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"TO COMPARE CLINICAL EFFICACY OF CLONIDINE AND FENTANYL AS ADJUVANT IN SUB-ARACHNOID BLOCK FOR ABDOMINAL HYSTERECTOMY ."

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ABSTRACT

AIM AND OBJECTIVES-The aim of this study was to assess the onset and duration, level of sensory and motor block, hemodynam ic parameters and adverse effects of combination of clonidine and fentanyl given intrathecally with hyperbaric 0.5% bupivacaine.

MATERIAL AND METHODS: In this Prospective, double blind study 120 patients posted for TAH were randomized into four groups. Group B received (0.5% Hyperbaric Bupivacaine 3.5 ml),Group BC received (0.5% Hyperbaric Bupivacaine 3.0 ml + clonidine 30 mcg with saline 0.3 ml)Group BF received (0.5% Hyperbaric Bupivacaine 3.0 ml+ Fentanyl 15mcgs with saline 0.2 ml)Group BCF (0.5% Hyperbaric Bupivacaine 3.0 ml with clonidine 30 mcg and fentanyl 15mcgs).The onset and duration of sensory and motor block, hemodynamic parameters and the incidence of side effects in all four groups were noted and compared.

RESULT-Significant prolongation of duration of sensory and motor block was found in group BCF. Fall in mean BP and heart rate was seen in BCF group at clinically acceptable levels without significant adverse effects.

CONCLUSION- Addition of low dose clonidine and fentanyl together intrathecally prolongs motor and sensory block, compared to fentanyl or clonidine alone as adjuvant to Bupivacaine without any hemodynamic instability.

INTRODUCTION

Neuraxial adjuvants have been used to improve or prolong analgesia, decrease the adverse effects associated with high doses of a single local anesthetic agent, to increase the speed of onset of neural blockade (reduce latency), improve the quality, and prolong the duration of neural blockade. Many drugs (fentanyl, morphine, vasoconstrictors such as epinephrine and phenylephrine, 2-agonists) have been used as an additive to local anesthetics.[1]

Clonidine is a selective partial agonist for 2 adrenergic receptors and it is the most studied drug used for neuraxial anesthesia.[7] It is more potent after neuraxial than systemic administration indicating spinal site of action and favoring neuraxial administration.[8] Recently, Clonidine has also been shown to increase acetylcholine (Ach) levels in lumbar cerebrospinal fluid, as cholinergic activation imparts analgesia.[8] It may also cause local vasoconstriction.[8]

Antinociceptive action of Clonidine exists for somatic and visceral pain.[2,3] Clinical efficacy of Intrathecal Clonidine to relieve visceral pain in well-established[4,5] but Clonidine is also associated with few side effects like bradycardia, hypotension and dry mouth. So, 30µg dose of Clonidine was chosen in our study, as higher doses (150ug) are also associated with significant risk of hypotension as reported by Chiari et, al.[6]

Fentanyl is a lipophilic µ receptor agonist opioid. Intrathecally It exerts its effect by combining with opioid receptor in the dorsal horn of spinal cord and may have a supraspinal spread and action. The effectiveness of Intrathecal opioids depends on their bioavailability,[9] so opioids can provide good perioperative analgesia. Reuben et al[10] used different doses (5, 10, 20, 40, 50µg) of fentanyl in their study and found that even 20µg of fentanyl in combination of 0.5 % of bupivacaine gave good amount of analgesia. So, we have used 15µg of fentanyl in our study.

This study largely focuses on the relative potencies, hemodynamic effects, relative degree of sensory and motor blockade and adverse effects with fentanyl and clonidine as adjuvants in patients who are undergoing total abdominal hysterectomy.

