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Intrathecal bupivacaine (0.5%) with clonidine (1µg/kg) versus intrathecal bupivacaine (0.5%) with fentanyl (25 µg): Effects on Hemodynamic changes

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Abstract
Bupivacaine controls pain at the axonal level by interfering with the nerve membrane. It physically blocks the sodium channel by reversibly binding to receptors on the intracellular side of the membrane. While the sodium channel is inactive, an action potential cannot form and nerve impulse conduction cannot be sent across the nerve membrane and to the brain. The result of this is a loss of feeling or numbness when the drug is given. This clinical study was conducted on 60 adult patients of ASA physical status 1 & 2 in the age group of 18 years to 60 years, of either sex, posted for elective lower limb, lower abdominal, gynaecological and urological surgeries under spinal anesthesia. The changes in diastolic blood pressure at 30 min and 60 min were statistically significant $p<0.05$ (here it is p=0.016 and p=0.001). There were not much differences in the diastolic blood pressure observed upto 180 minutes after the administration of the drugs except at 30 and 60 min. Majority of patients in clonidine group had significant sedation, $p<0.05$(here it is p=0.01) compared to fentanyl group.

Keywords: Bupivacaine, fentanyl, hemodynamic changes

Introduction
Spinal anaesthesia is the regional anaesthesia obtained by blocking the spinal nerves in the subarachnoid space. The anaesthetic agents are deposited in the subarachnoid space and act on the spinal nerve roots and not on the substance of the cord [1].
Bupivacaine, introduced in 1963 is a widely used amide local anaesthetic. It is an amino-amide compound that causes reversible blockade of nerve impulses to control pain. Bupivacaine is used for peripheral nerve blocks, caudal block, epidural block, sympathetic blocks and spinal block. The degree of neural blockade depends on the site of injection, which in return determines the amount of drug that reaches the target nerve [2].
The structure of bupivacaine is similar to that of lidocaine, except that the amide containing group is a butylpiperidine. It is four times as potent as lidocaine, is slower in onset but has a significantly longer duration of action.
Bupivacaine is the hydrochloride salt of (di)-1-butyle-2'6'-pipecoloxylidide and is presented as the racemic mixture.
Bupivacaine controls pain at the axonal level by interfering with the nerve membrane. It physically blocks the sodium channel by reversibly binding to receptors on the intracellular side of the membrane. While the sodium channel is inactive, an action potential cannot form and nerve impulse conduction cannot be sent across the nerve membrane and to the brain. The result of this is a loss of feeling or numbness when the drug is given [3].
It is thought that the local anaesthetic receptors are protein bound receptors located near the sodium channel. Bupivacaine is highly protein bound which results in a slower dissociation from the receptor and a subsequent prolonged effect. Once metabolized, bupivacaine and its metabolites are excreted by the kidneys through urine [4].
Fentanyl citrate is a synthetic phenylpiperidine opioid analgesic and chemical congener of the reversed ester of pethidine. It is a powerful, safe and rapidly acting analgesic. Fentanyl is highly lipid soluble and has a low molecular weight. Fentanyl is widely available for parenteral use and also in buccal, transdermal and aerosolised formulation. Fentanyl provides analgesia and muscle relaxation [5].
Clonidine is a partial agonist at α-adrenoceptors both within the central nervous system and in the periphery. It is more specific for α2-adrenoceptors than for α1-adrenoceptors with a ratio of affinities at these sites of approximately 200:1.
Within the central nervous system α_2-adrenoceptors are located both presynaptically on

terminals of neurons which release a variety of transmitters – norepinephrine, epinephrine, serotonin and acetylcholine, and postsynaptically on nor-adrenergic neurons. It is likely that clonidine acts at all central α_2-receptors, stimulation of which is associated with decreased neuronal excitability and inhibition of membrane – bound adenylate cyclase. High concentrations of clonidine may stimulate central α_1-adrenoceptors enhancing neuronal excitability.

Methodology

This clinical study was conducted on 60 adult patients of ASA physical status 1 & 2 in the age group of 18 years to 60 years, of either sex, posted for elective lower limb, lower abdominal, gynaecological and urological surgeries under spinal anesthesia. After approval from the hospital ethical committee, a prospective double blind randomized controlled study was carried out on 60 adult patients. Patients were randomly divided on an alternative basis into two groups of 30 each.

Group **"C"** - Bupivacaine plus clonidine group.

Group **"F"** - Bupivacaine plus fentanyl group.

