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Original Article

Anaesthesia Section

# Comparing Clonidine and Fentanyl as Adjuvants to Intrathecal Hyperbaric Ropivacaine in Elective Infraumbilical Surgeries- A Randomised Clinical Study

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## ABSTRACT

**Introduction:** Ropivacaine is popular as a safe intrathecal anaesthetic drug due to its higher safety profile over bupivacaine. Intrathecal additives are known to increase the quality of anaesthesia and analgesic duration.

**Aim:** To compare the effects of clonidine and fentanyl as intrathecal adjuvants to hyperbaric ropivacaine in elective infraumbilical surgeries.

**Materials and Methods:** This randomised, double-blinded, clinical study was undertaken at Krishnarajendra Hospital and Cheluvamba Hospital, attached to Mysore Medical College and Research Institute, Mysuru, Karnataka, India, from January 2018 to June 2018. Total 60 adult patients aged between 18-60 years of age, American Society of Anaesthesiologists (ASA) I and II status, and posted for infraumbilical surgeries, were randomised to two groups of 30 patients each i.e., group C patients receiving 2.5 mL of hyperbaric 0.42% ropivacaine and clonidine 15 mcg, and group F patients receiving 2.5 mL of hyperbaric 0.42% ropivacaine and fentanyl 25 mcg. The onset, extent and duration of sensory and motor blockade, heart rate, mean arterial pressure, prolongation of analgesia in the postoperative period, and any complications were observed. Statistical analysis was done using Student's t-test, and Chi-square test to test significance of variables. The p-value <0.05 was taken as statistically significant.

**Results:** Demographic characteristics were comparable in both the groups. The onset of sensory blockade and the maximum height of sensory blockade attained were similar in both groups i.e., group C-2.12±0.22 min vs group F-2.24±0.66 min, group C-4.94±0.91 min vs group F-5.12±1.38 min, respectively. The duration of sensory blockade was prolonged in group C (148.5±10.84 min vs 109.37±14.5 min), resulting in delayed demand for analgesic after surgery in this group. The onset of motor block and the complete motor blockade was prolonged in group C patients (3.22±1.01 min vs 1.16±0.3 min, 6.8±1.49 min vs 3.72±1.31 min). The recovery from motor blockade was also significantly delayed in Group C (125.17±13.29 min vs 95.47±13.08 min). The incidence of hypotension was similar in both the groups.

**Conclusion:** Clonidine, and fentanyl both provide early and adequate spinal anaesthesia, but the former (clonidine 15 mcg), prolongs the duration of spinal anaesthesia with ropivacaine 0.42% hyperbaric solution, and significantly increases the time for the demand for analgesia in the recovery period, compared to fentanyl.


**Keywords:** Anaesthetic adjuvants, Local anaesthetics, Spinal anaesthesia

## INTRODUCTION

Infraumbilical surgeries are commonly conducted under spinal anaesthesia. Ropivacaine, is a pure S-(-)-enantiomer, is a popular local anaesthetic of recent times due to its high safety profile over bupivacaine with reduced neurotoxicity and cardiac toxicity [1,2]. It has low lipid solubility and blocks nerve fibres involved in pain transmission to a greater degree than those involved in motor function [3,4].

The plain solution available commercially exhibits variable and less predictable effects resulting in either insufficient block level inadequate for surgery or excessively high levels causing side effects and also, has shorter duration of action [5].

Hyperbaric solutions made by the addition of dextrose to isobaric ropivacaine [6] had more predictable onset, with greater spread in the direction of gravity and less interpatient variability [7,8] after spinal anaesthesia. It provides adequate intra operative anaesthesia and has a shorter duration of action [9], making it an ideal agent for day care surgeries. However, patients complain of pain in the early postoperative period, necessitating the use of systemic drugs like Non Steroidal Anti-inflammatory Drugs (NSAIDs) and opioids. Hence, it requires monitoring in the postoperative period.

Adjuvants such as clonidine and fentanyl, are added to intrathecal local anaesthetics to improve the quality of intraoperative anaesthesia and prolong the postoperative analgesia. Clonidine, is a centrally acting partial $\alpha_2$ adrenergic agonist (220:1 $\alpha$2 to $\alpha$1) and provides dose dependent analgesia. Hypotension, bradycardia, sedation are some of its side-effects [10,11]. Fentanyl, a short-acting opioid, acts on $\mu_1$ and $\mu_2$ receptors. It facilitates reduction in dose of local anaesthetics and potentiates the afferent sensory blockade. Pruritis, urinary retention and respiratory depression are some of its side-effects [12,13].