MATERIAL AND METHODS

After getting approval from the institutional research and ethical committee and written informed consent, this prospective, randomized, controlled, double blind study was conducted at a tertiary care centre on 120 patients ,American Society of Anesthesiologists (ASA) physical status I & II, Aged 35 to 55 years, with normal coagulation profile and free from cardio-respiratory and autonomic dysfunction undergoing abdominal hysterectomy under SAB.After complete pre anesthetic check-up and investigations, Patients with contraindication to spinal anesthesia or major neurological, cardiovascular, metabolic, respiratory, renal disease,Age <35 and >55 years ,severe spinal deformity, allergy to local anesthetic or coagulation abnormalities were excluded from the study.All patients were kept nil orally for 6-8 hours. The procedure was explained to the patients and written informed consent was obtained.

Randomization was done by chit in box
method.120 patients were randomly divided into 4 groups of 30 patients each.

Group B (0.5% Hyperbaric Bupivacaine 3.5 ml) Control group.
Group BC (0.5% Hyperbaric Bupivacaine 3.0 ml + Clonidine 30 mcgs+0.3ml N.S.),

Group BF (0.5% Hyperbaric Bupivacaine 3.0 ml+ Fentanyl 15mcg+0.2ml N.S.) and

Group BCF (0.5% Hyperbaric Bupivacaine 3.0 ml with Clonidine 30 mcg and Fentanyl 15mcg).

To ensure double blindness of the study, the study drug solutions were prepared by the resident anesthesiologist while SAB was instituted by another anesthesiologist. None of them were further involved for data collection of the study.

Patients were pre-medicated with Tablet Ranitidine 150mg and Tab.Alprazolam0.5mg a night before. All the patients were administered oxygen via a Ventimask. For each patient a peripheral intravenous (IV) access was secured and lactated Ringer's infusion was started to replenish the overnight fasting at the rate of 10ml/Kg, 30 min prior to surgery. Before commencement of anesthesia, patients were explained about the methods of sensory and motor blockade assessments.

In the operating room, patients were monitored for heart rate (HR), electrocardiograph (ECG), non-invasive blood pressure (NIBP), percentage of oxygen saturation (SPO2). Under all aseptic precautions subarachnoid block was performed with the patient in the lateral position, using a 25G Quincke needle at the L3-L4 interspace. The study solution (3.5ml) was administered over 10 seconds. Patient was repositioned to supine position without elevation of extremities and tested every 2.5 minutes until maximal spread of sensory blockade, and then every 30 minutes during the surgery. A fall of MAP by 30% of the baseline was treated with rapid infusion of 100 ml of Ringer's Lactate and 6 mg aliquots of injection Ephedrine intravenously, in case there was no response to fluid administration. Bradycardia (<50/minute) was treated with 0.6 mg intravenous atropine sulfate. Pruritus was treated with nalbuphine (2.5 mg intravenously).Intraoperative nausea was treated with inj. Ondansetron 4 mg (i.v.).

Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), heart rate (HR), percentage saturation of oxygen (SPO2) and respiratory rate (RR) were recorded at 1,4,8,12,15,30,60,75,90 minutes

Sensory Block was assessed by loss of pinprick sensation at T10 level on each side and patients asked about the sensation. Onset of sensory block is defined as the time between injections of the drug to loss of sensation at T10 level.Level of maximum sensory block was defined as the highest dermatomal level reached with loss of sensation.Time for two segment regression was defined as the time period to regain sensation at two dermatomes lower to the initial level of highest dermatome.Time for rescue analgesia wasdefined as the time at which patient complained pain at the site of surgery intraoperatively or postoperatively.

The degree of motor block was assessed using "Bromage scale". (Grade1) Free movement of legs or feet. (Grade 2) Just able to flex knees with free movement of feet. (Grade 3)Unable to flex knees but with free movement of feet. (Grade 4)Unable to move legs or feet. Motor blockade was assessed at 4 minutes and then for every 30 seconds till grade IV block was achieved. And then every 30 minutes until return of normal motor function.Onset time for motor block was defined as the time between injection and grade IV block. Duration of motor block was defined as time from injection of drug into the subarachnoid space to achieve Bromage-1.

