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A COMPARATIVE STUDY OF THE EFFECTS OF INTRATHECAL BUPIVACAINE (0.5%) WITH CLONIDINE (1µg/kg) VERSUS INTRATHECAL BUPIVACAINE (0.5%) WITH FENTANYL (25µg) FOR SPINAL ANAESTHESIA

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ABSTRACT: BACKGROUND: Hyperbaric bupivacaine has been the gold standard drug for the safe conduct of spinal anaesthesia. It offers duration of 1.5 to 2.5 hours of anaesthesia and analgesia, various adjuvants are being used with local anesthetics for prolongation of intraoperative and postoperative analgesia. clonidine, an α_2 adrenergic agonist is new neuraxial adjuvant gaining popularity. **AIM:** The purpose of this study was to compare the efficacy of sensory and motor block, degree of postoperative analgesia, and adverse effects of clonidine and fentanyl used intrathecally with hyperbaric bupivacaine for spinal anaesthesia. **SETTINGS AND DESIGN:** the study was conducted in prospective, double blind manner, included 60 ASA class I and II patients undergoing lower limb, lower abdominal, gynaecological and urological surgeries under spinal anaesthesia after approval from hospital ethics committee with written and informed consent of patients. **MATERIALS AND METHODS:** the patients were randomly allocated into two groups (30 patients each), group C received hyperbaric bupivacaine 15mg with clonidine 1µg.kg⁻¹ and group F received hyperbaric bupivacaine 15mg with fentanyl 25µg. This randomized study was conducted to compare the effects with regards to, Onset and duration of block, degree of post-operative analgesia (evaluated by VAS scale) and side effects associated with the drugs were recorded. **RESULTS:** Patients in group C had significantly longer sensory and motor block times than group F. The mean onset of sensory block in group C was 136.67sec and in group F was 138.33 sec. The mean onset of motor block in group C was 200.00sec and in group F was 206.67 sec. There were no differences with respect to the onset of block. The mean duration of sensory block in group C was 343.67min and in group F was 250.83min. **CONCLUSIONS:** There were no differences in the onset of sensory and motor blockade. The duration of analgesia, two segment regressions, and recovery of motor blockade were prolonged when clonidine 1µg.kg⁻¹ was used as an additive to intrathecal hyperbaric bupivacaine compared to fentanyl 25µg for spinal anaesthesia, with side effects like bradycardia, hypotension and pruritus which did not require any treatment. Mild sedation was associated with intrathecal administration of clonidine 1µg.kg⁻¹ which did not require any treatment.

KEYWORDS: α_2 adrenoreceptor agonist, bupivacaine, clonidine, fentanyl, spinal anaesthesia.

INTRODUCTION: Hyperbaric bupivacaine has been the gold standard drug for the safe conduct of spinal anaesthesia.¹ It offers duration of 1.5 to 2.5 hours of anaesthesia and analgesia. Discovery of various spinal receptors like α_2 -adrenergic, cholinergic, opioid, NMDA, GABA,

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benzodiazepam receptors triggered the usage of drugs like eclonidine,² neostigmine,³ opioids,⁴ ketamine,⁵ midazolam⁶ for synergistic effect with hyperbaric bupivacaine (0.5%) in prolonging the duration of analgesia.

The administration of local anaesthetics in combination with opioids intrathecally is an established technique for managing postoperative pain. Local anaesthetics with opioids demonstrate significant synergy.⁷ They provide excellent analgesia with fewer drug requirements and decreased side effects.⁸ Fentanyl a newer opioid agent is said to offer some unique advantages, because of its greater lipophilicity and mu-receptor binding capacity, fastens the onset, prolongs the duration and improves the quality of postoperative analgesia.⁹

Intrathecal clonidine is being extensively evaluated as an alternative to neuraxial opioids for control of pain and has been proven to be a potent analgesic. It has been used as a sole agent. However there is still dearth of studies using intrathecal clonidine for postoperative analgesia in lower abdominal surgeries. Previous studies have used this drug intrathecally in higher dosages.

