*Original Research Article*

Indian Journal of Anesthesia and Analgesia
May – June 2020; 7(3): 791–797
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7320.21

# A Comparative Study of Mixture of Clonidine - Fentanyl Compared to Clonidine Alone as an Adjuvant to Intrathecal Hyperbaric Bupivacaine Under Spinal Anaesthesia for Infraumbilical Surgeries

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**Abstract**

*Aims:* Use of adjuvant drug along with inj. Bupivacaine for spinal anaesthesia is a well know modality & is being practiced to increase duration of anaesthesia & postoperative analgesia. The present study is carried out to study Clonidine + Fentanyl vs. only Clonidine when used as adjuvant to Bupivacaine increases the duration of spinal analgesia. Also the study was conducted to note the side effects of the adjuvant drugs when used for spinal anaesthesia *Methods:* It was a prospective, randomized, double-blind study, 60 ASA grade I-II patients (30 in each group), who were scheduled for elective infra-umbilical surgery under spinal anesthesia were recruited. Group- M patients received hyperbaric Bupivacaine (2.5ml) + Clonidine 30µg for spinal anaesthesia. Group- C patients received Bupivacaine (0.5%) 2.5ml + fentanyl (15µg) + Clonidine (15µg). The total volume of intra-thecal drug along with adjuvant drugs was constant (i.e. 3 ml, by adding normal saline) in both the groups. Onset and duration of sensory, motor block, effective analgesia, hemodynamic profile, post-operative pain score and side effects if any were recorded. *Results:* Duration of analgesia and duration of sensory and motor block were significantly longer in Group- C (165.02 ± 12.72 min) as compared to Group- M (130.78 ± 5.95 min). Haemodynamic profile showed significant low HR and MAP at certain time intervals in the Group- M as compared to Group- C. Patients of Group- M showed a significantly ($p < 0.05$) higher level of VAS as compared to Group- C at 60 min, 90 min and 120 min interval time. *Conclusion:* Low dose of Clonidine (15mcg) + Fentanyl (15mcg) as an adjuvant to intra-thecal %0.5 Bupivacaine for spinal anaesthesia produced prolonged post-operative analgesia in patients undergoing infra-umbilical surgeries with stable haemodynmics.

**Keywords:** Clonidine, Clonidine+Fentanyl as adjuvants, Hyperbaric Bupivacaine, Spinal anaesthesia, Infra-umbilical surgeries.

**How to cite this article:**

Sathesha M, Vandana Hebballi, Sathish Kumar. A Comparative Study of Mixture of Clonidine - Fntany Compared to Clonidine Alone as Adjuvant Intrathecal Hyperbaric Bupivacaine Under Spinal Anaesthesia for Infraumbilical Surgeries. Indian J Anesth Analg. 2020;7(3):791–797.

## Introduction

Surgeries below umbilicus (Infra-umbilical surgeries- Lower abdominal surgeries) and lower limb surgeries may be performed under local, regional, or general anaesthesia. Spinal anaesthesia is still the first choice of anaesthesiologists. Local anaesthestic Bupivacaine is the commonest drug used for spinal anaesthesia but its relatively shorter duration of action may lead to early rescue analgesic intervention in the post-operative period.[1] Many adjuvants were being added to local spinal anaesthetic drug for spinal anaesthesia to provide intraoperative as well as post-operative analgesia & to increase the duration of postoperative analgesia. Opioids are commonly used as intrathecal adjuvants

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**Received on** 13.02.2020, **Accepted on** 16.03.2020

to improve the quality of intraoperative analgesia and to prolong the post-operative analgesia period without significant motor or autonomic blockade. Among them Fentanyl is one of the most common adjuvant used.[2] Clonidine has been used as an adjuvant for regional anesthesia in various settings, including spinal anesthesia as a sole agent as well as in combination with opioids along with local anesthetics for labor analgesia, gynecological surgeries and in other surgeries too.[3] Most of the studies have used clonidine in the dose range of 75µg and above. In higher doses, Clonidine causes side effects e.g. Hypotension and bradycardia. Because of these clinically relevant side effects, there is a tendency to use the smaller doses of clonidine. By using low dose Clonidine and Fentanyl with Bupivacaine for spinal anaesthesia, the incidence of adverse effects/ side effects could be reduced.[4]