Inclusion criteria

1. ASA grade 1 and 2 patients.
2. Age group of 18 –60 yrs.
3. Patients giving valid informed consent.
4. Those patients scheduled to undergo elective lower abdominal, lower extremity, gynaecological or urological surgeries under subarachnoid block.

Exclusion criteria

1. Patient refusal.
2. Patients belonging to ASA grade 3 and grade 4.
3. Patients physically dependant on narcotics.
4. Patients with history of drug allergy.
5. Patients with gross spinal abnormality, localized skin sepsis, hemorrhagic diathesis or neurological involvement / diseases.
6. Head injury cases.
7. Patients with cardiac, pulmonary, hepatic or renal disorders.
8. Patients having inadequate subarachnoid blockade and who are later supplemented by general anaesthesia.
9. Obstetric cases for lower segment caesarean section because of drug dosage discrepancy.

Results

Table 1: Heart rate

Heart Rate	Group C		Group F		Significance
	Mean	SD	Mean	SD	
Baseline	79.07	15.667	80.8	2.809	*P*>0.05
5 min	76.7	5.059	78.23	3.441	*P*>0.05
10 min	72.52	5.369	74.3	3.344	*P*>0.05
15 min	68.53	5.764	70.53	3.014	*P*>0.05
30 min	65.97	6.446	69.13	2.389	*P*=0.014*
60 min	65.57	13.26	69.17	3.573	*P*>0.05
120 min	72.1	2.845	71.4	2.01	*P*>0.05
180 min	73.63	3.643	74.37	2.58	*P*>0.05

*Indicates significant value.

The heart rate change at 30 min were statistically significant $p<0.05$ (here it is p-0.014) There were not much differences in the heart rate observed upto 180 minutes after the administration of the drugs except at 30 min there were no significant changes in the heart rates between the 2 groups at corresponding time intervals with significance value more than 0.05.

Table 2: Systolic Blood Pressure (mmHg)

SBP (mmHg)	Group C		Group F		Significance
	Mean	SD	Mean	SD	
Baseline	119.8	5.665	121.13	5.374	*P*>0.05
5 min	113.8	5.665	116	5.32	*P*>0.05
10 min	109.43	5.655	111.83	6.08	*P*>0.05
15 min	103.87	5.68	106.07	5.159	*P*>0.05
30 min	99.3	8.809	102.43	5.823	*P*>0.05
60 min	102.2	7.761	105.67	4.845	*P*=0.042*
120 min	107.13	4.776	109.97	3.664	*P*>0.05
180 min	109.97	3.368	110.5	3.511	*P*>0.05

*Indicates significant value.

The changes in systolic blood pressure at 60 min were statistically significant $p<0.05$ (here it is p=0.042)There were not much differences in the systolic blood pressure observed upto 180 minutes after the administration of the drugs except at 60 min. Statistically there were no significant changes in the systolic blood pressure between the 2 groups at corresponding time intervals with significance value more than 0.05.

Table 3: Blood pressure: DBP(mmHg)

DBP(mmHg)	Group C		Group F		Significance
	Mean	SD	Mean	SD	
Baseline	79.33	5.313	80.27	5.747	*P*>0.05
5 min	73.87	5.728	76.67	5.665	*P*>0.05
10 min	69.43	4.546	71.8	5.665	*P*>0.05
15 min	65.23	5.131	67.03	5.732	*P*>0.05
30 min	60.84	4.608	64.11	5.101	*P*=0.016*
60 min	60.35	3.257	65.55	5.002	*P*=0.001*
120 min	68.27	3.814	68.47	4.485	*P*>0.05
180 min	70.1	4.139	69.7	3.834	*P*>0.05

*Indicates significant value.

The changes in diastolic blood pressure at 30 min and 60 min were statistically significant $p<0.05$ (here it is p=0.016 and p=0.001). There were not much differences in the diastolic blood pressure observed upto 180 minutes after the administration of the drugs except at 30 and 60 min. Statistically there were no significant changes in the diastolic blood pressure between the 2 groups at corresponding time intervals with significance value more than 0.05.

Table 4: Sedation score

Sedation_Score	Group C		Group F		Significance
	Mean	S.D	Mean	S.D	P=0.01*
	1.53	.507	.40	.498	

*Indicates significant value.
Significance value from Fisher's exact test is 0.856.

Majority of patients in clonidine group had significant sedation, $p<0.05$(here it is p=0.01) compared to fentanyl group.

Discussion

There were significant differences between the two groups with respect to the occurrences of bradycardia, hypotension, pruritus and in sedation scores as the significance values obtained from Fisher's exact test were less than 0.05 for each of these variables.

