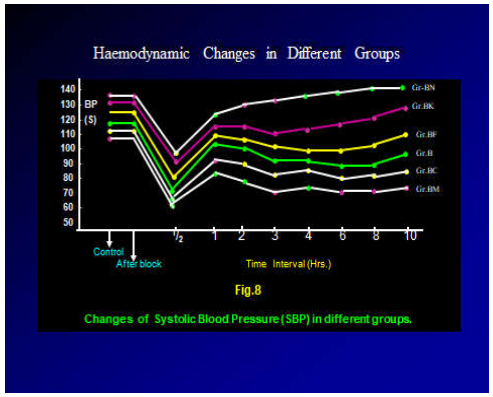


Fig.7 and 8 show haemodynamic changes were observed within 10-45 mins. of drug administration maximally thereafter reduction of heart rate in Group-BF, Group-BC, Group-B and minimal changes found in Group-BN and Group-BK, but increased heart rate maximally thereafter reduction of blood pressure in Group-BM, Group-BC and Group-B with minimal change in Group-BF and in Group-BK but increased in Group-BN

DISCUSSION

The results of the study showed that addition of clonidine to epidural bupivacaine provided prolonged peri-operative analgesia as compared to epidural bupivacaine alone[98].Onset of analgesia (sensory blockade) was found earlier in Group-BC than Group-B. The analgesic action of epidural clonidine results from direct stimulation of pre- and post-synaptic α_2-adrenoceptor in the dorsal horn grey matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters. Another theory is cholinergic mediated analgesia in which increased amount of Acetylcholine (Ach) occur in CSF and dorsal horn grey matter. This effect co-relates with the concentration of clonidine in the CSF but not that in plasma, was first demonstrated clinically in 1984.Degree and duration of motor blockade score is higher in Group-BC, BN and BF than other groups (Group-B, Group-BK and Group-BM). Epidural clonidine reduces the shivering threshold during perioperative period under epidural anaesthesia. Epidural clonidine acts by decreasing the core temperature that triggers shivering. Thereby increase tolerance for shivering. But in certain cases (6 cases) hypotension, bradycardia and sedation were found postoperatively for prolonged period. The antihypertensive effect (hypotensive cause) results from stimulation of α_2-inhibitory neurons in the medullary vasomotor Centre (Nucleus Reticularis Lateralis) of the brainstem which leads to a reduction in nor-epinephrine (NA) turnover and sympathetic nerve outflow from the CNS to the peripheral tissues. Epidurally administered clonidine also decreases the electrical activity of paraganglionic sympathetic nerves. Bradycardia is caused by an increase in vagal tone resulting from central stimulation of parasympathetic outflow as well as reduced sympathetic drive. Some patients (5 cases) complained of dryness of mouth.

Sedation after epidural clonidine results from activation of α_2-adrenoceptors in the *locus coeruleus*, an important modulator of vigilance. This suppresses the spontaneous firing rate of nucleus, thereby resulting in increased activity of inhibitory interneurons. Such as gamma-amino butyric acid (GABA)-ergic pathways, to produce CNS depression. Sedation appears to be dose dependent and as in the case of haemodynamic effects, is probably the results of systemic absorption and vascular redistribution of clonidine to higher centers rather than a consequence of cephaloid migration in the CSF. No significant respiratory depression was found with epidural clonidine (3 μg/Kg). No postoperative nausea-vomiting (PONV) was observed in Group-BC. Postoperative retention of urine was comparable with Group-B (not so prolonged in Group-BC than Group-B). Epidural fentanyl acts through opioid receptors at presynaptic and postsynaptic sites in the CNS (the brainstem and spinal cord). Carotid sinus baroreceptor reflex control of heart rate is markedly depressed by fentanyl, thereby bradycardia results, this is due to systemic absorption of the drug rather than rostral spread (fentanyl highly lipophilic in nature). Occasional decrease of blood pressure and cardiac output due to profound bradycardia produced by epidural fentanyl (7 patients). Epidural fentanyl quickly absorbs into circulation. Ventilatory depression (evidenced by decrease of SpO_2 and $\uparrow E_TCO_2$) due to systemic absorption the drug (4 cases), but not due to cephaloid migration of the drug, that is why delayed respiratory depression is not found in postoperative period in epidural fentanyl received cases.

