

A CLINICAL COMPARATIVE STUDY OF INTRATHECAL FENTANYL AND CLONIDINE AS ADJUVANT WITH HYPERBARIC ROPIVACAINE IN SPINAL ANESTHESIA FOR PATIENTS UNDERGOING LOWER LIMB SURGERIES: A DOUBLE BLIND, RANDOMIZED CONTROL STUDY

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ABSTRACT

Background: Intrathecal adjuvants enhance the quality and duration of spinal anesthesia. This study compared fentanyl and clonidine as adjuvants to hyperbaric ropivacaine for lower limb surgeries. The objective is to compare the onset, duration, hemodynamic effects, and adverse effects of intrathecal fentanyl 10 mcg versus clonidine 30 mcg when added to hyperbaric ropivacaine 0.75% in patients undergoing lower limb orthopedic surgery. **Materials and Methods:** A randomized, double-blind study was conducted at JNIMS, Imphal, involving 106 ASA I-II patients aged 18-60 years undergoing elective lower limb surgery. Patients were randomized into Group F (ropivacaine 21 mg + fentanyl 10 mcg, n=53) and Group C (ropivacaine 21 mg + clonidine 30 mcg, n=53). Primary outcomes included onset and duration of sensory and motor blockade and postoperative analgesia duration. Secondary outcomes included hemodynamic parameters and adverse effects. Data were analyzed using independent t-test, chi-square test, and ANOVA with p<0.05 considered significant. **Result:** Group F demonstrated significantly faster sensory (2.28±0.21 vs 3.08±0.26 minutes) and motor onset (6.55±0.49 vs 8.36±0.48 minutes, both p<0.001). Group C exhibited prolonged sensory duration (317.77±7.58 vs 218.32±8.46 minutes), motor duration (268.66±7.14 vs 187.23±7.52 minutes), and analgesia (339.02±9.64 vs 247.26±9.18 minutes, all p<0.001). Bradycardia occurred exclusively in Group C (26.4% vs 0%), while pruritus occurred only in Group F (28.3% vs 0%, both p<0.001). Both groups achieved 100% success without respiratory depression. **Conclusion:** Fentanyl provides faster onset with hemodynamic stability, ideal for rapid-onset requirements. Clonidine offers superior duration and postoperative analgesia but requires monitoring for bradycardia. Adjuvant selection should be individualized based on surgical requirements and patient factors.

INTRODUCTION

The landscape of perioperative medicine has witnessed remarkable evolution in pain management strategies, particularly in the realm of regional anesthesia for lower limb surgeries. Effective perioperative analgesia remains a cornerstone in modern surgical practice, directly influencing patient outcomes, early mobilization, reduced hospital stays, and overall patient satisfaction. Lower limb surgeries encompass a diverse spectrum of orthopedic, vascular, and trauma procedures that present unique challenges in achieving optimal intraoperative anesthesia and prolonged postoperative analgesia.

The quest for an ideal anesthetic technique that provides adequate surgical conditions while ensuring patient comfort and safety continues to drive clinical research in this domain.

Spinal anesthesia, also known as subarachnoid block, has emerged as the preferred anesthetic technique for lower limb surgeries owing to its reliability, rapid onset, profound sensory and motor blockade, hemodynamic stability, and favorable safety profile compared to general anesthesia. The technique offers several advantages including reduced blood loss, decreased incidence of thromboembolic complications, preservation of consciousness, avoidance of airway manipulation, and lower healthcare costs.^[1] Despite these numerous benefits,

conventional spinal anesthesia with local anesthetics alone suffers from inherent limitations, primarily the relatively short duration of action and inadequate postoperative analgesia. These limitations have prompted clinicians to explore various adjuvants that can enhance the quality and prolong the duration of spinal anesthesia without compromising patient safety.

The selection of an appropriate local anesthetic agent forms the foundation of successful spinal anesthesia. Among the various local anesthetics available, including bupivacaine, levobupivacaine, and ropivacaine, each possesses distinct physicochemical properties that influence their clinical profile.^[2-5] The ideal adjuvant should possess the ability to potentiate local anesthetic action, provide prolonged postoperative pain relief, maintain hemodynamic stability, and demonstrate a favorable adverse effect profile.^[6]

Among the various adjuvants investigated, opioids and alpha-2 adrenergic agonists have garnered the most attention in clinical practice. Opioids, particularly lipophilic agents like fentanyl, have been extensively studied and widely utilized as intrathecal adjuvants. Fentanyl, a synthetic phenylpiperidine derivative, functions as a potent μ -opioid receptor agonist with rapid onset and intermediate duration of action.^[7,8] However, the use of intrathecal opioids is not without potential adverse effects, including pruritus, nausea, vomiting, urinary retention, and in rare cases, respiratory depression, although the risk of clinically significant respiratory depression with low-dose lipophilic opioids administered intrathecally remains minimal.

Alpha-2 adrenergic agonists represent another important class of neuraxial adjuvants, with clonidine being the most extensively studied agent in this category.^[9,10]

The comparative evaluation of fentanyl and clonidine as adjuvants to hyperbaric ropivacaine holds significant clinical relevance. While both agents have individually demonstrated efficacy in enhancing spinal anesthesia, their relative benefits, optimal dosing, and comparative safety profiles when combined with ropivacaine specifically remain areas requiring further investigation.