Literature search reveals many studies comparing different doses of clonidine and fentanyl as intrathecal adjuvants to isobaric ropivacaine [14,15]. Not many studies have been conducted on hyperbaric ropivacaine, since, it is not commercially available. There are no studies with clonidine and fentanyl as intrathecal adjuvants to hyperbaric ropivacaine 0.42%.

Hence, the present study was initiated to compare clonidine and fentanyl as additives to hyperbaric 0.42% ropivacaine for spinal anaesthesia. The primary objectives were to study the onset, duration of sensory blockade, maximum sensory blockade attained and time taken for the same, time taken for two segment regression, and regression of sensory block to S1, time of administration of rescue analgesia. Also, to study the onset of motor blockade, quality of motor blockade, time taken for the maximum motor blockade and duration of motor blockade. The secondary objectives were to study

the haemodynamic changes such as hypotension, bradycardia and other side effects such as nausea, vomiting, shivering, pruritus and respiratory depression, if any.

## MATERIALS AND METHODS

A randomised, double-blinded, clinical study was undertaken at Krishnarajendra Hospital and Cheluvamba Hospital, attached to Mysore Medical College and Research Institute, from January 2018 to June 2018. The Scientific Review Board and Ethics Board had approved the study (IEC REG:ECR/134/Inst/KA/2013). A total of 60 patients were enrolled.

**Sample size calculation:** The sample size was calculated based on the mean and standard deviation of complete sensory regression of spinal block after spinal anaesthesia, on knee arthroscopy patients in a previous study [16]. To achieve a difference of 30 min in the time for regression of spinal anaesthesia, with an expected effect size to standard deviation ratio of 0.9, and an acceptable $\alpha$ error of 0.05 and power of 80%, only 20 patients were required in each group. However, 30 patients were enrolled in each group to increase the power of the study and to compensate for any drop-outs.

**Inclusion criteria:**

- Adult patients of either sex, aged between 18-60 years age.
- American Society of Anaesthesiologists (ASA) I and II status
- Admitted for infraumbilical surgeries.

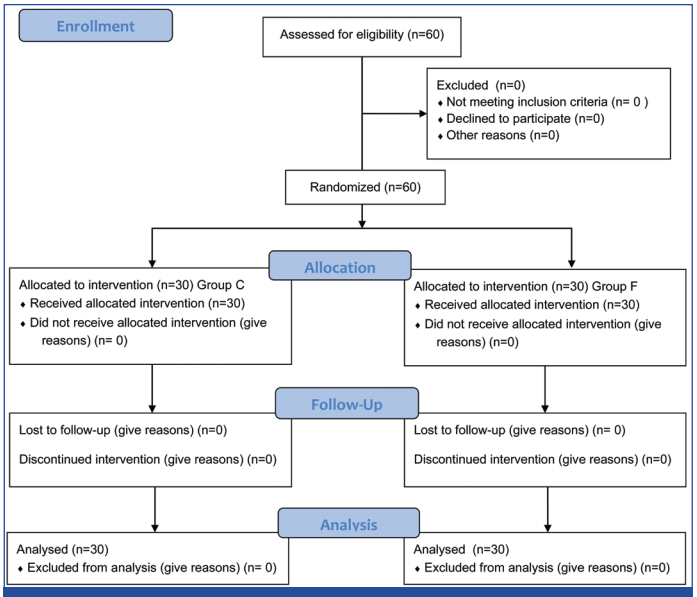
**Exclusion criteria:**

- Patients above ASA II status
- Chronic diseases such as diabetes and hypertension
- Known drug allergy
- Pregnant patients
- Patients with height less than 140 cm
- Body mass index ≥30 kg/m$^2$.

### Procedure

Patients were evaluated in the preoperative period for their fitness for surgery. They were explained about the study and their consent of participation was obtained in a pre-written format. They were randomised, using shuffled sealed envelope method into two groups [Table/Fig-1]:

- Group C: Received 2.5 mL of hyperbaric 0.42% ropivacaine (10.5 mg) with clonidine 15 mcg (0.1 mL).
- Group F: Received 2.5 mL of hyperbaric 0.42% ropivacaine (10.5 mg) with fentanyl 25 mcg (0.5 mL).