Mild modulation of motor blockade action may be due to it acts through peripheral tissues and its analgesic action of fentanyl. Mild sedation also found in some cases (4 cases) due to systemic absorption of the drug. Pruritus found only in 3 cases in Group-BF. Urinary retention also occur in Group-BF but not so severe, passed with conservative treatment (in 7 cases). Epidural fentanyl also reduces postoperative shivering (in perioperative period). Epidural fentanyl acts through decreasing body core temperature.PONV was also observed (12 cases) in Group-BF due to direct stimulation of CTZ. Epidural neostigmine produces analgesia by following mechanism. Neostigmine is highly polar; penetrate deeply into the cord to its site of action in the intermedio-lateral cell column-prevents breakdown of endogenous spinal neurotransmitter Acetylcholine (Ach), which causes analgesia, inhibition of motor neuron activity and excitation of sympathetic outflow, decrease in spinal level, mediated through muscarinic, causes hyperpolarization of neurons, decrease release of pro-nociceptive neurotransmitters or activation of NO (nitric oxide) – through cGMP pathways. Motor blockade property of epidural neostigmine due to decrease motor neuron activity (inhibition of motor neuron outflow). Incidence of nausea-vomiting in Group-BN quite high (14 cases) compared with other groups due to direct effect to brain stem.[48] Epidural neostigmine increases blood pressure and heart rate when administered single injection. It is due to excitatory action on preganglionic sympathetic neuron in spinal cord. But when administered with bupivacaine causes little change in heart rate or bradycardia. Decreased heart rate may be due to muscarinic cholinergic effect, probably systemic absorption of the drug (neostigmine). So, overall hemodynamic changes not significantly observed in Group-BN.

Mild sedation was observed in Group-BN, with no effect on shivering threshold was found. Due to transient increase respiratory rate decreases end-tidal carbon dioxide (E_TCO_2). Postoperative urinary retention is comparable with Group-B, in Group-BN. Epidural ketamine binds non-competitively to a subset of glutamate receptors stimulated by the excitatory amine N-methyl D-aspartate (NMDA), blockade of which leads to a decrease in activation of dorsal horn neurons. These receptors are located throughout the CNS as well as in the substantia gelatinosa in the spinal cord and play an important role in central pain processing and in neural plasticity in the spinal cord. While NMDA receptor block appears to be the primary mechanism of action, ketamine also binds to opioid receptors, with a preference for the μ-receptor. The analgesic action of ketamine is not reversed by naloxone. However, there were no differences between the groups (Group-BK and Group-B) in terms of motor blockade, urinary retention, postoperative sedation, PONV, shivering threshold. Neurobehavioral symptoms of epidural ketamine due to systemic absorption of the drug. Haemodynamic changes in Group-BK was not significantly noticed. Epidural (midazolam + bupivacaine) induced significantly better analgesia, with significant amnesia, sedation and more stable haemodynamics and respiratory conditions than epidural bupivacaine alone. Benzodiazepine receptors are present throughout the nervous system, including the spinal cord. It has been demonstrated that exogenous administration of benzodiazepines into the CSF / or epidural around the spinal cord reached benzodiazepine receptor in high concentration and could have a pronounced effect on local GABA activity. Thus, benzodiazepines can gain access to analgesic system mediated by GABA.

My study showed that addition of midazolam epidurally provided an enhancement and increased duration of sensory analgesia without delaying recovery to ambulation and ability to void. Lower blood pressure and respiratory rate in Group-BM are probably due to the systemic effect of midazolam (12 cases). Sedation and amnesia by epidural midazolam might be also ascribed to the systemic effect because the serum midazolam concentration after epidural injection of midazolam was high enough to induce systemic effect. Moderate sedation was found in Group-BM. ↓RR with ↓SpO_2 in 5 cases. There was no incidence of nausea-vomiting; itching; urinary retention or posdural puncture headache (PDPH) during follow up of these patients. So, adding midazolam to epidural bupivacaine for postoperative pain can provide a better analgesia, amnesia and sedation than bupivacaine alone without any harmful effects on haemodynamics and respiration.

Conclusion

In conclusion, adding of adjuvants (Clonidine, Fentanyl, Neostigmine, Ketamine and Midazolam) to epidural bupivacaine for postoperative pain can provide a better analgesia and better operative condition than bupivacaine alone without any significant remarkable effect on haemodynamics, respiration and other adverse effects (PONV – in Group-BF and Group-BN; urinary retention, nystagmus – in Group-BK; Salivation – in Group-BN; dry mouth – in Group-BC; pruritus – in Group-BF; Amnesia – in Group-BM) which were easily manageable (or treatable). Where prolonged surgery (as well as better relaxation) and prolonged postoperative analgesia will require, epidural clonidine-bupivacaine mixture is good choice. Where only prolonged postoperative analgesia and sedation will require, epidural midazolam – bupivacaine mixture is better choice.

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