This double-blind, randomized controlled study was designed to systematically compare the effects of intrathecal fentanyl and clonidine as adjuvants to hyperbaric ropivacaine in patients undergoing lower limb surgeries under spinal anesthesia.

Aim & Objectives: The aim of the current study was to compare the effects of fentanyl and clonidine as intrathecal adjuvant to hyperbaric ropivacaine in spinal anaesthesia for lower limb surgeries. Correspondingly, the objectives were made as (i) to compare the onset and duration of sensory and motor block of intrathecal hyperbaric Ropivacaine with fentanyl and clonidine (ii) to compare the hemodynamic changes and other side effects (iii) to compare post-operative analgesic profile and (iv) to assess the duration of analgesia.

MATERIALS AND METHODS

A double-blinded, randomized controlled trial was conducted in the Department of Anaesthesiology at Jawaharlal Nehru Institute of Medical Sciences, Porampat, Manipur. The duration of the study extended over a period of two years, from April 2024 to March 2026. All eligible patients presenting for elective lower limb surgeries during this period and meeting the inclusion criteria were considered for enrolment. Patients aged between 18-60 years who were categorised under ASA physical status I and II and were scheduled for lower limb surgery under spinal anaesthesia were the study participants. Pregnant women, having surgery of both lower limbs, BMI>30kg/m², patients with spine deformities, local infection near the injection site, history of allergy-sensitivity to study drugs, patients with conversion cases (in general anaesthesia) were excluded.

A sample size of 106 (53 each in the two arms of intervention) was calculated based on the onset time (SD) of 2.12 (0.22) minutes for sensory block to T10 dermatome derived from a previous study conducted by Lakshmi Priya et al.,^[11] Consecutive sampling was done until this sample size was achieved. Following enrolment, patients were randomly allocated into two groups (Group F: Fentanyl and Group C: Clonidine) using computer-generated randomization sequences sealed in opaque envelopes.

A detailed pre-anesthetic evaluation was conducted for all participating patients during the pre-operative visit. This evaluation included comprehensive history taking, thorough physical examination, and review of all relevant laboratory investigations. All patients were advised to maintain overnight fasting as per standard institutional protocols.

On the day of surgery, upon arrival to the operating theater, all patients were positioned comfortably on the operating table. Standard monitoring devices including non-invasive blood pressure (NIBP) cuff, pulse oximeter, and electrocardiogram (ECG) electrodes were applied to all patients. Baseline vital parameters including pulse rate, blood pressure, mean arterial pressure, and oxygen saturation (SpO₂) were recorded. Intravenous access was established using an 18-gauge cannula, and preloading was performed with Ringer's Lactate solution at a dose of 15 ml/kg administered over 20 minutes prior to the administration of spinal block. Premedication was administered in the form of intravenous Ondansetron 4 mg before the procedure.

Spinal anesthesia was performed with the patient positioned in the lateral decubitus position. Under strict aseptic precautions, the skin was prepared and draped. Local infiltration was performed at the intended puncture site using 2% lignocaine. A 25-gauge Quincke spinal needle was introduced at the L2-L3 interspace using the midline approach. After confirming free flow of clear cerebrospinal fluid, the study drug was administered according to group allocation. The randomization and drug preparation

were conducted by a designated consultant who was not involved in patient assessment or data collection. The drug codes were sealed in numbered opaque envelopes, which were opened immediately before the administration of anesthesia. Group F received 2.8 ml of hyperbaric ropivacaine 0.75% combined with 0.2 ml (10 micrograms) of fentanyl, making a total volume of 3 ml and Group C received 2.8 ml of hyperbaric ropivacaine 0.75% combined with 0.2 ml (30 micrograms) of clonidine, making a total volume of 3 ml.

Following the intrathecal injection, patients were immediately positioned supine, and continuous monitoring was initiated. Hemodynamic parameters including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and oxygen saturation were recorded at 2-minute intervals for the first 15 minutes, and subsequently at 15-minute intervals until the completion of surgery.

Continuous electrocardiographic monitoring was maintained throughout the surgical procedure. The level of sensory block was assessed using the pin-prick method with a 26-gauge hypodermic needle. Sensory testing was performed at 1-minute intervals for the first 15 minutes following intrathecal injection, and subsequently at 15-minute intervals until the completion of surgery. The onset of sensory block was defined as the time interval from the intrathecal injection of the study drug until loss of sensation to pin-prick at the T6 dermatome. The highest level of sensory block achieved and the time taken to reach this level were documented. The duration of sensory block was defined as the time taken for regression of the sensory level from the highest dermatome achieved to the L1 dermatome, and this was recorded in the postoperative period. Motor block was assessed using the Modified Bromage Scale. Motor block assessment was performed at regular intervals from the time of drug administration until the start of surgery. The onset of motor block was defined as the time from intrathecal injection until Modified Bromage Grade 3 was achieved. Complete motor block was considered when Modified Bromage Grade 3 was attained. The duration of motor block was defined as the time taken for regression from Modified Bromage Grade 3 to Grade 0, which was assessed in the postoperative period.

