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		Print Only	Online Only	Print Only	Online Only
Dermatology International	Semiannual	5500	5000	430	391
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Indian Journal of Diabetes and Endocrinology	Semiannual	8000	7500	597	560
Indian Journal of Genetics and Molecular Research	Semiannual	7000	6500	547	508
Indian Journal of Hospital Administration	Semiannual	7000	6500	547	508
Indian Journal of Hospital Infection	Semiannual	12500	12000	938	901
Indian Journal of Medical & Health Sciences	Semiannual	7000	6500	547	508
Indian Journal of Pathology: Research and Practice	Bi-monthly	12000	11500	938	898
Indian Journal of Preventive Medicine	Semiannual	7000	6500	547	508
International Journal of Neurology and Neurosurgery	Quarterly	10500	10000	820	781
International Physiology	Triannual	7500	7000	586	547
Journal of Cardiovascular Medicine and Surgery	Quarterly	10000	9500	781	742
Journal of Global Medical Education and Research	Semiannual	5900	5500	440	410
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Journal of Organ Transplantation	Semiannual	26400	25900	2063	2023
Journal of Orthopedic Education	Triannual	5500	5000	430	391
Journal of Pharmaceutical and Medicinal Chemistry	Semiannual	16500	16000	1289	1250
Journal of Practical Biochemistry and Biophysics	Semiannual	7000	6500	547	508
Journal of Radiology	Semiannual	8000	7500	625	586
New Indian Journal of Surgery	Bi-monthly	8000	7500	625	586
Ophthalmology and Allied Sciences	Triannual	6000	5500	469	430
Otolaryngology International	Semiannual	5500	5000	430	391
Pediatric Education and Research	Quarterly	7500	7000	586	547
Physiotherapy and Occupational Therapy Journal	Quarterly	9000	8500	703	664
Urology, Nephrology and Andrology International	Semiannual	7500	7000	586	547
Indian Journal of Maternal-Fetal & Neonatal Medicine	Semiannual	9500	9000	742	703
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Indian Journal of Emergency Medicine	Quarterly	12500	12000	977	938
Indian Journal of Trauma and Emergency Pediatrics	Quarterly	9500	9000	742	703
Journal of Emergency and Trauma Nursing	Semiannual	5500	5000	430	391
Indian Journal of Forensic Medicine and Pathology	Quarterly	16000	15500	1250	1211
Indian Journal of Forensic Odontology	Semiannual	5500	5000	430	391
Indian Journal of Legal Medicine	Semiannual	8500	8000	664	625
International Journal of Forensic Sciences	Semiannual	10000	9500	781	742
Journal of Forensic Chemistry and Toxicology	Semiannual	9500	9000	742	703
Community and Public Health Nursing	Triannual	5500	5000	430	391
Indian Journal of Surgical Nursing	Triannual	5500	5000	430	391
International Journal of Pediatric Nursing	Triannual	5500	5000	430	391
International Journal of Practical Nursing	Triannual	5500	5000	430	391
Journal of Gerontology and Geriatric Nursing	Semiannual	5500	5000	430	391
Journal of Nurse Midwifery and Maternal Health	Triannual	5500	5000	430	391
Journal of Psychiatric Nursing	Triannual	5500	5000	430	391
Indian Journal of Ancient Medicine and Yoga	Quarterly	8000	7500	625	586
Indian Journal of Law and Human Behavior	Semiannual	6000	5500	469	430
Indian Journal of Medical Psychiatry	Semiannual	8000	7500	625	586
Indian Journal of Biology	Semiannual	5500	5000	430	391
Indian Journal of Library and Information Science	Triannual	9500	9000	742	703
Indian Journal of Research in Anthropology	Semiannual	12500	12000	977	938
Indian Journal of Waste Management	Semiannual	9500	8500	742	664
International Journal of Political Science	Semiannual	6000	5500	450	413
Journal of Social Welfare and Management	Triannual	7500	7000	586	547
International Journal of Food, Nutrition & Dietetics	Triannual	5500	5000	430	391
Journal of Animal Feed Science and Technology	Semiannual	7800	7300	609	570
Journal of Food Additives and Contaminants	Semiannual	5000	4500	391	352
Journal of Food Technology and Engineering	Semiannual	5000	4500	391	352
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## Comparison of Intrathecal Fentanyl and Clonidine with 0.5% of Bupivacaine Heavy in Spinal Anaesthesia in Elderly Urological Surgeries