As there are not many studies comparing efficacy of intrathecal bupivacaine (0.5%) with clonidine and intrathecal bupivacaine (0.5%) with fentanyl, we decided to compare these two drugs in our present study and assess their efficacy and quality of block, also the possible side effects, correlating it with degree of postoperative analgesia.

MATERIALS AND METHODS: This clinical study was conducted on 60 adult patients of ASA physical status I & II 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 anaesthesia.

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.

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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.

METHOD OF STUDY: Pre anaesthetic checkup was carried out preoperatively with a detailed history, general physical examination and systemic examination. Airway assessment and spinal column examination were done.

The following laboratory examination was done in selected cases:

- Haemoglobin
 - Urine analysis
 - Blood sugar
 - Blood urea
 - Serum creatinine
 - Coagulation profile
 - Blood grouping and Rh typing
 - ECG-for patients over 40 years of age
 - Chest X- ray
- Preoperatively:-
- Patient's informed consent was taken.
 - Nil per oral status was confirmed.
 - The procedure of subarachnoid block was explained and the patient was informed to communicate to the anaesthesiologist about perception of any pain or discomfort during the surgery.
 - They were pre medicated with tab diazepam 10 mg and tab ranitidine 150 mg orally 10:00 pm at night before surgery and at 7:00am on the morning of surgery.

In the pre-operative room, intravenous line was secured and the patients were preloaded with 15 ml / kg Ringer's lactate, 30 minutes prior to spinal anaesthesia.

In each case, spinal anaesthesia was performed under strict aseptic precautions by inserting 25 gauge Quincke's spinal needle into subarachnoid space at L₂₋₃ or L₃₋₄ interspace. Patients belonging to group 'C' received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus 1 µg.kg⁻¹ of clonidine. Patients of group 'F' received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus (25 µg) of fentanyl. After injection, patient was immediately turned to supine position.

Standard monitoring was carried out in the form of pulse oximetry, ECG and non-invasive arterial blood pressure monitoring. Pulse rate, respiratory rate, arterial blood pressure and oxygen saturation were recorded every 3mins for first 10 mins, every 5 mins for next half an hour and then every 10 mins intra operatively. Bolus doses of Inj mephenteramine 6 mg i.v. were given to maintain arterial blood pressure within 20 % of baseline and inj atropine 0.6 mg i.v. was given when the patient developed bradycardia (PR < 50 beats/min).

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No other sedative or analgesic was given in the study period. Sensory block was assessed by pin pricks in mid clavicular line bilaterally using 25 gauge hypodermic needle. The onset of sensory block was considered as the time taken from intrathecal injection to the highest level of the sensory block. The duration of sensory block was taken from the time of intrathecal injection to regression of the level of sensory block to L₁ dermatome. Duration of motor block was recorded from onset time to time when the patient was able to lift the extended leg.

MODIFIED BROMAGE SCALE:

Grade 0 - Full flexion of knees and feet.

Grade 1 - Just able to flex knees, full flexion of feet.

Grade 2 - Unable to flex knees, but some flexion of feet possible.

Grade 3 - Unable to move legs or feet.

The duration of complete analgesia was taken from the time of intrathecal drug administration to the first report of pain. The duration of effective analgesia was taken from the time of intrathecal drug administration to the time of first supplementation with rescue analgesic. Injection diclofenac sodium 1.0 mg / kg intramuscular was the rescue analgesic given if VAS was found to be 5 or more.

Sedation scores were assessed every 15 minutes both intra and post operatively using a four point score described by Chernik et al.

Grade 0 – patient wide awake.

Grade 1 – patient is sleeping comfortably, but responding to verbal commands.

Grade 2 – deep sleep, but arousable.

Grade 3 – deep sleep, unarousable.

Post operatively, monitoring of vital signs, VAS scores and sedation scores was continued every 30 minutes until the time of regression of sensory block to L₁ dermatome. The incidence of hypotension (arterial blood pressure < 20 % of baseline), bradycardia (heart rate <50beats/min), pruritus, nausea, vomiting and urinary retention were monitored in the recovery room and then shifted to the ward.