We have conducted the present study to evaluate and compare efficacy of addition of low dose Clonidine + Fentanyl vs. Clonidine alone added to Bupivacaine as adjuvants for spinal anaesthesia in patients posted for elective infra-umbilical surgeries.

**Material and Methods**

*Inclusion Criteria*

(a) Patients who are willing to give written informed consent

(b) Patients posted for infraumbilical surgeries.

(c) Age group 18- 60 years, of either sex.

(d) American Society of Anaesthesiologists (ASA) grade 1 and 2

(e) Weight 50-80kg.

(f) Height 150cm to 180cm.

*Exclusion Criteria*

(a) No consent

(b) Allergy to local anesthetics, opioids and clonidine.

(c) Uncontrolled diabetes mellitus, hypertension, recent myocardial infarction.

(d) Pregnancy.

(e) Contraindications/relative contraindications to spinal anaesthesia.

(f) Hypovolemic shock, Bleeding diathesis and coagulopathy.

(g) Psychiatric disorder.

Sixty patients of physical status- ASA grade-1and grade-2 of either sex, undergoing infra-umbilical surgeries lasting more than 30 minutes fulfilling inclusion criteria were included in the study after ethical committee clearance. Preoperative evaluation of the patient was done a day before the surgery day. On explaining the procedure, written and informed consent was obtained. Patients were randomized in to two groups: Group- M & Group-C of 30 patients in each group & these patients received the intrathecal drugs for spinal anaesthesia as follows:

1. Group- M: (n=30) received Bupivacaine (0.5% heavy) 2.5ml with Clonidine 30µg. [Total volume of spinal anaesthetic drug to be deposited was 3ml. The diluent used was normal saline to make the total volume of spinal drug= 3ml]
2. Group- C: (n=30) received Bupivacaine (0.5% heavy) 2.5ml with Clonidine 15µg + Fentanyl 15µg. [Total volume of spinal anaesthetic drug to be deposited was 3ml. The diluent used was normal saline to make the total volume of spinal drug= 3ml]

All patients' were given orally tablet Alprazolam 0.5mg and tablet Ranitidine 150mg a night before the day of surgery. All Patients were kept 6-8 hrs fasting overnight prior to surgery. In the operating room, intravenous line was secured with 18G cannula. Baseline heart rate (HR), non-invasive systolic and diastolic blood pressures (SBP, DBP), percentage of oxygen saturation (SpO2), respiratory rate (RR) and electrocardiogram (ECG) was recorded using multi-parameter monitor. Each patient was preloaded with 500ml of ringer's lactate solution. Later injection Ranitidine 50mg IV was administered. Under strict aseptic precautions the drug under study was injected over a period of 10-15 seconds into subarachnoid space at L3-L4 intervertebral level with sterile 26G Quincke spinal needle & patient in lateral position. The time at which injection was completed was noted as zero time of the study and all measurements were recorded from this point.

Following the subarachnoid block, onset of sensory loss was assessed by loss of pinprick sensation using 23G sterile hypodermic needle and dermatomal levels were tested every 2 minutes until the highest level was achieved and later no change in the highest level for four consecutive tests. Intraoperatively, vital parameters e.g. heart rate, non-invasive blood pressure and oxygen saturation were recorded every 2minute for the first 10 minutes; then every 5minutes till 1hour; then every 15 minutes till the completion of surgery

& postoperatively, every 1hour till the patient complaints of pain. A 20% or more fall in systolic blood pressure from baseline, was managed with intravenous fluids and intravenous Injection ephedrine 6mg and heart rate less than 60 beats per min from baseline was treated with intravenous Injection atropine 0.6 mg.