Patients in whom the desired level of anesthesia was not achieved or who complained of pain during surgery were converted to general anesthesia and were excluded from the study analysis.

The duration of analgesia was defined as the time interval from the intrathecal injection to the time when the first rescue analgesic was administered for pain management in the postoperative period. The quality of analgesia was assessed using the Visual Analog Scale (VAS), which ranged from 0 to 10, where 0 represented no pain, 1-3 represented mild pain, 4-6 represented moderate pain, and 7-10 represented severe pain. VAS scores were recorded at the end of surgery and at 4 hours postoperatively.

Effective analgesia was defined as the period during which the VAS score remained 3 or less. When the pain score exceeded 3 on the VAS, intramuscular diclofenac 75 mg was administered as rescue analgesia. Intraoperative and postoperative adverse effects were meticulously documented. These included hypotension, bradycardia, nausea, vomiting, shivering, pruritus, respiratory depression, and urinary retention. The severity and timing of these complications were recorded.

In the postoperative period, patients were transferred to the Post-Anesthesia Care Unit (PACU) where continuous monitoring was maintained. Parameters assessed included the level of sensory and motor block, vital signs, regression characteristics of sensory and motor blockade, quality of postoperative analgesia, and time to first requirement of rescue analgesia. Patients were followed up for 24 hours postoperatively to assess the complete recovery profile and document any delayed adverse effects.

All collected data were entered into MS Excel spreadsheet and subsequently transferred to SPSSv23. Data were presented in a structured tabular format for clarity and ease of interpretation. Categorical variables were described as frequencies and percentages. Continuous variables were presented as mean (SD). For comparison of hemodynamic parameters and block characteristics between the two groups, Student's t-test was employed for normally distributed data. For multiple time-point comparisons of hemodynamic variables, ANOVA with repeated measures was utilized. The duration of analgesia, time to first rescue analgesic requirement, and VAS scores were compared between groups using Student's t-test. Categorical outcomes such as incidence of adverse effects were compared by using Chi-square test or Fisher's exact test as appropriate based on expected cell frequencies. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Completed data sets could be collected from 106 study participants. The mean (SD) ages in the Group F and Group C were 40.17 (9.42) years and 40.58 (9.68) respectively ($p=0.825$). The various age categorization in the two groups were comparable ($p=0.912$). The sex distribution in the two groups was also comparable ($p=0.845$). Again, both groups were comparable with respect to baseline demographic characteristics including weight ($p=0.935$), height ($p=0.871$), and ASA physical status distribution ($p=0.827$). Baseline hemodynamic parameters were comparable between both groups with no statistically significant differences. Mean heart rate ($p=0.870$), systolic blood pressure ($p=0.934$), diastolic blood pressure ($p=0.923$), mean arterial pressure ($p=0.918$), and oxygen saturation ($p=0.763$) were similar at baseline, confirming that both groups started with equivalent hemodynamic status prior to intervention.

The distribution of various types of lower limb surgeries was similar across both groups ($p=0.968$), indicating that the surgical case mix was comparable. Femur mid shaft fractures requiring plating/ORIF were the most common (17.9%), followed by tibial

fractures (16.0%) and ankle ORIF (15.1%). Patella fractures requiring TENS wiring constituted 9.4% of cases. This homogeneous distribution eliminates surgical type as a potential confounding variable.

Table 1: Sensory Block Characteristics

Parameter	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	Mean Difference (95% CI)	p-value
Onset of Sensory Block to T10 (min), Mean $\pm$ SD	2.28 $\pm$ 0.21	3.08 $\pm$ 0.26	-0.80 (-0.89 to -0.71)	<0.001 ^{a*}
Maximum Sensory Level T5, n (%)	23 (43.4%)	23 (43.4%)	-	0.998 ^b
Maximum Sensory Level T6, n (%)	30 (56.6%)	30 (56.6%)	-	
Time to Reach Maximum Sensory Level (min), Mean $\pm$ SD	8.38 $\pm$ 0.62	10.23 $\pm$ 0.58	-1.85 (-2.11 to -1.59)	<0.001 ^{a*}
Duration of Sensory Block (min), Mean $\pm$ SD	218.32 $\pm$ 8.46	317.77 $\pm$ 7.58	-99.45 (-102.61 to -96.29)	<0.001 ^{a*}

^a Independent t-test ^b Chi-square test *Statistically significant ($p<0.05$)

The onset of sensory block to T10 dermatome was significantly faster in Group F (2.28 $\pm$ 0.21 minutes) compared to Group C (3.08 $\pm$ 0.26 minutes) with a mean difference of 0.80 minutes ($p<0.001$). However, the duration of sensory block was significantly prolonged in Group C (317.77 $\pm$ 7.58 minutes) compared to Group F (218.32 $\pm$ 8.46

minutes), with a mean difference of 99.45 minutes ($p<0.001$). The maximum sensory level achieved was comparable between groups, with 43.4% achieving T5 level in both groups ($p=0.998$). Group F demonstrated faster onset characteristics while Group C provided substantially longer duration of sensory blockade. [Table 1]