Neurological examination was done to rule out any neurological deficits at discharge. The anaesthesiologist who performed subarachnoid block was not involved in the assessment of patients and observers were blinded. The Statistical software namely SPSS 17.0, Stata 8.0, were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

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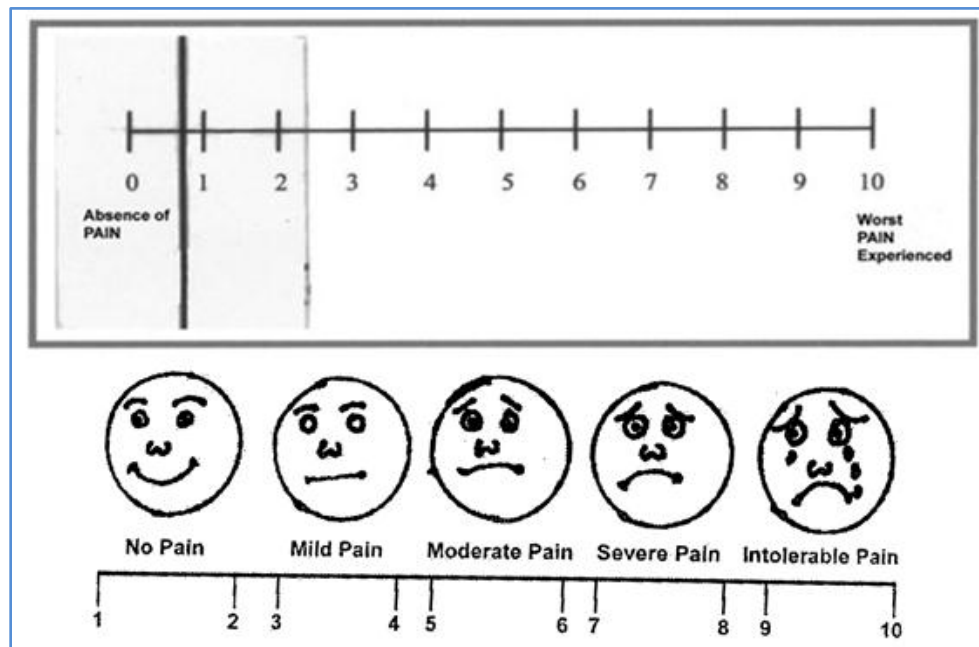


Figure 1: Linear Visual Analog Scale

VAS Score	Intensity of pain
0 – 2	No pain to slight pain
2 – 5	Mild pain.
5 – 7	Moderate pain.
7 – 9	Severe pain.
10	Worst possible pain.

Table 1: Linear Visual Analog Scale Score

RESULTS: This randomized study was conducted to compare the effects with regards to,

- Onset and duration of block.
- Degree of post-operative analgesia.
- Side effects associated with the drugs.

ONSET OF ANALGESIA AND MOTOR BLOCK:

	Group C		Group F		Significance
	Mean	SD	Mean	SD	
Onset of Analgesia(sec)	136.67	49.989	138.33	35.727	P > 0.05
Onset of Motor Block(Sec)	200.00	63.463	206.67	36.325	