Post-operatively, the haemodynamic variables and oxygen saturation were recorded in the post anaesthesia care unit (PACU) until complete recovery from sensory and motor blockade. The incidence of adverse events such as hypotension, bradycardia, shivering, nausea, vomiting, pruritus, respiratory depression were noted and treated accordingly.

## Results

In the study there was no significant difference in mean age, weight, Height and BMI between two groups (Table 1 and Fig .1).

In the study there was clinically and statistically significant difference in mean 2 Dermatome Sensory Block Regression Time, Total Duration of Sensory Block, Duration of Motor Block and Time For First Analgesic Dose between two groups. All

**Table 1:** Mean Age,Weight and Height and BMI Comparison Between Two Groups

| | Group | | | | | | *p* value |
|---|---|---|---|---|---|---|---|
| | Group C | | Group M | | Total | | |
| | Mean | SD | Mean | SD | Mean | SD | |
| Age | 41.11 | 7.12 | 41.07 | 6.72 | 41.09 | 6.88 | 0.976 |
| Weight (Kg) | 62.71 | 8.18 | 61.67 | 6.73 | 62.19 | 7.47 | 0.510 |
| Height (M) | 1.60 | .05 | 1.61 | .05 | 1.60 | .05 | 0.324 |
| BMI | 24.54 | 2.59 | 23.83 | 2.10 | 24.18 | 2.37 | 0.159 |

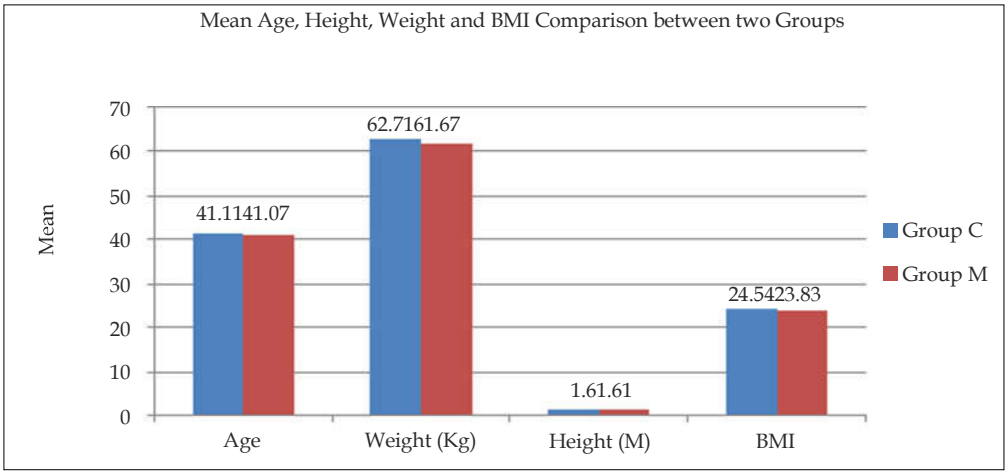


**Fig. 1:** Bar diagram showing mean age, height, weight and BMI Comparison between two groups

**Table 2:** Mean of Dermatome Sensory Block Regression Time, Total Duration of Sensory Block, Duration of Motor Block, Time For First Analgesic Dose Comparison between two groups

| | Group | | | | | | *p* Value |
|---|---|---|---|---|---|---|---|
| | Group C | | Group M | | Total | | |
| | Mean | SD | Mean | SD | Mean | SD | |
| 2 Dermatome Sensory Block Regression Time (Minute) | 122.49 | 9.76 | 103.44 | 8.01 | 112.97 | 13.06 | < 0.001* |
| Total Duration Of Sensory Block (Minute) | 165.02 | 12.72 | 130.78 | 5.95 | 147.90 | 19.85 | < 0.001* |
| Duration Of Motor Block (Minutes) | 208.27 | 21.39 | 144.00 | 6.78 | 176.13 | 35.96 | < 0.001* |
| Time For First Analgesic Dose (Minutes) | 176.29 | 14.45 | 140.76 | 16.17 | 158.52 | 23.49 | < 0.001* |

the above parameters were significantly higher in Group C compared to Group M. (Table 2 and Fig. 2)