**[Table/Fig-1]:** CONSORT flow chart.

**Drug preparation of hyperbaric ropivacaine:** Hyperbaric ropivacaine 0.42% was prepared by adding 0.5 mL of 50% dextrose to 2.5 mL of 0.5% isobaric ropivacaine. After addition of dextrose, the total volume 3 mL of the prepared drug contained 12.5 mg of ropivacaine and 250 mg of dextrose. Only 2.5 mL of the above preparation was taken and 0.1 mL of clonidine (15 mcg) or 0.5 mL of fentanyl (25 mcg) was added and given intrathecally. Thus, each millilitre of the study drug contained 4.2 mg of ropivacaine and 83.33 mg of dextrose. Sterile autoclaved ampoules of 50% dextrose were used. Samples of the prepared drug were tested in the laboratory for specific gravity and any possible bacterial contamination. The mean specific gravity of the sample drug was noted to be 1.0396 (specific gravity of CSF- 1.0004-1.00067). Culture sensitivity test was negative.

In the operation theatre, standard monitors were applied and the basal Heart Rate (HR), Mean Arterial Pressure (MAP), oxygen saturation ($SpO_2$), Electrocardiogram (ECG) readings were obtained. Intravenous (IV) access was secured and patient was administered Ringer's solution.

Lumbar puncture was performed by a junior anaesthetist with patient in the lateral recumbent posture in L2-L3/L3-L4 space with 25 G Quincke needle and the prepared study drug injected in intrathecal space under full asepsis. The patient was placed supine for the surgery, and the below study parameters were noted by the observer who was not aware of the composition of the drug. The patients were also unaware of the composition of the study drug. Monitoring of the HR, MAP, $SpO_2$, and ECG were done every minute for the first 5 minutes post spinal anaestheisa, thereafter every 5 minutes upto 30 minutes, and then every 10 minutes till the end of surgery, and for half hour after surgery. The patient and the observer were unaware of the composition of the study drug.

**Parameters studied:** The onset of sensory anaesthesia, maximum sensory level and the time taken for the same, onset of motor block, time for complete block, two segment sensory regression time, complete regression to S1, complete motor recovery was checked and recorded. Sensation was checked using pin prick with blunt needle. Modified Bromage scale was used for assessing the quality of motor blockade [Table/Fig-2] [17].

| Scale | Motor blackade |
|---|---|
| 0 | No motor block |
| 1 | Inability to raise extended leg; able to move knees and feet |
| 2 | Inability to raise extended leg and move knee; able to move feet |
| 3 | Complete block of motor limb |

**[Table/Fig-2]:** Modified bromage scale.

**Visual Analogue Scale (VAS):** In the postoperative period, analgesia was assessed using Visual Analogue Scale (VAS), wherein 0=no pain, and 10=severe pain.

**Ramsay sedation scale:** Sedation was assessed at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90 min after injection of the study drug using the Ramsay sedation scale, wherein;

1: patient anxious, agitated or restless or both.

2: patient cooperative, oriented and tranquil.

3: patient responds to commands only.

4: patient exhibits brisk response to light glabellar tap or loud auditory stimulus.

5: patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.

6: patient exhibits no response.

Hypotension, defined as a fall in systolic blood pressure of >20% from the baseline or MAP <60 mmHg, was treated with Inj. mephenteramine 6 mg i.v. increments. Bradycardia, defined as HR<50 beats per minute, was treated with Inj. atropine 0.6 mg i.v.

Rescue analgesia was with Inj. diclofenac 75 mg i.m. in the post operative period for a VAS score >4 and the time for the same was noted. Complications such as sedation, vomiting, shivering, pruritus, respiratory depression, if any, in the postoperative period were noted in a prepared proforma.

## STATISTICAL ANALYSIS

Data entry was done in Microsoft Excel and analysed by Statistical Package for the Social Sciences (SPSS) software version 20.0. Continuous data was expressed in mean±SD and categorical data was expressed in count (%) respectively. Student's t-test was used to test significance for a continuous variable across two groups. Chi-square's test was used to test significance across categorical variables. The p-value <0.05 was considered as statistically significant.