Complications such as nausea, vomiting, pruritis and shivering were recorded and treated accordingly .All the patients were kept under observation in the postoperative period.

In the present study, the data was collected, entered into the Excel Sheet and then transferred to online statistical software for final analysis. The mean and standard deviation of Systolic Blood Pressure, Diastolic Blood Pressure, Mean Blood Pressure, Heart Rate, Respiratory Rate and SPO2 scores between different groups at same time interval was analyzed using one way Analysis of Variance (ANOVA) followed by Tukey's Post hoc test.

Side effects (anticholinergic, antiemetic, vasopressor, shivering, and pruritis) were compared using non parametric Kruskall Wallis Test.

For sensory and motor blockade profile mean and standard deviation was calculated for duration of onset of motor block and time for D2 regression. The variation was analysed using one way Analysis of Variance (ANOVA) followed by Tukey's Post hoc test. While Kruskall Wallis Test was used to compare motor block on Bromage Scale and sensory level attained, pairwise comparison was done using Mann Whitney u test. A P value ≤ 0.05 was considered as statistically significant. The final data was represented in the form of tables and graphs.

RESULTS

Data of all 120 patients enrolled in the study were included in the analysis. Patients of all groups were statistically comparable regarding mean age, weight, ASA physical status.[Table 1].

The Baseline heart rate was comparable between Group B, Group BC, Group BF and Group BCF (P>0.05), while after injection of drug there was a steady fall in mean Heart rate at all intervals , intraoperatively till 90 minutes . It was higher in Group B (control group) in comparison to Group BC, Group BF and Group BCF (P<0.05). When the mean heart rate was compared in between the groups at different time intervals, there was a statistically significant difference (P<0.05) at all intervals intraoperatively, with lowest mean Heart rate in Group BCF in comparison to other groups.

The mean respiratory rate and mean SpO2 at all the time intervals was comparable between the four groups.

There was fall in systolic blood pressure from base line values in all the groups. However the fall was significantly more in BCF group as compared to other groups at all intervals (p<0.05) except at 12 min interval where group BF had the lowest mean systolic blood pressure that was statistically significant.

When the mean diastolic blood pressure was compared in between the groups at different time intervals, there was a statistically significant difference (P<0.05) at 1 min., 12 min., 20 min. and 30 min. intraoperatively, with a lowest mean diastolic blood pressure in BCF group in comparison to other groups.

When the Mean blood pressure was compared in between the groups at different time intervals, there was a statistically significant difference (P<0.05) at all intervals intraoperatively, with lowest Mean blood pressure in BCF group in comparison to other groups except at 15 minutes where Group BC had lowest value.

The onset of sensory block i.e. time taken to reach sensory level till T10 of Group B was 6.63±1.351 min, in Group BC was 6.63±1.098 min, in Group BF was at 6.97±1.033 min and in Group BCF was at 6.07±.944 min. the time taken was least in Group BCF and maximum for Group B patients. The difference was statistically significant (P = 0.021*).At 5 minutes from injection of drug, the average sensory level achieved was between T8-T12 in all 4 groups. At 10 minutes from injection of drug, the average sensory level achieved was between T5-T8 in all 4 groups.

Time to sensory regression of two dermatomes was significantly extended in patients of Group BCF(140.50±16.158 min) as compared to patients of Group BF (121.13±10.231 min), Group BC (118.13±13.195 min) and Group B(81.47±5.387 min.) . (P =0.000**).

Onset of motor block i.e Defined as the time between injection and grade IV motor block was (8.63±1.351 min) in patients of Group B ,(8.13±1.196 min) in patients of Group BC,(9.03±0.999 min) in patients of Group BF(Bupivacaine plus Fentanyl) and (8.10±0.885 min) in Group BCF. The onset was fastest in Group BCF followed by Group BC and Group B and at last in Group BF with statistically significant difference in between the groups.