In the study there was significant difference in mean HR between two groups from 8 min to 105 min. At these intervals mean HR was significantly lower in Group M compared to Group C. At other intervals there was no significant difference in mean HR between two groups (Table 3 and Fig. 3).

### *Comparison of Mean Arterial Pressure Between Two Groups*

In the study there was significant difference in mean MAP between two groups at 10min and 24hr post op. At these intervals mean MAP was significantly

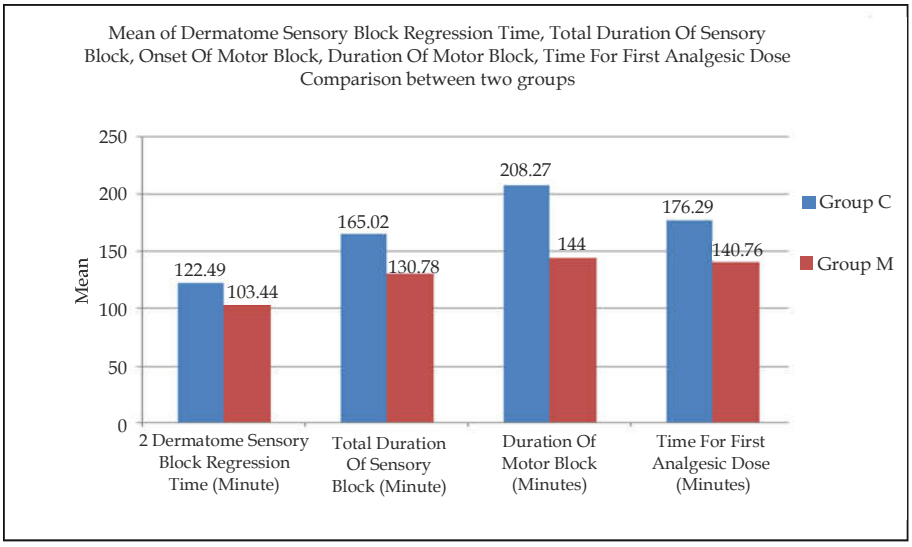


**Fig. 2:** Bar diagram showing mean of dermatome sensory block regression time, total duration Of sensory block, onset and duration of motor block, time for first analgesic dose comparison between two groups in study subjects.

**Table 3:** Heart Rate comparison between two groups

| Pulse | Group | | | | *p* Value |
|---|---|---|---|---|---|
| | Group M | | Group C | | |
| | Mean | SD | Mean | SD | |
| Baseline | 83.18 | 8.28 | 83.58 | 9.02 | 0.827 |
| 2min | 83.13 | 7.23 | 82.51 | 8.67 | 0.712 |
| 4min | 79.69 | 7.08 | 80.56 | 7.87 | 0.584 |
| 6min | 77.22 | 7.41 | 79.31 | 7.98 | 0.202 |
| 8min | 75.04 | 7.25 | 78.82 | 8.69 | 0.028* |
| 10min | 72.24 | 7.20 | 77.38 | 8.20 | 0.002* |
| 15min | 70.04 | 7.47 | 76.27 | 8.80 | 0.001* |
| 20min | 68.04 | 8.05 | 75.87 | 9.58 | < 0.001* |
| 25min | 65.89 | 8.41 | 75.98 | 9.27 | < 0.001* |
| 30min | 64.51 | 8.12 | 76.78 | 9.16 | < 0.001* |
| 35min | 63.68 | 8.47 | 76.14 | 9.40 | < 0.001* |
| 40min | 62.53 | 8.68 | 75.02 | 7.51 | < 0.001* |
| 45min | 62.26 | 8.44 | 75.42 | 7.46 | < 0.001* |
| 50min | 62.45 | 9.20 | 73.76 | 8.38 | < 0.001* |
| 55min | 61.70 | 7.46 | 76.10 | 9.18 | < 0.001* |
| 60min | 61.31 | 6.28 | 76.18 | 8.18 | < 0.001* |
| 75min | 61.55 | 6.12 | 74.50 | 8.02 | < 0.001* |
| 90min | 61.47 | 6.38 | 75.92 | 4.80 | < 0.001* |
| 105min | 64.50 | 8.47 | 76.57 | 3.64 | 0.004* |
| 120min | 62.40 | 7.70 | 63.00 | 1.41 | 0.921 |
| Immediate Post Op | 71.29 | 8.98 | 70.98 | 7.26 | 0.857 |
| 1hr | 71.64 | 9.43 | 71.51 | 5.91 | 0.936 |