Table 2: Onset of Analgesia and Motor Block

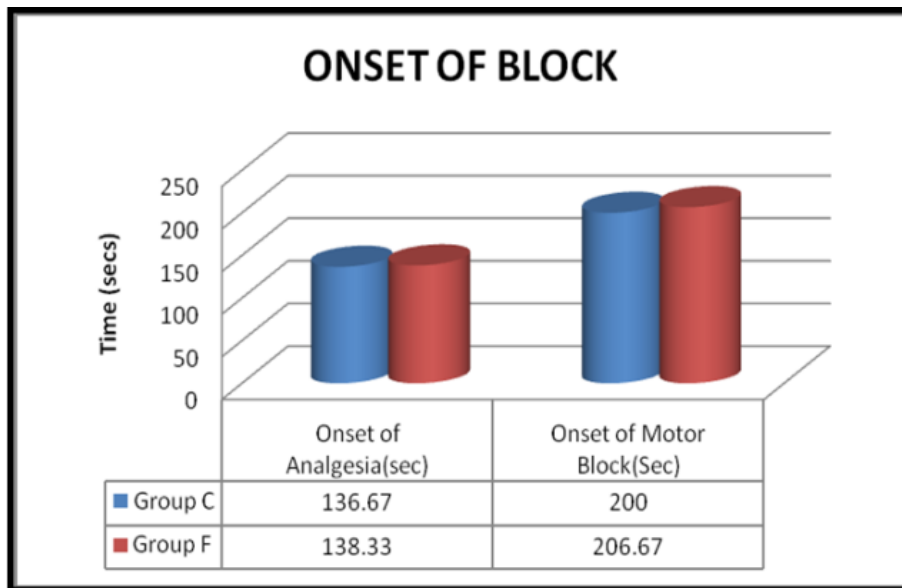


Figure 2: Onset of Analgesia and Motor

- The mean onset of sensory block in group C was 136.67 sec and in group F was 138.33 sec.
 - The mean onset of motor block in group C was 200.00 sec and in group F was 206.67 sec.
- There were no differences between the two groups with respect to the onset of block as significance value obtained from independent sample's t test was more than 0.05 (here it is 0.882 and 0.619). This means that there were no differences in the onset of sensory and motor block between clonidine and fentanyl groups.

DURATION OF ANALGESIA:

Duration of analgesia (min)	Group C		Group F		Significance
	Mean	SD	Mean	SD	P=0.01*
	343.67	34.59	250.83	33.22	

Table 3: Duration of Analgesia

*Indicates significant value.

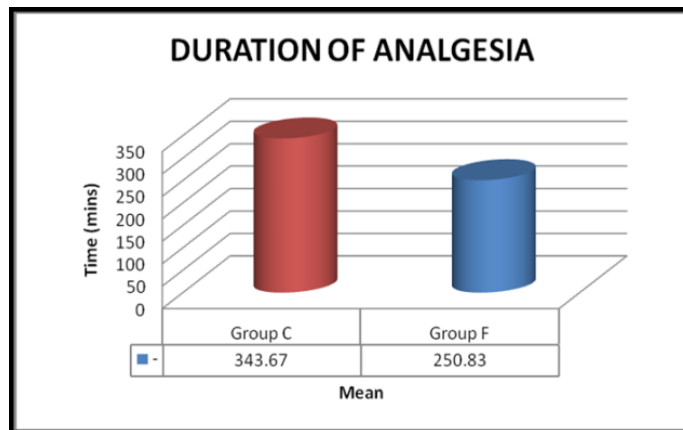


Figure 3: Duration of Analgesia Block

The mean duration of sensory block in group C was 343.67 min and in group F was 250.83 min. There were differences between the two groups with respect to the duration of block as significance value obtained from independent sample's t test was less than 0.05 (here it is 0.01). This means that clonidine group has prolonged durations of sensory block compared to fentanyl group and statistically highly significant.

TWO SEGMENT REGRESSIONS:

Two Segment Regression (Min)	Group C		Group F		Significance
	Mean	SD	Mean	SD	
	249.67	36.245	174.50	18.586	

Table 4: Two Segment Regression

*Indicates significant value.