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### Abstract

**Background:** Lipophilic opioids (fentanyl) and alpha-2 agonist (clonidine) are increasingly being administered intrathecally as adjuncts. They enhance the effect of spinal anaesthesia without prolonging motor recovery and discharge time. **Aims and objectives:** To work out the influence of intrathecal fentanyl vs intrathecal clonidine with low dose (2.5 ml) bupivacaine in urological surgeries. **Materials and methods:** The study was a randomized, prospective study conducted as a double blind trial at the tertiary care hospital. Total 60 patients were included in this study, after fulfilling standard criteria. The study population have patients of either sex, ASA physical status I and II in the range of 50-70 years. Patients were randomly assigned to Fentanyl (F) group and Clonidine (C) group. They were assessed for analgesia time, complications, hemodynamic changes and sensory and motor block. **Statistical tests:** All the data was collected and entered in Microsoft Excel sheet and transferred to SPSS software ver.17 for analysis. Chi-Square test, unpaired student 't' test and paired 't' test was used. P - Value of <0.05 was considered statistically significant and that of < 0.001 was considered statistically highly significant. **Results:** Time of onset of motor block (min) was significantly faster in group C ( $2.21 \pm 0.6$ ) as compared to group F ( $5.4 \pm 0.8$ ). Time of onset of sensory block (min) was significantly faster in group C ( $2.44 \pm 0.5$ ) as compared to group F ( $6.12 \pm 0.7$ ). **Conclusion:** The onset of sensory and motor blockade was faster with clonidine. Clonidine offered good post-operative analgesia. Fentanyl may be a better choice for surgeries requiring minimal hospital stay.

**Keywords:** Intrathecal Anaesthesia, Bupivacaine, Fentanyl, Clonidine, Urological, Surgeries.

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### Introduction

Spinal anaesthesia is most frequently used for urological surgeries like, prostate, bladder, and genital surgeries [1].

Neuraxial anaesthesia by using only local anaesthetic drug provides suboptimal anaesthesia with lower side effects. Many drugs have been added to local anaesthetic drug to provide the greatest anaesthesia with minimal side effects and

the adjuncts are opioids, midazolam, epinephrine, clonidine, magnesium, and ketamine [2,3].

Lipophilic opioids (fentanyl) and alpha-2 agonist (clonidine) are increasingly being administered intrathecally as adjuncts to local anaesthetic drug. They enhance the effect of spinal anaesthesia without prolonging motor recovery and discharge time [4].

Opioids are usually used for providing better analgesia and reducing side effects. Fentanyl has close structural similarities to local anaesthetic

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drug and has demonstrable local anaesthetic effect on sensory C primary afferent nerve fibres, which may provide analgesic effect [5,6].

Fentanyl is commonly given intrathecally and epidurally with local anaesthetics. It has high lipid solubility causing more local effects with less respiratory depression.

However, the superior analgesia has to be rationalised against side effects such as sickness-nausea/vomiting, pruritus, bradycardia, arterial hypotension and respiratory depression. Evidence showed that even a single administration of an opioid can cause a long lasting increase in pain sensitivity threshold which leads to delayed hyperalgesia [7].

On the other hand, stimulation of  $\alpha_2$ -adren-receptors by clonidine also has antihyperalgesic properties [8,9,10] with effect similar to norepinephrine and its antihyperalgesic mechanism that partially depends on fortification of noradrenergic inhibitory controls in the dorsal horn of the spinal cord [11].