| Pulse | Group | | | | *p* Value |
|---|---|---|---|---|---|
| | Group M | | Group C | | |
| | Mean | SD | Mean | SD | |
| 2hr | 74.44 | 6.49 | 73.56 | 6.28 | 0.511 |
| 3hr | 73.82 | 6.41 | 75.18 | 6.18 | 0.310 |
| 4hr | 76.16 | 4.72 | 77.64 | 6.45 | 0.215 |
| 8hr | 78.98 | 5.73 | 79.27 | 6.91 | 0.830 |
| 12hr | 77.49 | 6.10 | 80.18 | 6.95 | 0.054 |
| 16hr | 80.71 | 6.59 | 81.22 | 8.69 | 0.754 |
| 20hr | 82.33 | 6.39 | 82.47 | 9.23 | 0.937 |
| 24hr | 82.56 | 6.97 | 83.71 | 9.19 | 0.503 |

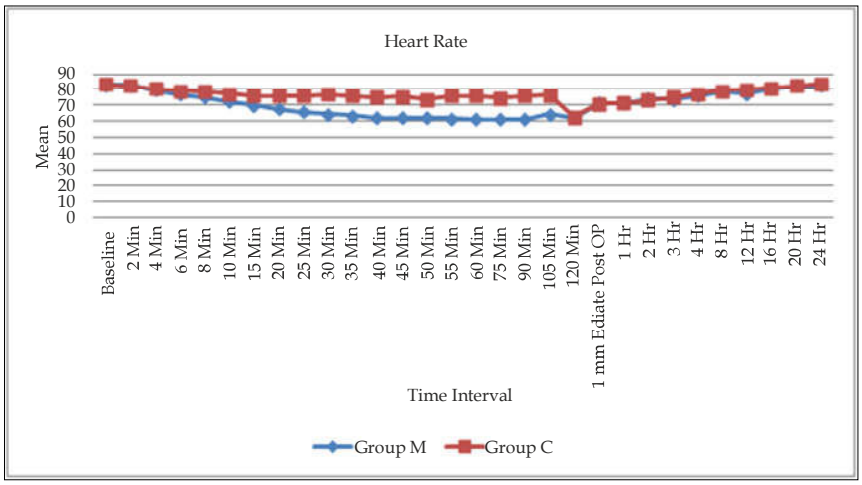


**Fig. 3:** Line diagram showing mean heart rate comparison between two groups at different time interval in study subjects

lower in Group M compared to Group C. At other intervals there was no significant difference in mean MAP between two groups (Fig. 4).

In the study there was significant difference in mean VAS score between two groups from immediate post op to 24 hr post op period. Mean VAS score was higher in Group M from Immediate post op to 6 hr from 12 hr to 24 hr Mean compared to group C (Table 4 and Fig. 5).