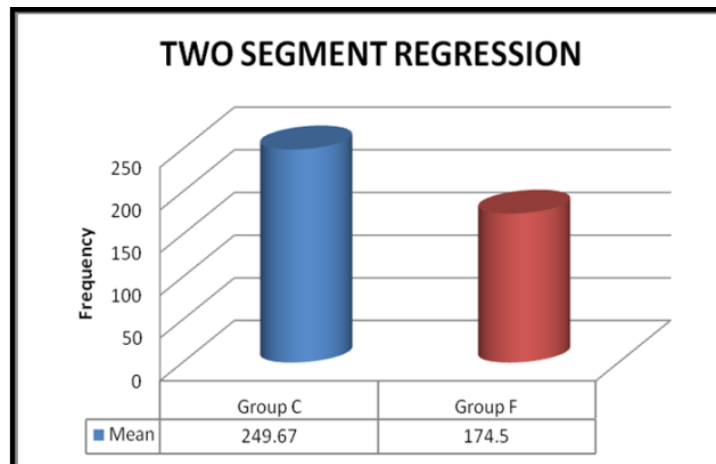


Figure 4: Two Segment Regression

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The mean duration of two segment regression in group C was 249.67 min and in group F was 174.50 min. There were differences between the two groups with respect to the two segment regression as significance value obtained from independent sample's t test was less than 0.05 (here it is 0.01). The mean time from injection to regression of the level of sensory analgesia by two segments was longer in the Clonidine group than in Fentanyl group ($P < 0.01$)

SEDATION SCORE:

Sedation_Score	Group C		Group F		Significance
	Mean	S.D	Mean	S.D	
	1.53	.507	.40	.498	

Table 5: Distribution of sedation scores

*Indicates significant value.

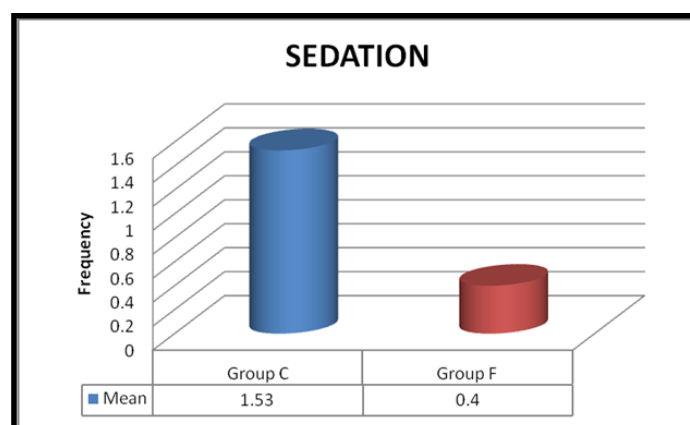


Figure 5: Distribution of sedation scores

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.

VAS SCALE:

VAS	Group C		Group F		Significance
	Mean	SD	Mean	SD	
2 hours	0	0	1.8519	0.53376	P=0.01*
3 hours	2.1071	0.31497	3.1852	0.55726	P=0.01*
4 hours	2.5714	0.79015	4.5926	0.57239	P=0.01*
5 hours	3.7857	0.73822	4.9	0.31623	P=0.01*

Table 6: Distribution of VAS Scale

*Indicates significant value.

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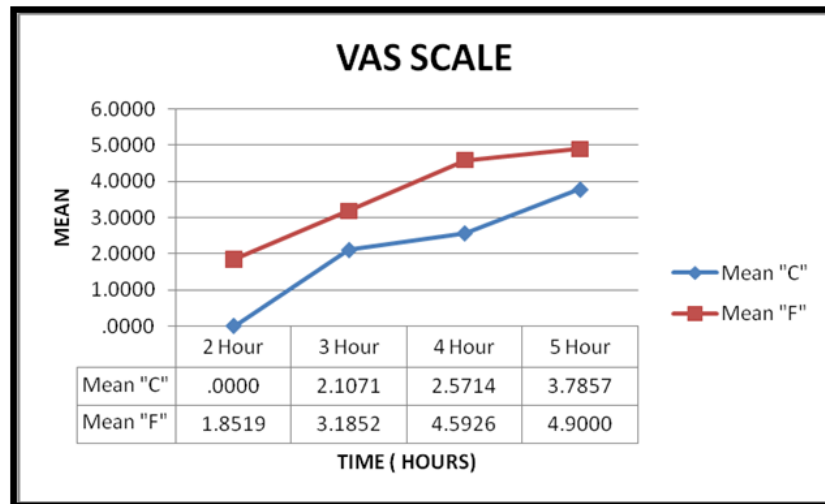


Figure 6: Distribution of VAS Scale

SIDE EFFECTS:

Side effects	Clonidine	Fentanyl
Bradycardia	5	0
Hypotension	2	0
Nausea	0	1
Pruritus	0	8
U.Retention	0	1
Vomiting	1	1