Clonidine is known for treatment of high blood pressure by stimulating  $\alpha_2$ -receptors in the brain, which reduces peripheral vascular resistance (PVR) thus lowering blood pressure. It has specificity for the presynaptic  $\alpha_2$ -receptors in the vasomotor centre in the brainstem. This binding reduces presynaptic calcium levels and hence inhibits the release of norepinephrine and this decreases the sympathetic tone [12]. It has been found that the antihypertensive effect of clonidine is a result of its action on agonist of the I1-receptor (imidazoline receptor), which mediates the sympatho-inhibitory actions of imidazolines to decrease blood pressure [13]. The safety of intrathecal clonidine has been widely evaluated in humans, obstetric anaesthesia, and animals [14].

In our study, we have compared the effects of low dose 0.5% bupivacaine heavy (2.5 ml) with fentanyl (25 ug) and clonidine (25 ug) in elderly patients to who will undergo urological surgeries.

#### *Aims and objectives*

1. To study the effect of intrathecal fentanyl vs intrathecal clonidine with low dose (2.5 ml) bupivacaine in urological surgeries.
2. To compare their effects on the basis of
  - a) Analgesic efficacy
  - b) Intraoperative hemodynamic changes
  - c) Incidence of intraoperative and postoperative complication

- d) To compare the duration of motor and sensory block
- e) To analyse the total duration of postoperative analgesia

#### **Material and methods**

After obtaining acceptance from hospital research and ethics committee this study was conducted as a double blind trial from May 2016 to October 2017 at the tertiary care hospital. Total 60 patients were included in this study, after taking valid informed written consent as per ethical committee protocol. The study population included patients if either sex, ASA physical status I and II in the range of 50-70 years. All the included patients were acquainted with the VAS-visual analogue scale. Visual analogue is a 10 cm scale in that '0' suggest no pain and 10 suggest worst imaginable pain.

#### *Study design*

The study was a randomized, prospective study on patients who were assessed thoroughly in preoperative anaesthesia clinic.

*Clonidine group:* 2.5 ml of 0.5% bupivacaine (heavy)+25 micrograms of clonidine

*Fentanyl group:* 2.5 ml of 0.5% bupivacaine (heavy)+25 micrograms of fentanyl

#### **Methodology**

All the patients were fasted overnight and standard monitoring applied. No patient has received any sedative or narcotic premedication before going to the operation theatre. Inside operation theatre, standard monitoring attached and baseline vital parameters documented.

Intravenous cannula secured and Hartmann's solution was started 15 min before the time of intrathecal drug administration. All patients were given Inj. ondansetron 4 mg i.v. and Inj. ranitidine 150 mg i.v. Lumbar puncture was done in sitting position under aseptic technique at L3-4 or L4-5 intervertebral space by using midline approach with 25G Quincke spinal needle. Patients received one of the above two drug combination. Then patient was made to lie on back and surgery was allowed in lithotomy position after adequate motor and sensory block.

*Change in following parameters were studied*

### 1) Sensory block

Following parameters for sensory block were noted like onset of sensory block, time from injection to highest sensory level, highest sensory level attained. The cephalic spread of analgesia was noted. The level of sensory blockade was checked as analgesia to loss sensation to pin prick method. Time taken for sensory regression to L1 dermatome was documented.

### 2) Onset of motor block

Onset of motor block and the time taken for the motor block to wear off were recorded.

Motor blockade was assessed according to the modified Bromagescale.

Grade I: Free movement of Leg and feet

Grade II: Just able to flex knees with free movement of feet

Grade III: Unable to flex knees, but with free movement of feet

Grade IV: Unable to move legs or feet

### 3) Total analgesia time

It is the time interval from the onset of block to the administration of first rescue analgesic, when the VAS score is 5. Inj. Paracetamol 1 gm i.v. was used as rescue analgesia.

### 4) Hemodynamic changes

The parameters such as heart rate, non-invasive blood pressure, ECG, and oxygen saturation (SpO<sub>2</sub>) were monitored every 5 minutes from the time of injection for the first 20 minutes, then at half an hour interval and then hourly until the patient complained of pain or VAS of 5 in the postoperative period.