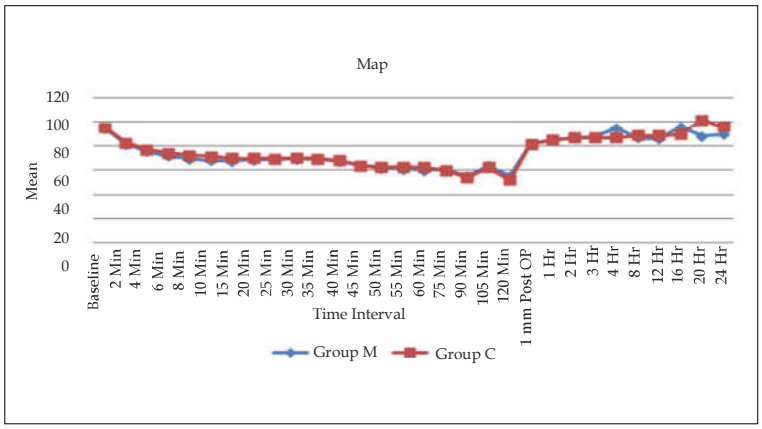


**Fig. 4:** Line diagram showing Mean MAP Comparison between two groups at different time interval.

**Table 4:** Visual Analogue Scale Score (Vas)

| VAS Score | Group | | | | P Value |
|---|---|---|---|---|---|
| | Group C | | Group M | | |
| | Mean | SD | Mean | SD | |
| Immediate Post Operative | .22 | .42 | .62 | .75 | 0.002* |
| 1hr | 1.93 | .65 | 2.71 | .97 | < 0.001* |
| 2hr | 3.02 | .92 | 4.78 | 1.02 | < 0.001* |
| 6hr | 6.20 | .73 | 6.49 | .51 | 0.031* |
| 12hr | 5.73 | .84 | 5.40 | .58 | 0.031* |
| 24hr | 5.64 | .91 | 5.24 | .53 | 0.012* |