Table 7: side effects

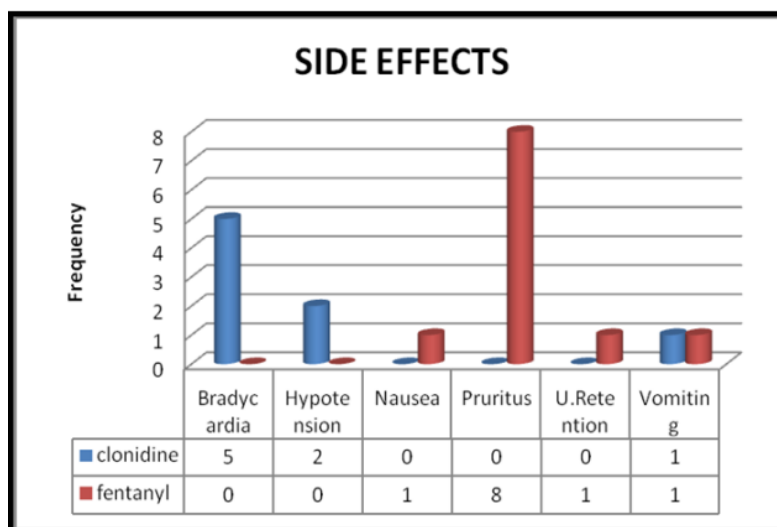


Figure 7: Side effects

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DISCUSSION: Effective pain control is essential for optimum care of patients in the postoperative period. However, despite advances in the knowledge of pathophysiology of pain, the pharmacology of analgesics and the development of more effective techniques, patients continue to experience considerable pain after surgery.

Subarachnoid block with bupivacaine has been most extensively used for lower abdominal¹⁰ and lower limb surgeries¹¹ because of its simplicity, speed, reliability and minimal exposure to depressant drugs. However, a single intrathecal injection of bupivacaine provides analgesia for only 2-2.5 hours. Most patients require further analgesia during post-operative period.

Various adjuvants to intrathecal local anaesthetics such as opioids,⁹ ketamine,⁵ neostigmine³ are often added to enhance the duration and quality of spinal anesthesia. Their use is limited because of significant adverse effects such as pruritus, urinary retention, respiratory depression, haemodynamic instability, nystagmus, nausea and vomiting.¹²

Neuraxial administration of opioids along with local anaesthetics improves quality of intra operative analgesia and also provides post-operative pain relief for longer duration.⁹ Fentanyl, a highly lipophilic opioid, has rapid onset of action following intrathecal administration.¹³ It is associated with fewer side effects compared to morphine.¹⁴ It has become very popular additive to hyperbaric bupivacaine in recent times. However, fentanyl has side effects like pruritus, nausea and vomiting and even a possible serotonin syndrome related to intrathecal fentanyl has been reported.¹²

Clonidine is a mixed α_1 and α_2 adrenoceptor agonist with a predominant α_2 action. Its primary effect is sympatholysis and it reduces peripheral norepinephrine release by stimulation of the prejunctional inhibitory α_2 -adrenoceptors. Further uses based on its sedative, anxiolytic and analgesic properties are being developed.

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

Several other investigators have studied the effect of intrathecal clonidine. B.S. Sethi et al. has demonstrated that addition of clonidine to bupivacaine in the dose of 1 μ g.kg⁻¹ significantly increases 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 show that addition of 1 μ g.kg⁻¹ of clonidine to intrathecal bupivacaine is safe and likely to be as effective as higher dosages minimizing the side effects.

Many authors are studying clonidine as an adjuvant to intrathecal bupivacaine for prolonging the post-operative analgesia. The aim of various studies has been to optimise the dose of intrathecal clonidine for prolonging the duration of postoperative analgesia with least side effects.

B S Sethi et al in 2007, has chosen 1 μ g.kg⁻¹ of clonidine for the study as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study we chose 1 μ g.kg⁻¹ clonidine as an additive to hyperbaric bupivacaine.