### 5) Intraoperative complications

Any specific complications such as breathing discomfort, nausea, vomiting, bradycardia, hypotension, shivering, pain, itching, arrhythmia and any other side effects were recorded. The need for additional medications was noted. Respiratory depression considered as a respiratory rate of less than or equal to 8/min or SpO<sub>2</sub> of ≤ 85%. Vomiting and nausea were treated with Inj. Ondansetron 4 mg i.v. and rigors, shivering, itching, postoperative pruritus were controlled with 120 mg of oral Fexofenadine (a nonselective H1 antagonist).

The level of sedation was assessed using the sedation score described by Chernik et al. as follow:

Grade 0: Wide awake

Grade II: Sleeping comfortably, responding to verbal commands

Grade II: Deep sleep but arousable

Grade III: Deep sleep, not arousable

Total duration of surgery was noted. Post-operatively all patients were assessed half hourly for first 3 hours and then every hour for 12 hours in recovery room. Any additional requirement of medications was documented.

IV fluids were administered depending on the weight of the patient and further adjusted as per hemodynamics and blood loss during surgery. A fall in systolic blood pressure of preoperative value was treated with rapid infusion of fluids and if there is no response to fluids 6 mg of injection ephedrine was administered intravenously. Bradycardia (heart rate less than 60/min) was treated with intravenous atropine sulphate. All patients were observed in the post anaesthesia recovery room and then in the ward. Pain was measured as per the pain score.

The results were tabulated and data was subjected to standard statistical tests.

### Statistical Analysis

All the data was collected and entered in Microsoft Excel sheet and transferred to SPSS software ver.17 for analysis. For qualitative data, the Chi-Square test was used, for two group comparison. Unpaired student 't' test for inter group comparisons and for intragroup comparisons. Paired 't' test was used. P - Value of < 0.05 was considered statistically significant and that of <0.001 was considered statistically highly significant.

### Results

Group C (30 Patients): Clonidine (25 µg)

Group F (30 Patients) - Fentanyl (25 µg)

The observations were compiled in tabulated manner and results were statistically analysed using Stat graphics Centurion Version 17.1.12 software.

Statistically, there was no significant difference among the groups in relation to age, gender, weight, height, ASA grading, sedation score and complications.

**Table 1:** Time of onset of motor block (min) amongst different study population

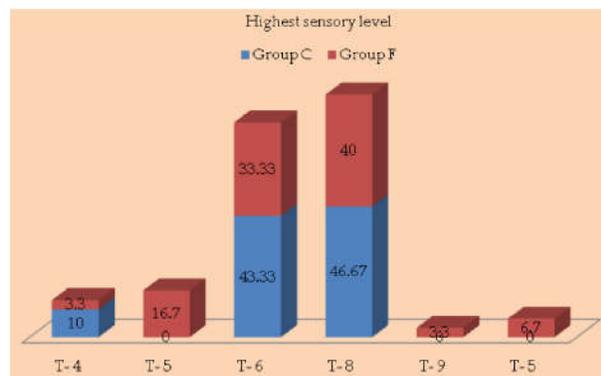
	Group C		Group F		P value
	Mean	SD	Mean	SD	
Time of onset of motor block (min)	2.21	0.6	5.4	0.8	0.0001

Time of onset of motor block (min) was significantly faster in group C ( $2.21 \pm 0.6$ ) as compared to group F ( $5.4 \pm 0.8$ ) amongst study population. (Table 1).

**Table 2:** Time of onset of sensory block (min) amongst different study population

	Group C		Group F		P value
	Mean	SD	Mean	SD	
Time of onset of sensory block (min)	2.44	0.5	6.12	0.7	0.0001

Time of onset of sensory block (min) was significantly faster in group C ( $2.44 \pm 0.5$ ) as compared to group F ( $6.12 \pm 0.7$ ) amongst study population.