## RESULTS

Both the groups of patients were comparable with respect to age, sex, height and body weight characteristics. There was also no significant difference in the type or duration of surgery [Table/Fig-3].

| Parameters | Group C | Group F | p-value (Chi-sqaure test) |
|---|---|---|---|
| Age (years) | 45.6±4.31 | 46.4±5.94 | 0.553 |
| Gender (M/F) | 19/11 | 14/16 | 0.194 |
| ASA Status (I/II) | 13/17 | 14/16 | 0.234 |
| Weight (kg) | 64.83±4.59 | 65.2±5.5 | 0.780 |
| BMI (kg/m$^2$) | 23.03±0.99 | 23.41±1.61 | 0.385 |
| Height (cm) | 166.23±5.38 | 166.73±5.28 | 0.237 |
| Total duration of surgery (min) | 50.83±12.87 | 51.33± 11.81 | 0.094 |

**[Table/Fig-3]:** Patient characteristics.
p-value <0.05 was considered as statistically significant; values are presented as Mean±SD or as numbers

**Sensory block characteristics:** The mean onset time to T10 dermatomal level was similar in groups C and F (2.12±0.22 min vs 2.24±0.66 min). The mean maximum sensory block height achieved of T6 and the time to achieve the same (4.94±0.91 vs 5.12±1.38 min) was also similar in group C and group F patients [Table/Fig-4].

Group C patients took longer time for regression of sensory block by two segments to T8 as compared to group F (115.07±6.69 min vs 76.3±10.72 min). The total regression time to S1 also was prolonged in group C (148.5±10.84 min vs 109.37±14.5 min) in comparison to group F [Table/Fig-4].

| Block characteristics | Group C Mean±SD | Group F Mean±SD | p-value (Student's t-test) |
|---|---|---|---|
| Onset time to T10 (min) | 2.12±0.22 | 2.24±0.66 | 0.365 |
| Time for maximum sensory block (min) | 4.94±0.91 | 5.12±1.38 | 0.566 |
| Maximum sensory height | T6 | T6 | - |
| Time for 2 segment regression (min) | 115.07±6.69 | 76.3±10.72 | <0.05 |
| Time for S1 regression (min) | 148.5±10.84 | 109.37±14.5 | <0.05 |
| Time to first rescue analgesia (min) | 190.83±20.6 | 128.83±16.38 | <0.05 |

**[Table/Fig-4]:** Characteristics of sensory block.
p-value <0.05 was considered as statistically significant

**Motor block characteristics:** The onset of motor block was slow and time to achieve a complete motor blockade was also delayed in group C (3.22±1.01 min vs 1.16±0.3 min, 6.8±1.49 min vs 3.72±1.31 min) compared to group F. Complete motor blockade was achieved in all the patients (Bromage score 3). The recovery from motor blockade was also significantly delayed in group C when compared to group F (125.17±13.29 min vs 95.47±13.08 min) [Table/Fig-5].

Time to first request for rescue analgesia in the recovery room was significantly delayed in the group C patients compared to group F patients (190.83±20.6 min vs 128.83±16.38 min) [Table/Fig-4].

| Motor block characteristics | Group C Mean±SD | Group F Mean±SD | p-value (Student's t-test) |
|---|---|---|---|
| Onset of motor block (min) | 3.22±1.01 | 1.16±0.3 | <0.05 |
| Time for complete motor block (min) | 6.8±1.49 | 3.72±1.31 | <0.05 |
| Duration of motor block (min) | 125.17±13.29 | 95.47±13.08 | <0.05 |
| Maximum Bromage score achieved | 3 | 3 | |

**[Table/Fig-5]:** Characteristics of motor blockade.
p-value <0.05 was considered as statistically significant

**Haemodynamic parameters:** Basal Heart Rate (HR) and Mean Arterial Pressure (MAP) were found to be comparable in both group of patients. Heart rate was found to be lower in group C patients from the 1st minute post spinal to the end of surgery which was statistically significant when compared to group F though clinically none of the patients required correction with atropine. Similarly, there were statistically significant variation in the mean arterial pressures between both the groups at various time intervals [Table/Fig-6,7].