Table 2: Motor Block Characteristics

Parameter	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	Mean Difference (95% CI)	p-value
Onset of Motor Block (min), Mean $\pm$ SD	6.55 $\pm$ 0.49	8.36 $\pm$ 0.48	-1.81 (-2.01 to -1.61)	<0.001 ^{a*}
Duration of Motor Block (min), Mean $\pm$ SD	187.23 $\pm$ 7.52	268.66 $\pm$ 7.14	-81.43 (-84.28 to -78.58)	<0.001 ^{a*}

^a Independent t-test *Statistically significant ($p<0.05$)

Motor block onset was significantly faster in Group F (6.55 $\pm$ 0.49 minutes) compared to Group C (8.36 $\pm$ 0.48 minutes), with a mean difference of 1.81 minutes ($p<0.001$). The duration of motor block was significantly prolonged in Group C (268.66 $\pm$ 7.14 minutes) compared to Group F (187.23 $\pm$ 7.52

minutes), showing a mean difference of 81.43 minutes ($p<0.001$). These findings indicate that while fentanyl as an adjuvant provides faster onset of motor blockade, clonidine significantly extends the duration of motor block by approximately 81 minutes. [Table 2]

Table 3: Intraoperative Hemodynamic Parameters at Key Time Points

Time Point	Parameter	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	p-value
15 minutes	Heart Rate	64.38 $\pm$ 3.82	60.15 $\pm$ 4.26	<0.001 ^{a*}
	SBP (mmHg)	104.38 $\pm$ 3.94	101.89 $\pm$ 4.38	0.002 ^{a*}
	DBP (mmHg)	66.38 $\pm$ 3.71	62.64 $\pm$ 4.52	<0.001 ^{a*}
	MAP (mmHg)	79.04 $\pm$ 3.52	75.72 $\pm$ 4.18	<0.001 ^{a*}
30 minutes	Heart Rate	66.38 $\pm$ 3.94	58.26 $\pm$ 4.84	<0.001 ^{a*}
	SBP (mmHg)	108.38 $\pm$ 4.12	103.21 $\pm$ 5.16	<0.001 ^{a*}
	DBP (mmHg)	70.38 $\pm$ 3.82	64.75 $\pm$ 4.92	<0.001 ^{a*}
	MAP (mmHg)	83.04 $\pm$ 3.72	77.57 $\pm$ 4.86	<0.001 ^{a*}
60 minutes	Heart Rate	70.38 $\pm$ 4.02	62.49 $\pm$ 5.28	<0.001 ^{a*}
	SBP (mmHg)	114.38 $\pm$ 4.28	110.45 $\pm$ 5.84	<0.001 ^{a*}
	DBP (mmHg)	74.38 $\pm$ 3.94	68.87 $\pm$ 5.42	<0.001 ^{a*}
	MAP (mmHg)	87.71 $\pm$ 3.88	82.73 $\pm$ 5.48	<0.001 ^{a*}
120 minutes	Heart Rate	78.00 $\pm$ 4.18	76.60 $\pm$ 5.62	0.142 ^a
	SBP (mmHg)	122.00 $\pm$ 4.64	128.30 $\pm$ 6.18	<0.001 ^{a*}
	DBP (mmHg)	82.00 $\pm$ 4.12	82.26 $\pm$ 5.84	0.803 ^a
	MAP (mmHg)	95.33 $\pm$ 4.18	97.61 $\pm$ 5.76	0.023 ^{a*}

^a Independent t-test *Statistically significant ($p<0.05$) SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure

Significant hemodynamic differences were observed between the groups at various time points. Group C demonstrated significantly lower heart rates at 15, 30,

and 60 minutes ($p<0.001$) compared to Group F, reflecting the bradycardic effect of clonidine. Blood pressure parameters (SBP, DBP, MAP) were also

significantly lower in Group C during the initial 60 minutes of surgery ($p<0.001$), indicating greater sympatholytic effect of clonidine. By 120 minutes, hemodynamic parameters began to converge, with heart rate showing no significant difference ($p=0.142$), though blood pressure remained slightly higher in Group C as the block began to recede. [Table 3]

The incidence of hypotension was comparable between Group F (30.2%) and Group C (28.3%) with no statistically significant difference ($p=0.832$). The mean dose of mephentermine required for treating hypotension was also similar between groups ($p=0.198$). However, bradycardia occurred exclusively in Group C, affecting 26.4% of patients (14/53), while no patient in Group F experienced bradycardia ($p<0.001$). Atropine 0.6 mg was administered to manage bradycardia in Group C

patients. This highlights the significant alpha-2 adrenergic agonist effect of clonidine on heart rate, which is the primary hemodynamic concern with this adjuvant.

The mean duration of surgery was comparable between Group F (92.06 ± 17.24 minutes) and Group C (98.34 ± 19.82 minutes) with no statistically significant difference ($p=0.084$), confirming similarity in surgical complexity and duration between groups. However, the duration of postoperative analgesia (time to first rescue analgesic requirement) was significantly prolonged in Group C (339.02 ± 9.64 minutes) compared to Group F (247.26 ± 9.18 minutes), with a mean difference of 91.76 minutes ($p<0.001$). This represents approximately 1.5 hours of additional pain-free time in the clonidine group, demonstrating superior postoperative analgesic efficacy.