**Graph 1:** Highest sensory level amongst different study population

Chi square - 9.53, df-5, P value 0.09 (NS)

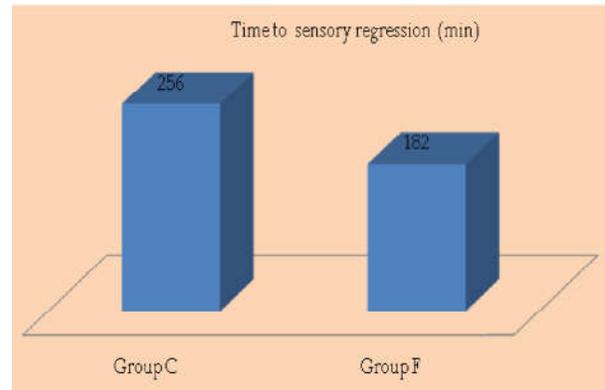
As seen in the above graph 1, highest sensory level was between T6 (Group C -43.33% vs Group F -33.33%) to T8 (Group C - 46.67% vs Group F - 40%) in both the groups. There was no significant difference between highest sensory level and different study groups. (p value - 0.09)

**Table 3:** Time to reach peak sensory level (min) amongst different study population

	Group C		Group F		P value
	Mean	SD	Mean	SD	
Time of reach peak sensory level (min)	20.13	5.3	14.59	3.7	0.0001

As seen in the above table 3, time of reach peak sensory level (min) was significantly faster in group F ( $14.59 \pm 3.7$ ) as compared to group C ( $20.13 \pm 5.3$ ) amongst study population.

amongst study population.



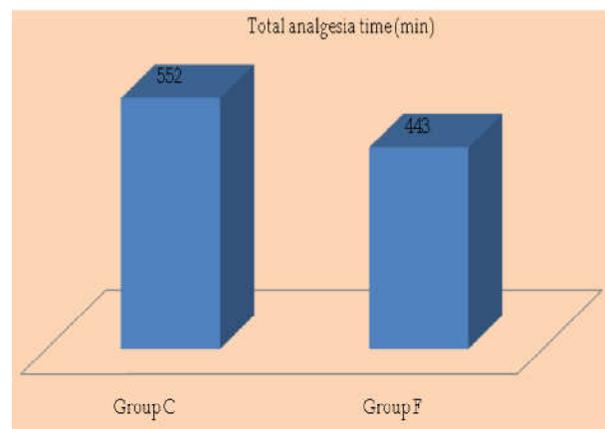
**Graph 2:** Time to sensory regression L1 (min) amongst different study population

As seen in the above Graph 2, time to sensory regression L1 (min) was significantly faster ( $P = 0.0001$ ) in group F ( $182 \pm 33.4$ ) as compared to group C ( $256 \pm 46.4$ ) amongst study population.

**Table 4:** Time to complete motor regression (min) amongst different study population

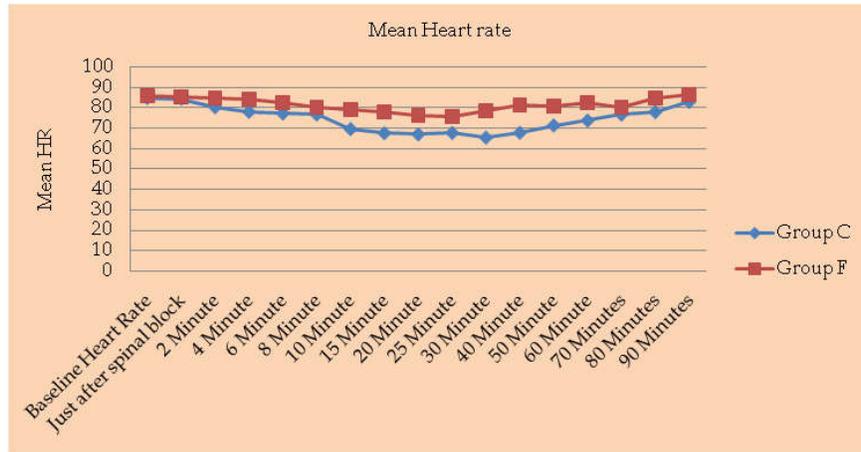
	Group C		Group F		P value
	Mean	SD	Mean	SD	
Time to complete motor regression (min)	283	55.3	199	41.2	0.0001

As seen in the above table 4, time to motor regression (min) was significantly faster in group F ( $199 \pm 41.2$ ) as compared to group C ( $283 \pm 55.3$ ) amongst study population.