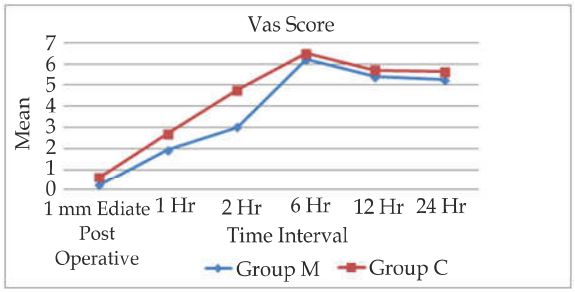


**Fig. 5:** Line Diagram Showing Mean Vas Score Comparison Between two Groups in Study Subjects

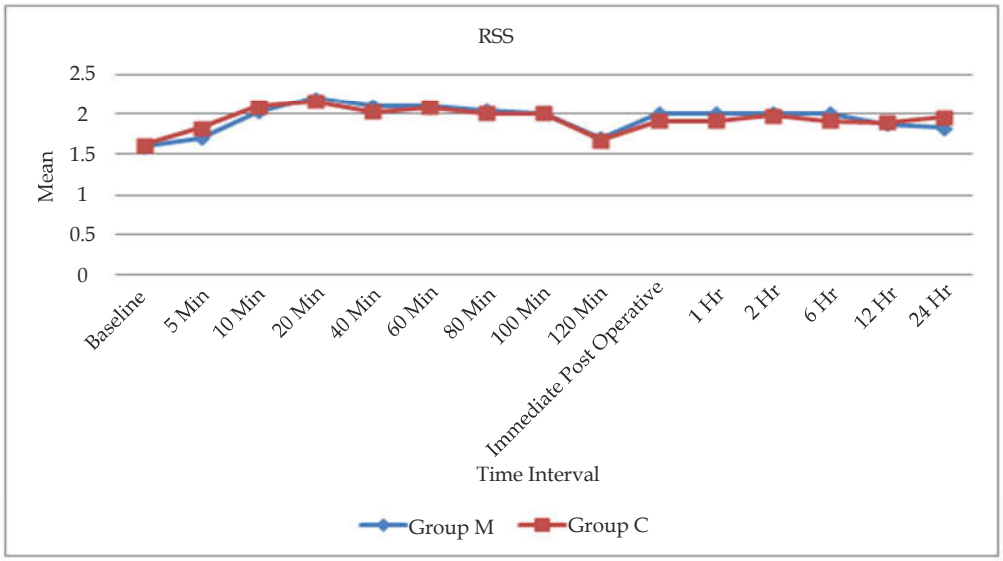


**Fig. 6:** Line diagram showing Mean Ramsey Sedation Score Comparison between two groups at different time interval

## Discussion

Opioids are commonly used as intrathecal adjuvants to improve the quality of intraoperative analgesia and prolong it in post-operative period without significant motor or autonomic blockade.[5]

Fentanyl is a potent, short acting, highly lipophilic, synthetic opioid. It has been commonly used as an adjuvant for postoperative analgesia in neuraxial block.

Clonidine is a selective partial alpha2 adrenergic agonist. It inhibits the central transmission of nociceptive impulses probably by affecting descending noradrenergic tract in spinal cord that plays an important role in pain modulation by a non-opioid mechanism. The analgesic effect of clonidine is also believed to result from inhibition of release of substance P which inhibits the cGMP for its analgesic effect.[6] But Clonidine in higher doses can cause hypotension and bradycardia. A marked decrease in arterial blood pressure (BP) was observed with 75µg of intrathecal clonidine.[4] Addition of intrathecal clonidine 150mcg, decreased MAP significantly as compared with plain bupivacaine. However, in the dose range of 150–450µg, clonidine causes marked sedation.[7]

Because of this side effect associated with higher doses of clonidine there is a tendency toward the use of smaller doses. Such doses of clonidine producing only minimal side effects would be a true alternative to other technical or pharmacological procedures aimed at prolonging spinal anesthesia and analgesia. In our study we have used very low dose of clonidine and fentanyl as adjuvant, we didn't observe any side effects of any significant hemodynamic variations which requires treatment. Ahmed, et al. conducted study on combination of Clonidine (25µg)–fentanyl (25µg) combination with intrathecal bupivacaine for postoperative analgesia and concluded that duration of postoperative analgesia prolonged with

good haemodynamic stability and non-significant adverse effects.[2]

In our study also combination of Clonidine (15 µg)- Fentanyl (15 µg ) with intrathecal bupivacaine was used and showed prolonged post-operative analgesia with good haemodynamic stability. Chopra P. at al. conducted study on low dose intrathecal clonidine and fentanyl added to hyperbaric bupivacaine for prolongation of analgesic effect in gynecological surgery. They found out that low dose (30µg) Clonidine and Fentanyl (25µg) mixture added to bupivacaine increases duration of analgesic effect compared to clonidine and bupivacaine group.[3] In our study, we had similar observations to above one and we have used Clonidine 15µg + Fentanyl 15µg in one group with Bupivacaine and Clonidine 30µg in other group with Bupivacaine. Combination of Clonidine and Fentanyl group showed slight prolongation of analgesic effect.

Benhamou D, et al. conducted study on intrathecal Clonidine and Fentanyl with hyperbaric Bupivacaine improves analgesia during caesarean section. They found improved intraoperative analgesia by adding clonidine to bupivacaine, combination of Clonidine and Fentanyl further improved analgesia with no increase in side effects.[8] Our study was similar to above study, combination of Clonidine-Fentanyl showed slight prolonged analgesia with very less side effects. The haemodynamic stability was observed in both the groups.

## Conclusion

For spinal anaesthesia, a low dose combination of Clonidine (15mcg) + Fentanyl (15mcg) as an adjuvant to intrathecal 0.5% Bupivacaine (heavy) shown to have prolonged postoperative analgesia in patients undergoing infra-umbilical surgeries with stable haemodynamic parameters

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