In our study heart rate change at 30 min were statistically significant $p<0.05$ (here it is p-0.014) There were not much differences in the heart rate observed up to 180 minutes after the administration of the drugs except at 30 min there were no significant changes in the heart rates between the 2 groups at corresponding time intervals with significance value more than 0.05.

The changes in systolic blood pressure at 60 min were statistically significant $p<0.05$ (here it is p-0.042). There were not much differences in the systolic blood pressure observed upto 180 minutes after the administration of the drugs except at 60 min. Statistically there were no significant changes in the systolic blood pressure between the 2 groups at corresponding time intervals with significance value more than 0.05.

The changes in diastolic blood pressure at 30 min and 60 min were statistically significant $p<0.05$ (here it is p-0.016 and p-0.001). There were not much differences in the diastolic blood pressure observed upto 180 minutes after the administration of the drugs except at 30 and 60 min. Statistically there were no significant changes in the diastolic blood pressure between the 2 groups at corresponding time intervals with significance value more than 0.05.

A study done in 2007, B.S. Sethi *et al.* Low dose intrathecal clonidine as adjuvant to bupivacaine found statistically significant decrease in mean arterial pressure (MAP) and heart rate was noted in the Clonidine group compared to the Control group, none of the patients required any therapeutic intervention for either [6].

Racle *et al.* in their study using isobaric bupivacaine spinal anaesthesia with epinephrine and clonidine for hip surgery in elderly found that intrathecal clonidine (150 μg) for patients aged 75 years or more resulted in a decrease in systolic blood pressure of only 15% from resting values.

Filos *et al.* reported significant decrease in arterial blood pressure after administration of 150μg of clonidine, but heart rate was unaffected in their study.

Mercier *et al.* observed a 63% incidence of hypotension (systolicblood pressure < 95 mmHg or decreased by > 25%) with clonidine 30 μg and sufentanil 5 μg versus a 12% incidence with sufentanil alone.

D'Angelo *et al.* similarly found a 60% incidence of hypotension (< 20% decrease in systolic blood pressure) with clonidine 50 μg, bupivacaine 2.5 mg, and sufentanil 7.5 μg, compared with 33% in the IT bupivacaine-sufentanil control group.

B S Sethi, 2007, demonstrated that addition of clonidine to bupivacaine in the dose of $1\mu g.kg^{-1}$significantly increase the duration of analgesia following its placement in subarachnoid space as compared to bupivacaine alone. These doses have an effect on sedation level, heart rate and mean arterial pressure which does not however, require any therapeutic intervention. The results of their study showed that addition of $1\mu g.kg^{-1}$of clonidine to intrathecal bupivacaine is safe and likely to be as effective as higher dosages minimizing the side effects [6].

Negri *et al.*, 1997, looked at the interactions and effects on the cardiovascular system of spinal anaesthesia with clonidine and bupivacaine in young humans and found the addition of 105 μg clonidine to hyperbaric bupivacaine 1% was particularly useful in unilateral spinal anaesthesia, exerting minimal influence on haemodynamic parameters and guarantying a satisfactory postoperative analgesia [7].

Chiari *et al.*, 1998, in a dose response study using intrathecal clonidine as sole analgesic during first stage of labour found that 50-200μg of intrathecal clonidine produces dose dependent analgesia. Although the duration and quality of analgesia were more pronounced with 100μg (60-180min) and 200μg (75-210min) than with 50μg (25-150 min), the high incidence of hypotension required caution with use of 200 μg for labor analgesia [8].

Gary M. stocks, 2001 found that combination of 2.5 mg bupivacaine with 25 μg fentanyl is associated with high success rates for provision of analgesia in labor. study aimed to determine the median effective dose (ED50) of intrathecal bupivacaine, defined as the minimum local analgesic dose (MLAD), and then use this to assess the effect of different doses of fentanyl.[9] There was a dose-dependent increase in both pruritus and duration of spinal analgesia with increasing fentanyl. Under the conditions of this study, the addition of intrathecal fentanyl 5 mg offers a similar significant bupivacaine dose-sparing effect as 15 and 25 mg. analgesia in the first stage of labor can be achieved using lower doses of fentanyl, resulting in less pruritus but with a shortening of duration of action.

Conclusion

Intrathecal administration of clonidine $1\mu g.kg^{-1}$ as additive to intrathecal hyperbaric bupivacaine was associated with side effects like bradycardia and hypotension which did not require any treatment.

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