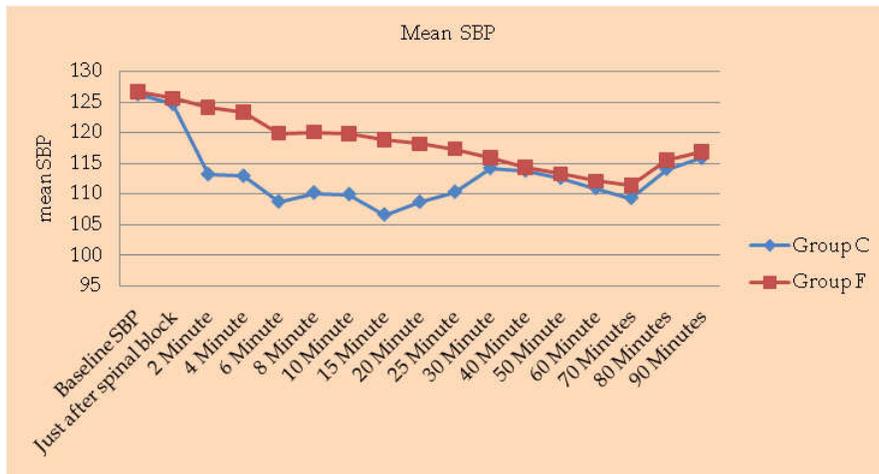


**Graph 3:** Total analgesia time (min) amongst different study population

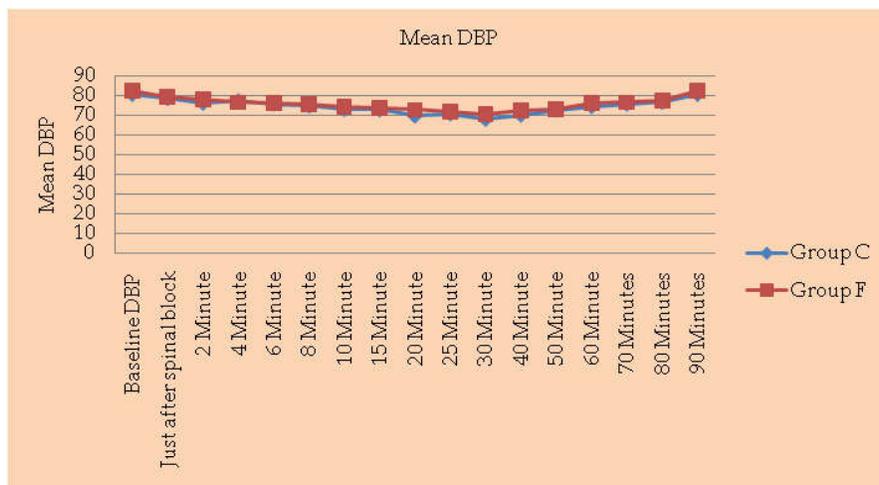
As seen in the above Graph 3, total analgesia time (min) was significantly more ( $p = 0.0001$ ) in group C (552) as compared to group F (443) amongst study population.



Graph 4: Heart rate amongst different study population at different time interval



Graph 5: SBP amongst different study population at different time interval



Graph 6 DBP amongst different study population at different time interval

There was significant decrease ( $p = 0.001$ ) in heart Rate was observed in Group C as compared to Group F from 2 minute onwards till 90 minutes.

There was significant decrease ( $p > 0.05$ ) in SBP was observed in Group C as compared to Group F from 2 minute onwards till 25 minutes.