Total Duration of motor block was significantly extended in patients of Group BCF (120.27±81217) as compared to patients of Group BF (118.43±8.369) , Group BC (118.60±1.558) and Group B(100.90±6.310) . (P =0.000**).

Anticholinergic drugs i.e glycopyrollate 0.2mg IV was given when heart rate went below 50 per min(Bradycardia). It was given to 5% of the patients of Group B , 20% patients in Group BC, 12% in

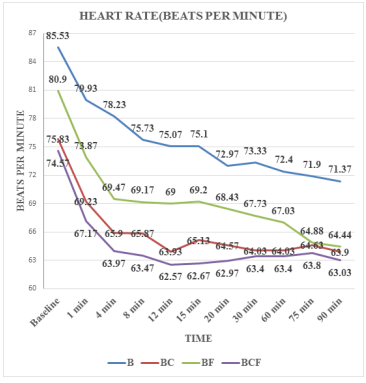
Group BF where as in Group BCF it was given in 23% of patients. The difference is statistically significant.(p= 0.047).

The incidence of nausea/vomiting, hypotension, shivering, pruritus were not statistically significant.

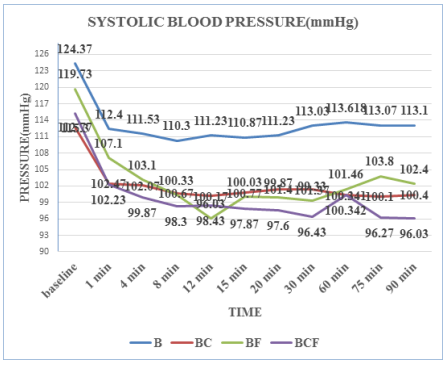
Table 1. Patient Characteristics

	GROUPS			
	B	BC	BF	BCF
AGE (in years)	41.6±3.891 (MEAN±SD)	41.36±5.122 (MEAN±SD)	40.96±4.197 (MEAN±SD)	42.53±5.210 (MEAN±SD)
WEIGHT (in kgs)	58.7±7.944 (MEAN±SD)	56.76±5.481 (MEAN±SD)	54.76±7.609 (MEAN±SD)	58.5±5.876 (MEAN±SD)
ASA GRADE I/II	27/3	22/8	25/5	24/6

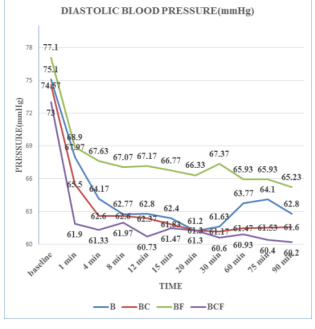
Data are presented as mean±SD or absolute numbers. ASA: American Society of Anesthesiologist, SD: Standard deviation



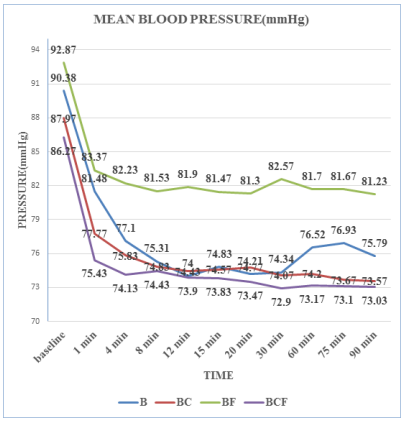
Graph 1: The above graph shows the mean heart rate (beats per minute) comparison between the four groups at different time intervals



Graph 2: The above Graph shows the mean systolic blood pressure comparison between the four groups at different time intervals.



Graph 3: The above graph shows the mean diastolic blood pressure comparison between the four groups at different time intervals.



Graph 4: The above graph shows the Mean blood pressure comparison between the four groups at different time intervals.