Table 4: Visual Analog Scale (VAS) Scores

Time Point	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	p-value
VAS at End of Surgery, Mean $\pm$ SD	0.04 ± 0.19	0.02 ± 0.14	0.547 ^a
VAS at End of Surgery = 0, n (%)	51 (96.2%)	52 (98.1%)	0.558 ^b
VAS at 4 hours postoperatively, Mean $\pm$ SD	1.70 ± 0.82	0.87 ± 0.68	<0.001 ^{a*}
VAS at 4 hours = 0, n (%)	4 (7.5%)	21 (39.6%)	<0.001 ^{b*}
VAS at 4 hours = 1, n (%)	16 (30.2%)	23 (43.4%)	
VAS at 4 hours = 2, n (%)	22 (41.5%)	7 (13.2%)	
VAS at 4 hours = 3, n (%)	11 (20.8%)	2 (3.8%)	

^a Independent t-test ^b Chi-square test *Statistically significant ($p<0.05$)

Pain scores at the end of surgery were minimal and comparable in both groups ($p=0.547$), with 96.2% of Group F and 98.1% of Group C patients reporting VAS score of 0. At 4 hours postoperatively, Group C demonstrated significantly lower pain scores (0.87 ± 0.68) compared to Group F (1.70 ± 0.82), with $p<0.001$. Notably, 39.6% of patients in Group C remained completely pain-free (VAS=0) at 4 hours

compared to only 7.5% in Group F ($p<0.001$). The distribution of pain scores showed that 83.0% of Group C patients had VAS ≤ 1 , while only 37.7% of Group F patients achieved this level of analgesia. These findings demonstrate superior quality of postoperative analgesia with clonidine as an adjuvant. [Table 4]

Table 5: Intraoperative Adverse Effects

Adverse Effect	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	p-value	Relative Risk (95% CI)
Hypotension, n (%)	16 (30.2%)	15 (28.3%)	0.832 ^a	0.94 (0.52-1.69)
Bradycardia, n (%)	0 (0%)	14 (26.4%)	<0.001 ^{a*}	-
Nausea, n (%)	7 (13.2%)	6 (11.3%)	0.766 ^a	0.86 (0.31-2.36)
Vomiting, n (%)	0 (0%)	0 (0%)	1.000	-
Shivering, n (%)	6 (11.3%)	7 (13.2%)	0.766 ^a	1.17 (0.42-3.23)
Pruritus, n (%)	15 (28.3%)	0 (0%)	<0.001 ^{a*}	-
Respiratory Depression, n (%)	0 (0%)	0 (0%)	1.000	-

^a Chi-square test / Fisher's exact test *Statistically significant ($p<0.05$)

The intraoperative adverse effect profile differed significantly between groups for two specific complications. Pruritus occurred in 28.3% of patients in Group F (15/53) but was completely absent in Group C ($p<0.001$), representing a classic opioid-related side effect. Conversely, bradycardia was observed exclusively in Group C, affecting 26.4% of patients (14/53) with no cases in Group F ($p<0.001$), reflecting the alpha-2 agonist effect of clonidine. Hypotension occurred with similar frequency in both groups (30.2% vs 28.3%, $p=0.832$). Nausea and shivering were comparable between groups. No patient in either group experienced vomiting or

respiratory depression, confirming the safety profile of both adjuvants at the doses used. [Table 5]

In the postoperative period, pruritus continued to be the most distinctive adverse effect, occurring in 30.2% of Group F patients but absent in all Group C patients ($p<0.001$). Postoperative nausea was significantly higher in Group F (15.1%) compared to Group C (3.8%) with $p=0.046$, suggesting a relationship with opioid use. Urinary retention showed no significant difference between groups (11.3% vs 15.1%, $p=0.562$), nor did shivering (13.2% vs 15.1%, $p=0.782$). No patient in either group experienced postoperative vomiting or respiratory

depression. The overall postoperative adverse effect profile favored Group C, with lower incidence of

opioid-related side effects while maintaining comparable rates of other complications.

Table 6: Summary of Primary Outcome Variables

Primary Outcome	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	Mean Difference	p-value	Effect Size (Cohen's d)
Sensory Block					
Onset Time (min)	2.28 ± 0.21	3.08 ± 0.26	-0.80 min	<0.001*	3.39
Duration (min)	218.32 ± 8.46	317.77 ± 7.58	-99.45 min	<0.001*	12.38
Motor Block					
Onset Time (min)	6.55 ± 0.49	8.36 ± 0.48	-1.81 min	<0.001*	3.71
Duration (min)	187.23 ± 7.52	268.66 ± 7.14	-81.43 min	<0.001*	11.14
Analgesia					
Duration (min)	247.26 ± 9.18	339.02 ± 9.64	-91.76 min	<0.001*	9.76
VAS at 4 hours	1.70 ± 0.82	0.87 ± 0.68	0.83	<0.001*	1.12