There was significant decrease ( $p > 0.05$ ) in DBP was observed in Group C as compared to Group F at 20 minutes.

Table 5: Rescue analgesia amongst different study population

Rescue analgesia		Group C	Group F	Total
Required	N	5	9	14
	%	17	30.00	23.33
Not Required	N	25	21	46
	%	83.33	70.00	76.67
Total	N	30	30	60
	%	100%	100%	100%

Chi square - 1.49, df-1, P value 0.22

Rescue analgesia was required more commonly in Group F (30%) as compared to Group C (17%). There was no significant difference between Rescue analgesia and different study groups. ( $p$  value - 0.22) (Table 5).

## Discussion

The spinal anesthesia is preferred for urological surgeries as it is simple, easy to perform, and economical with rapid onset of anesthesia and complete muscle relaxation. Bupivacaine is relatively long acting local anesthetic. For short duration surgeries low dose of bupivacaine can be used. Addition of adjuvant to low dose of Bupivacaine is expected to provide good surgical anesthesia and extended period of analgesia. It also provides advantage of reduced sympathetic blockade because of reduced dose of bupivacaine and thereby giving hemodynamic stability intraoperatively [15].

The important determinant of both successful surgical anaesthesia and time until recovery is the dose of local anaesthetic drug. Low dose hyperbaric bupivacaine may be inadequate and addition of adjuvant likes fentanyl, clonidine improves the quality of analgesia [16].

Administration of neuraxial opioids in combination with local anaesthetics increases the quality of intra operative analgesia and prolongs the duration of postoperative analgesia [16].

Local anaesthetics and opioids cause their antinociceptive effect in the spinal cord by different mechanisms. Fentanyl exerts its action by opening  $K^+$  channels and reducing  $Ca^{++}$  influx which resulting in inhibition of transmitter release. Bupivacaine, exert action mainly by blockade of voltage-gated  $Na^+$  channels in the axonal membrane, Local anaesthetics may also interfere with synaptic transmission by a presynaptic inhibition of  $Ca^{++}$  channels in addition to their effects

on nerve conduction. These effects may describe the observed synergism between bupivacaine and fentanyl in our study group.

Fentanyl, an adjuvant to 0.5% hyperbaric bupivacaine, is a lipophilic  $\mu$  receptor agonist opioid. Fentanyl intrathecally provides its effect by combining with opioid receptors in the dorsal horn of spinal cord and have a supraspinal spread and action. Intrathecal effectiveness of opioids depends on the bioavailability [17]. Hence, good perioperative analgesia can be provided by opioids [18].

Clonidine is the most studied drug which is used for neuraxial analgesia [19]. Clonidine is moderately lipid soluble and easily crosses the blood-brain barrier leading to spinal and supraspinal receptor binding and produces effective and long-time postoperative analgesia.

Clonidine produces its mechanism by intrathecal  $\alpha_2$  adrenoceptor (atpresynaptic c-fibers and postsynaptic dorsal horn neurons) agonists which prolong the motor and sensory block of local anesthetics [20].

It's analgesic actions are predominantly due to the inhibition of the release of c-fibre transmitters and hyperpolarization of postsynaptic dorsal horn neurons. Prolonged analgesia effect is a result of synergism between local anesthetics and  $\alpha_2$ -adrenergic agonists at motor neurons in the dorsal horn [21]. Intrathecal  $\alpha_2$ -receptor agonists have also antinociceptive action for both visceral and somatic pain [22].

## Conclusion

1. This study suggests that use of both fentanyl and clonidine as adjuvant with low dose bupivacaine for urological surgeries is quite effective by increasing spread and duration of analgesia.
2. The onset of sensory and motor blockade was faster with clonidine.
3. Time taken to reach highest sensory level was faster with fentanyl.
4. Clonidine offered good post-operative analgesia.
5. Fentanyl may be a better choice for surgeries requiring minimal hospital stay due to its early motor recovery.
6. For in hospital stay, clonidine has definite beneficial effect.

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