Sensory blockade profile

Parameters			Group B	Group BC	Group BF	Group BCF	COMAPRATIVE ANALYSIS	P Value
Sensory Block	Onset of sensory block		6.63±1.351 (mean±SD)	6.63±1.098 (mean±SD)	6.97±1.033 (mean±SD)	6.07±.944 (mean±SD)	4<1≤2<3 (Tuckey's posthoc)	0.021*
	Sensory level attained	5 mins	(T8-T12) (Range)				NA	0.228
		10 mins	(T5-T7) (Range)				NA	0.083
	Time For D2 Regression (Min)		81.47±5.387 (mean±SD)	118.13±13.195 (mean±SD)	121.13±10.231 (mean±SD)	140.50±16.158 (mean±SD)	4≤3<2≤1 (Tuckey's posthoc)	0.000**
P≤0.05= Significant*, P≤0.001= Highly Significant**								

Table 2: Comparison of Sensory blockade profile

Motor Blockade Profile

Parameters		Group B	Group BC	Group BF	Group BCF	COMAPRATIVE ANALYSIS	P Value
Motor Block	Onset Of Motor Block	8.63±1.351 (mean±SD)	8.13±1.196 (mean±SD)	9.03±0.999 (mean±SD)	8.10±0.885 (mean±SD)	4≤2<1<3 (Tuckey's posthoc)	0.004*
	Total Duration of Motor Block	100.90±6.310 (mean±SD)	118.60±1.558 (mean±SD)	118.43±8.369 (mean±SD)	120.27±81217 (mean±SD)	1<3≤2≤4 (Tuckey's posthoc)	0.000**
	Bromage Scale	5 mins	I-IV (Range)	4<3<2<1 (Mann Whitney U test)	0.000**		
		10 mins	IV (just one value)			NA	1.000

Table 3: The above table shows the motor blockade parameters between the groups.

Comparison of side effects

SIDE EFFECT	GROUP B(%)	GROUP BC(%)	GROUP BF(%)	GROUP BCF(%)
Hypotension	10	24.9	20	25
Bradycardia	5	20	12	23

Nausea/Vomiting	9.2	25.6	20	24.9
Shivering	28.3	9.2	12.7	9.3
Pruritus	0	0	3.3	0

Table 4: Comparison of side effects

Discussion

In our study, there was a statistically significant difference (P<0.05) at all intervals intraoperatively, with lowest mean Heart rate in Group BCF in comparison to other groups. Our findings were similar to those of the study conducted by Krishnakumar Srinivasagam et al[11] patients received 50µg of clonidine, 25µg of fentanyl and 75µg of buprenorphine respectively in group BC,BF and BB as adjuvants to 15mg of 0.5% hyperbaric bupivacaine (3.0ml). Heart rate was found to be lower in group BC as compared to group BF and BB.

Clonidine affects arterial blood pressure in a complex manner because of opposing actions at mutiple sites. The a2-adrenergic agonists produce sympathicolysis and reduce arterial blood pressure through effects at specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal cord, effects that are counteracted by direct vasoconstriction resulting from the a2-adrenergic agonists on the peripheral vasculature.Combining a2-adrenergic agonists with local anesthetic can potentially increase the degree of sympatholysis and the resulting hypotension.[15] In our study ,we observed fall in systolic,diastolic and mean blood pressure from base line values in all the groups with a lowest mean systolic ,diastolic and Mean blood pressure in BCF group in comparison to other groups. The findings were in concordance with results obtained In a study by Tilkar et al.[12] , in patients of group (bupivacaine 3ml+ fentanyl 50 mcg) there was a moderate decrease of BP (10–15% drop from baseline value), which gradually returned to baseline value within an hour, whereas in group (bupivacaine 3 ml+clonidine 150 mcg), there was a significant decrease of BP (>20–30% decrease from the baseline value) after 5 min of spinal block, but BP does not raise to baseline value after treatment with vasopressors but then sustains to the accepted limit throughout the intraoperative and postoperative period. Whereas in a study by Ahmed F, et al [8] , In all four groups, patients were hemodynamically stable in intraoperative and postoperative period. There were no significant differences among groups regarding the incidence of perioperative adverse effects.In study conducted by Anil Thakur et al[13], 30 mcg clonidine was associated with more incidence and duration of hypotension than 15 µg of clonidine.In study conducted by Krishnakumar Srinivasagam et al[11], Patients were randomly allocated into three groups (n=30) and received 50µg of clonidine, 25µg of fentanyl and 75µg of buprenorphine respectively in group BC,BF and BB as adjuvants to 15mg of 0.5% hyperbaric bupivacaine (3.0ml). Mean BP was found to be lower in group BC as compared to group BF and BB.