*Statistically significant (p<0.05) Effect Size Interpretation: Small (0.2-0.5), Medium (0.5-0.8), Large (>0.8)

All primary outcome variables demonstrated statistically significant differences between the two groups (p<0.001 for all comparisons). Group F (fentanyl) showed significantly faster onset of both sensory (2.28 vs 3.08 minutes) and motor blockade (6.55 vs 8.36 minutes), with large effect sizes (Cohen's d = 3.39 and 3.71 respectively). However, Group C (clonidine) demonstrated markedly prolonged durations of sensory block (99.45 minutes

longer), motor block (81.43 minutes longer), and postoperative analgesia (91.76 minutes longer), with very large effect sizes (Cohen's d > 9.0), indicating clinically significant advantages. Pain scores at 4 hours were substantially lower in Group C (0.87 vs 1.70), with a large effect size (Cohen's d = 1.12). These findings indicate that while fentanyl provides faster onset, clonidine offers substantially superior duration and quality of analgesia. [Table 6]

Table 7: Overall Comparison of Key Clinical Parameters

Parameter	Group F (Fentanyl) n=53	Group C (Clonidine) n=53	Clinical Significance
Advantages			
Faster Onset (Sensory)	✓ (2.28 min)	-	35% faster
Faster Onset (Motor)	✓ (6.55 min)	-	22% faster
Lower Bradycardia	✓ (0%)	26.4%	Significant
No Pruritus	-	✓ (0%)	Significant
Duration Benefits			
Longer Sensory Block	218.32 min	✓ (317.77 min)	45% longer
Longer Motor Block	187.23 min	✓ (268.66 min)	43% longer
Longer Analgesia	247.26 min	✓ (339.02 min)	37% longer
Better VAS at 4hr	1.70	✓ (0.87)	49% reduction
Hemodynamic Stability			
Similar Hypotension	30.2%	28.3%	Not significant
Bradycardia Risk	Lower ✓	Higher	Significant
Overall Success Rate			
No conversion to GA	53/53 (100%)	53/53 (100%)	Equivalent
Adequate surgical anesthesia	53/53 (100%)	53/53 (100%)	Equivalent

✓ indicates superiority for that parameter GA: General Anesthesia

This comprehensive comparison demonstrates that both adjuvants achieved 100% success rate in providing adequate surgical anesthesia without any conversions to general anesthesia. Group F (fentanyl) demonstrated advantages in faster onset times (approximately 22-35% faster) and complete absence of bradycardia, making it suitable for shorter procedures or situations where rapid onset is prioritized. Group C (clonidine) exhibited substantial advantages in prolonging block duration (43-45% longer) and postoperative analgesia (37% longer with 49% better pain scores), along with complete absence of pruritus. [Table 7]

DISCUSSION

Onset Characteristics of Sensory & Motor Blockade: The significantly faster sensory onset

observed with fentanyl in our study (2.28±0.21 minutes) compared to clonidine (3.08±0.26 minutes, mean difference 0.80 minutes) aligns remarkably well with the findings of Priya et al, who reported sensory onset times of 2.12±0.22 minutes with ropivacaine-fentanyl 25 mcg versus 2.48±0.36 minutes with ropivacaine-clonidine 15 mcg (p<0.001).^[11] Saran et al reported comparable results in their three-arm study.^[12] The consistency across these studies, despite variations in patient populations and surgical types, reinforces the fundamental pharmacokinetic advantage of lipophilic opioids in producing rapid neural blockade. Motor block onset in our study demonstrated a similar pattern, with fentanyl producing significantly faster onset (6.55±0.49 minutes) than clonidine (8.36±0.48 minutes), representing a 1.81-minute or 22% reduction in onset time (p<0.001). This finding is

corroborated by Gupta et al, who reported motor block onset of 4.67 ± 1.15 minutes with isobaric ropivacaine 0.75% plus fentanyl 25 mcg compared to 6.40 ± 1.35 minutes with ropivacaine alone ($p < 0.001$), demonstrating fentanyl's contribution to accelerated motor blockade even at higher doses.^[13] The slightly faster absolute onset times in their study may reflect differences in baricity (isobaric vs hyperbaric solutions) and patient positioning. Ben-David et al observed similar acceleration of motor block with low-dose bupivacaine-fentanyl combinations, attributing this to synergistic interactions at the spinal cord level where opioid receptors on motor neurons can modulate neurotransmitter release and enhance local anesthetic effects.^[14] Singh et al, in their dose-response study of intrathecal clonidine (0, 30, 50, and 75 mcg) with bupivacaine, reported sensory onset times ranging from 5.15 ± 0.68 minutes (control) to 3.25 ± 0.52 minutes (75 mcg clonidine), demonstrating a dose-dependent reduction in onset time that plateaus at higher doses.^[15] Korhonen et al demonstrated that rapid-onset spinal anesthesia with bupivacaine-fentanyl combinations improved patient satisfaction scores and reduced the need for supplemental sedation in outpatient knee arthroscopy procedures.^[16] Duration of Sensory and Motor Blockade:

The most clinically striking finding of our study was the substantial prolongation of both sensory and motor block durations achieved with clonidine compared to fentanyl. These results are remarkably concordant with the literature. Priya et al reported sensory block durations of 302.30 ± 29.83 minutes with ropivacaine-clonidine 15 mcg compared to 210.80 ± 21.86 minutes with ropivacaine-fentanyl 25 mcg ($p < 0.001$), a difference of 91.5 minutes that closely parallels our findings.^[11] Saran et al observed even more pronounced differences in their study, with clonidine 30 mcg producing sensory duration of 355.33 ± 42.57 minutes versus 267.67 ± 28.54 minutes with fentanyl 25 mcg ($p < 0.001$), and 184.33 ± 23.89 minutes with ropivacaine alone ($p < 0.001$).^[12] The longer absolute durations in their study may reflect differences in the definition of sensory block endpoint or variations in surgical stimulation intensity. Motor block duration exhibited a parallel pattern, with our study demonstrating 268.66 ± 7.14 minutes in Group C versus 187.23 ± 7.52 minutes in Group F, an 81.43-minute (43%) prolongation with large effect size (Cohen's $d = 11.14$, $p < 0.001$). Singh et al investigated the dose-dependent effects of intrathecal clonidine and reported progressive increases in motor block duration from 145.25 ± 18.62 minutes with bupivacaine alone to 194.25 ± 24.37 minutes with 30 mcg clonidine, 259.75 ± 32.84 minutes with 50 mcg clonidine, and 324.25 ± 36.48 minutes with 75 mcg clonidine ($p < 0.001$ for trend), demonstrating a clear dose-response relationship that plateaus at doses above 50 mcg.^[15] Our findings with clonidine 30 mcg fall appropriately within this dose-response curve. Agarwal et al studied elderly patients (age 60-80 years) receiving hyperbaric bupivacaine

with clonidine 30 mcg and reported motor block duration of 329.67 ± 33.42 minutes compared to 198.33 ± 23.50 minutes with bupivacaine alone ($p < 0.0001$), representing a 66% prolongation.^[9]

The clinical implications of these duration differences are profound. For surgeries expected to last 2-3 hours, fentanyl's duration may be adequate for intraoperative anesthesia but offers limited postoperative coverage, necessitating early administration of rescue analgesics. Conversely, clonidine's prolonged duration provides extended intraoperative anesthesia suitable for complex procedures and offers substantial postoperative pain relief, potentially reducing opioid requirements and facilitating early mobilization—key components of Enhanced Recovery After Surgery (ERAS) protocols.^[17,18]

Postoperative Analgesia & Pain Scores: The duration of postoperative analgesia was significantly prolonged in Group C compared to Group F. Priya et al reported similar findings.^[11] Saran et al. observed even more dramatic differences in their study.^[12] The VAS scores at 4 hours postoperatively further illustrated the superior analgesic quality provided by clonidine. These findings are consistent with the dose-response study by Singh et al, who observed progressive improvements in postoperative VAS scores with increasing clonidine doses, with the 30 mcg dose providing a balanced analgesic profile without excessive sedation.^[15]

Elia et al, in a systematic review and meta-analysis of 22 randomized controlled trials involving 1,445 patients, concluded that intrathecal clonidine (doses 15-150 mcg) significantly prolonged the duration of both sensory and motor blockade and improved postoperative analgesia compared to local anesthetic alone (weighted mean difference in analgesia duration: 130 minutes, 95% CI: 90-170 minutes).^[19] Their analysis revealed a dose-dependent effect with optimal benefit-to-risk ratio at doses between 30-75 mcg, beyond which hemodynamic side effects increased without proportional analgesic gains. Our choice of 30 mcg clonidine was therefore evidence-based and falls within this optimal range.

Hemodynamic Effects and Cardiovascular Stability: Baseline hemodynamic parameters were comparable between groups, confirming successful randomization. However, intraoperative hemodynamic profiles differed significantly between the two adjuvants, reflecting their distinct mechanisms of action. Group C demonstrated significantly lower heart rates at 15 minutes, 30 minutes and 60 minutes, reflecting clonidine's bradycardic effect mediated through central and peripheral alpha-2 receptor activation.^[20,21] Blood pressure parameters demonstrated similar patterns, with Group C showing significantly lower systolic, diastolic, and mean arterial pressures during the first 60 minutes of surgery, followed by gradual convergence and eventual reversal by 120 minutes. The incidence of clinically significant hypotension was comparable between groups, and the mean dose

of mephentermine required for treatment was similar. These findings suggest that clonidine 30 mcg produces moderate sympatholysis without excessive hypotension in healthy, euvoletic patients. In stark contrast, bradycardia occurred exclusively in Group C, affecting 26.4% of patients compared to 0% in Group F. These findings align with those of Agarwal et al, who reported bradycardia in 30% of elderly patients receiving bupivacaine-clonidine 30 mcg compared to 6.7% with bupivacaine alone ($p<0.01$).^[9]

The clinical implications of these hemodynamic findings are important for patient selection and perioperative management. Clonidine should be used cautiously in patients with pre-existing bradyarrhythmias, high-degree atrioventricular block, severe coronary artery disease, or those receiving beta-blockers, calcium channel blockers, or other bradycardic medications.^[20,21] Conversely, fentanyl demonstrates excellent cardiovascular stability and may be preferred in hemodynamically fragile patients or those with cardiac conduction abnormalities.