| Group heart rate (min) | Group C Mean±SD | Group F Mean±SD | p-value (Student's t-test) |
|---|---|---|---|
| At baseline | 91.87±4.54 | 90.87±6.74 | 0.503 |
| At 1 min | 87.2±3.95 | 91.77±5.27 | <0.05 |
| At 2 min | 83.73±4.27 | 90.83±4.79 | <0.05 |
| At 3 min | 80.07±4.78 | 83.5±4.55 | <0.05 |
| At 5 min | 73.73±4.54 | 79.47±4.93 | <0.05 |
| At 10 min | 75.8±7.27 | 78.47±3.35 | 0.073 |
| At 15 min | 70.43±7.78 | 80±4.76 | <0.05 |
| At 20 min | 75.3±6 | 73.47±4.13 | 0.173 |
| At 30 min | 75.3±5.83 | 77.33±6.09 | 0.192 |
| At 40 min | 76.67±6.44 | 79.07±5.11 | 0.115 |
| At 50 min | 78.53±5.95 | 62.2±3.12 | <0.05 |
| At 60 min | 77.97±6.69 | 76.17±5.29 | 0.253 |
| At 70 min | 79.9±4.79 | 82.93±6.47 | 0.044 |
| At 80 min | 84.77±4.41 | 80±4.84 | <0.05 |

**[Table/Fig-6]:** Intraoperative heart rate (min) presented as Mean±SD.
p-value <0.05 was considered as statistically significant

| Mean arterial pressure (mmHg) | Group C Mean±SD | Group F Mean±SD | p-value (Student's t-test) |
|---|---|---|---|
| At baseline | 89.57±5.64 | 86.3±6 | <0.05 |
| At 1 min | 87.77±4.58 | 80.6±4.34 | <0.05 |
| At 2 min | 83.7±4.79 | 74.93±3.78 | <0.05 |
| At 3 min | 72.47±7.37 | 68.93±3.92 | <0.05 |
| At 5 min | 67.5±5.22 | 66.47±4.35 | 0.408 |
| At 10 min | 63.27±2.26 | 66.6±4.55 | <0.05 |
| At 15 min | 62.2±3.12 | 70.13±3.71 | <0.05 |
| At 20 min | 76.17±5.29 | 78.93±3.78 | <0.05 |
| At 30 min | 82.93±6.47 | 79.8±4.82 | <0.05 |
| At 40 min | 80±4.84 | 77.33±4.01 | <0.05 |
| At 50 min | 78.93±3.78 | 74.57±3.78 | <0.05 |
| At 60 min | 78.47±3.35 | 72.2±6.31 | <0.05 |
| At 70 min | 79.33±3.87 | 79.67±4.49 | 0.408 |
| At 80 min | 82.13±4.03 | 84.67±5.16 | <0.05 |

**[Table/Fig-7]:** Mean Arterial Pressure (MAP) (mmHg) presented as Mean±SD.
p-value <0.05 was considered as statistically significant

However, clinically significant hypotension requiring correction with mephentermine 6 mg occurred in nine patients in group C and in four patients in group F. Statistically, there was no significant difference in the number of patients developing hypotension in both the groups (p-value=0.117). All the patients in both the groups had a sedation score of 2 on Ramsay sedation scale and were awake and cooperative

post spinal anaesthesia. Rest of the adverse effects such as nausea, vomiting, pruritus, shivering or respiratory depression did not occur in any of the patients in the postoperative period.

**Respiratory parameters:** At all points of time in the intra operative period, the oxygen saturation ($SpO_2$) was between 99% and 100% in both groups of patients, throughout the procedure and no significant difference between the groups (p-value >0.05).

## DISCUSSION

Ropivacaine is one of the popular intrathecal anaesthetics and is available as isobaric solution commercially. Intrathecal isobaric ropivacaine has been reported to cause inadequate or variable block [5]. Addition of dextrose makes the drug hyperbaric which has been shown in various studies to produce a consistent block and less variation in sensory and motor block [6,7,8]. Complete regression occurs sooner, thus, patients can be mobilised sooner. However, these beneficial effects are offset by the perception of pain in the post operative period, hence, necessitating the use of intrathecal adjuvants. Clonidine, an $\alpha_2$ adrenergic receptor agonist by producing dose dependent analgesia and fentanyl, a short acting opioid potentiating afferent sensory blockade, they facilitate dose reduction of intrathecal local anaesthetics. Hence, the present study compared clonidine 15 mcg and fentanyl 25 mcg as additives to 0.42% hyperbaric ropivacaine.