Clonidine is an alpha 2 agonist, which potentiates both sensory and motor blockade of local anesthetics[4].In a study conducted by Krishnakumar Srinivasagam et al[11] Although Clonidine group had fastest onset. There was no significant difference in onset time of sensory block in three groups (463.8±54.42 seconds, 477. 6±55.2 seconds, and 477.6±61.8 seconds in group BC, BF and BB respectively) (P>0.5). In study conducted by Anil Thakur et al[13], the addition of 15 mcg and 30 mcg clonidine to bupivacaine was found to be equally effective in duration and quality of sensory block.In a study conducted by Singh et al[15]and Strebel et al,[14] they concluded that fentanyl as well as Clonidine does not alter the onset of sensory block.

In our study Time to sensory regression of two dermatomes was significantly extended in patients of Group BCF(140.50±16.158 min) as compared to patients of Group BF (121.13±10.231 min), Group BC (118.13±13.195 min) and Group B(81.47±5.387 min.). (P =0.000**) is consistent with the observation made by Elia et al, [16] time taken for two segment regression was prolonged with 150 microgram dose of Clonidine although associated with hypotension.

The Duration of Onset of motor block as observed in our study is consistent with the observation made by Krishnakumar Srinivasagam et al[11] The difference in mean onset of motor block (Bromage 3) was statistically significant in all three groups being 142.66±33.99 seconds, 222±52.06 seconds and 274±56.11 seconds in group BC, BF and BB respectively (p value<.001). Clonidine significantly prolongs the duration of motor block up to 254.67±72.05 minutes.

Total Duration of motor block was significantly extended in patients of Group BCF consistent with the observation made by Elia et al[68] and Jain et al.[67] However this was in contrast to the study of kabbachi et al [69], who concluded that the addition of 2µg/kg Clonidine (= 100µg) to hyperbaric 0.5 % bupivacaine does not prolong the duration of motor block. The incidence of nausea/vomiting, hypotension, shivering, pruritus were not statistically significant.

Incidence of shivering observed in our study is inconsistent with the observation made by Jeon et al. who found that intrathecal clonidine 150 mcg failed to prevent post-spinal shivering and confirmed that IV clonidine 1 mcg/kg is an effective method to prevent shivering in patients undergoing spinal anesthesia for orthopedic surgery.[17] Dobryndjov et al. noted postoperative nausea and vomiting in four patients (one each in group B and BC30 and two patients in BC30).[18] but it was insignificant in our study. Sedation is another central effect of a2-adrenergic agonists that can occur after their administration via systemic, epidural, or intrathecal routes. The sedative effect of clonidine is dose dependent and thus explains the absence of sedative effects in our study. Dobryndjov et al. reported similar findings. Khanna and singh[16] reported high incidence of pruritus and desaturation with fentanyl added to intrathecal bupivacaine in geriatric patients while it was insignificant in our study.

In conclusion, Group BCF is a better drug combination resulting in increased duration of sensory and motor blockade, maintaining perioperative hemodynamics without causing any significant hemodynamic side effects in a patient undergoing Total Abdominal Hysterectomy.

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