Adverse Effects Profile: The adverse effect profiles of the two adjuvants were markedly different, reflecting their distinct pharmacological mechanisms and receptor targets. Pruritus emerged as the most distinctive complication in Group F, occurring in 28.3% of patients (15/53) both intraoperatively and extending into the postoperative period (30.2%, 16/53 patients), while being completely absent in Group C ($p<0.001$ for both comparisons). This finding is entirely consistent with the known side effect profile of intrathecal opioids, where pruritus represents one of the most common complications, with reported incidences ranging from 30-90% depending on opioid type, dose, and patient factors.^[22-24]

Clinical Implications & Adjuvant Selection: The comprehensive analysis of our results, contextualized within the broader literature, reveals that both fentanyl and clonidine are effective and safe adjuvants to hyperbaric ropivacaine for lower limb surgeries, but their distinct pharmacological profiles suggest different optimal clinical applications. Fentanyl emerges as the preferred adjuvant when rapid onset is paramount—for example, in emergency surgery, highly anxious patients requiring rapid reassurance, or busy surgical schedules where minimizing preparation time enhances workflow efficiency. The 22-35% faster onset of both sensory and motor blockade, complete absence of bradycardia, and excellent hemodynamic stability make fentanyl particularly attractive for patients with cardiac conduction abnormalities, those receiving rate-limiting cardiac medications, or elderly patients with limited cardiovascular reserve. However, fentanyl's duration-limiting pharmacokinetics make it less suitable for prolonged procedures or situations where extended postoperative analgesia is desired. For surgeries expected to last less than 2 hours with anticipated multimodal postoperative pain

management, fentanyl provides adequate coverage. For longer procedures or inadequate postoperative analgesic planning, fentanyl's limitations become apparent, necessitating supplementation or conversion to general anesthesia. The 28-30% incidence of pruritus, while generally mild and self-limiting, can be distressing for some patients and may require treatment, particularly in the obstetric population where patient satisfaction is paramount.^[22,23] Clonidine, conversely, excels in situations requiring prolonged surgical anesthesia and extended postoperative analgesia. The 43-45% prolongation of block duration and 37% extension of analgesia, translating to approximately 1.5 hours of additional pain-free time, make clonidine ideally suited for complex orthopedic procedures such as total knee replacements, femoral shaft fracture fixations, or multi-level lower limb reconstructions. The complete absence of pruritus is particularly advantageous for patients with sensitive skin, those with anxiety about itching, or populations where pruritus management is challenging. The superior VAS scores at 4 hours (49% reduction compared to fentanyl) and the dramatic difference in pain-free patients (39.6% vs 7.5%) suggest that clonidine better aligns with Enhanced Recovery After Surgery (ERAS) principles by facilitating early mobilization and reducing postoperative opioid requirements.^[17,18]

Study limitations: There were some limitations in the study. First, our study was conducted at a single tertiary care center, potentially limiting generalizability to other settings or populations. Second, we evaluated only one dose of each adjuvant (fentanyl 10 mcg, clonidine 30 mcg), precluding dose-response analysis. While these doses are well-established in the literature, evaluation of alternative doses (e.g., fentanyl 15-25 mcg, clonidine 15-75 mcg) would provide more comprehensive guidance. Third, our study included only ASA I-II patients aged 18-60 years undergoing elective surgery, excluding elderly patients, those with significant comorbidities, emergency procedures, and obstetric populations where adjuvant effects might differ. Fourth, we did not assess long-term outcomes such as chronic pain development, functional recovery trajectories, or patient-reported quality of life, which increasingly are recognized as important endpoints.

CONCLUSION

Both fentanyl 10 mcg and clonidine 30 mcg are effective and safe adjuvants to hyperbaric ropivacaine 0.75% for spinal anesthesia in lower limb surgery, though with distinctly different clinical profiles that suit different clinical scenarios. Fentanyl provides significantly faster onset of sensory (35% faster) and motor (22% faster) blockade with excellent hemodynamic stability and no bradycardia, making it ideal for rapid-onset requirements, emergency surgery, and patients with cardiac conduction abnormalities. However, its analgesic

duration is limited (approximately 4 hours), and it carries a 28-30% pruritus risk. Clonidine, conversely, produces substantially longer sensory (45% longer), motor (43% longer), and analgesic (37% longer) durations with superior postoperative pain control (49% lower VAS scores at 4 hours) and complete absence of pruritus, making it optimal for prolonged procedures and when extended postoperative analgesia is desired. However, it carries a 26.4% bradycardia risk requiring vigilant monitoring and appropriate patient selection. The choice of adjuvant should be individualized based on surgical duration, desired recovery profile, patient comorbidities, and institutional resources. Both adjuvants achieved 100% clinical success without conversion to general anesthesia, confirming their roles as evidence-based options for enhancing spinal anesthesia quality in contemporary practice.

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