In the present study, the time of onset of sensory block, maximum height of block, and the time taken for maximum sensory block was similar in group C and group F. These findings were consistent with findings of Bathari R et al., [16] who compared 15 mg of hyperbaric ropivacaine with 30 mcg of fentanyl or 15 mcg of clonidine in their study. In yet another study by Chhabra A et al., [14], comparing 15 mg of 0.5% isobaric ropivacaine with 25 mcg of fentanyl or 60 mcg clonidine, the sensory onset and time taken for maximum sensory blockade was longer in both their groups compared to the current study. This could be due to the isobaricity of ropivacaine. Similar study using isobaric ropivacaine was done by Sharan R et al., where they also found that the onset time of sensory block in both clonidine and fentanyl groups were comparable; the maximum height attained was T6, similar to the present study [15]. However, the time taken for attaining the maximum height was delayed in both clonidine and fentanyl groups. They compared 30 mcg clonidine and 25 mcg of fentanyl with 18.75 mg of isobaric ropivacaine. This delay could be explained due to the isobaricity of the study drug.

The sensory regression to S1 was delayed in group C (148.5±10.84 vs 109.37±14.5 min) compared to group F (p-value <0.05). However, in the study by Bathari R et al., [16], the sensory regression was prolonged and almost comparable in both the groups (262.5±37.7 vs 262.6±44.67 min). The prolonged sensory blockade in their study could be due to the higher dose of hyperbaric ropivacaine 15 mg whereas, the authors used only 10.5 mg and higher dose of fentanyl of 30 mcg in their study vs 25 mcg in the present study.

Prolongation of sensory regression to L5 was more in the clonidine group, when compared to fentanyl group which is similar to the findings by Chhabra A et al., [14]. Similar findings of delayed sensory regression to L5 were seen by Sharan R et al., [15].

Onset of motor block and complete motor blockade in the present study was faster in the group F compared to group C (1.16± 0.3 min vs 3.22±1.01 min, 3.72±1.31 min vs 6.8±1.49 min) respectively. Chhabra A et al., also reported early onset of and complete motor blockade in the fentanyl group compared to clonidine group [14]. Shashikala TK et al., also reported early onset of motor block in their fentanyl group of patients [18].

Complete motor recovery was delayed in group C in the present study (125.17±13.29 min vs 95.47±13.08 min) compared to group F. This is consistent with findings in the clonidine group versus fentanyl group in the study by Bathari R et al., (156±42.4 min vs 128.2±24.9 min) and in the study by Chhabra A et al., in the clonidine group versus fentanyl group (248.51±55 min vs 212.60±43.52 min) [14,16].

Time for administering the rescue analgesic in the postoperative period was significantly prolonged in the clonidine group compared to the fentanyl group (190.83±20.6 min vs 128.83±16.38 min) in the present study. This is comparable with the findings of Chhabra A et al., (354±46.73 min vs 234.44±8.76 min) for clonidine and fentanyl group respectively [14]. However, Bathari R et al., [16] found no significant difference in the time for postoperative rescue analgesia in the clonidine and fentanyl groups (382.5±122.35 vs 390.5±82.5 min), respectively. This could be because of the higher dose of ropivacaine 15 mg and fentanyl 30 mcg in their study compared to 10.5 mg of ropivacaine and 25 mcg of fentanyl in the present study.

Hypotension was observed in nine patients in clonidine group and four in fentanyl group. Other adverse effects such as shivering, vomiting, pruritus or respiratory depression were not seen in any of the patients in both the groups. Addition of clonidine and fentanyl to hyperbaric ropivacaine, prolonged the duration of sensory anaesthesia without any effect on the onset of sensory or motor blockade, or any haemodynamic changes in the present study.

### Limitation(s)

Extreme caution is required while preparing the drug to prevent contamination. The exact density could not be measured, and only specific gravity of the prepared drug was measured, which is comparable with the specific gravity of hyperbaric solution mentioned in the literature available. Also, there is a difference in the total volume of the drug administered intrathecally after addition of adjuvants.

## CONCLUSION(S)

Spinal anaesthesia with 15 mcg of clonidine or 25 mcg fentanyl added to 0.42% hyperbaric ropivacaine, improved the quality of sensory and motor blockade, significantly delayed the recovery time from sensory blockade, thus, prolonging the analgesia in the postoperative period, effects being more prominently seen with clonidine than fentanyl. Additionally, use of low dose of clonidine 15 mcg and fentanyl 25 mcg did not cause any significant haemodynamic changes or side effects, thus, rendering them as safe intrathecal adjuvants.

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