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Harbhej singh et al, BN Biswas et al, Khanna MS et al have chosen 25 µg of fentanyl as an additive to intrathecal hyperbaric bupivacaine in their studies.¹⁵ Hence in our study, we chose 25 µg of fentanyl as an additive to hyperbaric bupivacaine.

- Patients of group C received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus 1 µg.kg⁻¹ of clonidine.
- Patients belonging to group F received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus 25 µg of fentanyl.

The results of the clinical study are discussed under the following headings;

ONSET OF SENSORY BLOCKADE: The mean onset of sensory block in fentanyl group was 138.33 sec and in clonidine group, mean onset of sensory block was 136.67 sec. Similar values were obtained with regard to the onset of sensory block in clonidine group in the studies conducted by B S Sethi et al, Medge D. Owen et al, Alex Tiong-Heng Sia et al. There were no differences between the two groups with respect to the onset of block as significance value obtained from independent sample's t test was more than 0.05 (here it is 0.882).

DURATION OF SENSORY BLOCKADE: The mean duration of sensory block in group C was 343.67 min and in group F, mean duration of sensory block was 250.83 min. There was a significant difference ($P < 0.01$) in the mean duration of analgesia between the two groups. A study done in 2007, B.S. Sethi et al. Low dose intrathecal clonidine as adjuvant to bupivacaine found out that mean duration of analgesia between the two groups, the recordings being, 614min (480– 1140min) in the Clonidine group as against 223 min (150- 300 min) in the Control group.

SIDE EFFECTS: There were significant differences between the two groups with respect to the occurrences of bradycardia, hypotension and 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 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.

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.

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

There were no significant differences between the two groups with respect to the occurrence of nausea as the significance value obtained from Fisher's exact test was more than 0.05. The association of pruritus with fentanyl was statistically significant as the significance value from Fisher's exact test was less than 0.05. Pruritus was mild and didn't require any treatment. None of the patients in our study had any post-operative complications like urinary retention, respiratory depression, lower limb weakness or any other neurological deficits.

CONCLUSION: The present study concludes that,

1. There were no differences in the onset of sensory and motor blockade when clonidine 1µg.kg⁻¹ or fentanyl 25 µg was used as additive to intrathecal hyperbaric bupivacaine for spinal anaesthesia.
2. The duration of analgesia, two segment regression and recovery of motor blockade were prolonged when clonidine 1µg.kg⁻¹ was used as an additive to intrathecal hyperbaric bupivacaine compared to fentanyl 25 µg for spinal anaesthesia.
3. Intrathecal administration of clonidine 1µg.kg⁻¹ as additive to intrathecal hyperbaric bupivacaine was associated with side effects like bradycardia and hypotension which did not require any treatment.
4. Intrathecal administration of fentanyl as additive to intrathecal hyperbaric bupivacaine was associated with side effects like pruritus which did not require any treatment.
5. Mild sedation was associated with intrathecal administration of clonidine 1µg.kg⁻¹ which did not require any treatment.

SUMMARY: A clinical study was undertaken to compare the effects of intrathecal clonidine 1µg.kg⁻¹ and fentanyl 25 µg as additives to intrathecal bupivacaine 0.5 % for spinal anaesthesia. Patients belonging to group C received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus clonidine 1µg.kg⁻¹. Patients of group F received 3 ml (15 mg) of hyperbaric bupivacaine 0.5 % plus fentanyl 25µg. Standard monitoring was carried out in the form of pulse oximetry, ECG and non-invasive arterial blood pressure monitoring. Pulse rate, respiratory rate, arterial blood pressure and oxygen saturation were recorded every 3mins for first 10mins, every 5mins for next half an hour and then every 10mins intra operatively. The following parameters were observed - onset and duration of block, degree and durations of postoperative analgesia and any side effects associated with these drugs.

1. The present study concludes that there were no differences in the onset of block.
2. The duration of analgesia, two segment regressions and recovery of motor blockade were prolonged when clonidine 1µg.kg⁻¹ was used as additive to intrathecal hyperbaric bupivacaine for spinal anaesthesia.

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

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