Research Article

Comparison of the Effect of Intrathecal Morphine and Intrathecal Fentanyl as Adjuvants to 0.5% Levobupivacaine in Total Knee Replacement Surgery

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Abstract

Background: Intrathecal opioids are commonly used as adjuvants to local anaesthetics to prolong spinal analgesia. Morphine (hydrophilic) provides prolonged analgesia; fentanyl (lipophilic) provides rapid onset but shorter duration. This study compared intrathecal morphine and fentanyl as adjuvants to 0.5% hyperbaric levobupivacaine in total knee replacement (TKR) surgery.

Methods: In this prospective, randomized comparative study, 50 patients aged 45–75 years, belonging to ASA physical status I or II and undergoing total knee replacement surgery, were included after obtaining institutional ethics committee approval and written informed consent. Patients were randomly allocated to either Group LM (3 mL of 0.5% hyperbaric levobupivacaine + 100 µg morphine) or Group LF (3 mL of 0.5% hyperbaric levobupivacaine + 25 µg fentanyl), with each solution made up to a total volume of 3.5 mL with normal saline (n = 25 per group). VAS pain scores were recorded up to 24 hours; rescue analgesia (8 mL 0.125% ropivacaine epidural) was given for VAS>4.

Results: Baseline demographics and haemodynamics were similar between groups. Fentanyl produced significantly faster onset of sensory and motor block ($p<0.001$). Morphine produced significantly lower postoperative VAS scores, longer time to first rescue analgesia (5.56±0.71 vs 3.88±0.88 h; $p<0.001$), and fewer rescue doses in 24 h (1.52±1.05 vs 5.64±1.41; $p<0.001$). Nausea/vomiting, pruritus and haemodynamic parameters showed no significant difference between groups.

Conclusion: Intrathecal morphine (100 µg) with 0.5% hyperbaric levobupivacaine provides significantly superior and more prolonged postoperative analgesia than intrathecal fentanyl (25 µg), with similar haemodynamic stability and side-effect profile, making it a preferable adjuvant for TKR spinal anaesthesia.

Keywords: Total knee replacement, spinal anaesthesia, hyperbaric levobupivacaine, intrathecal morphine, intrathecal fentanyl, postoperative analgesia, rescue analgesia, VAS.

Introduction

Effective postoperative pain control after TKR facilitates early mobilisation, functional recovery, and patient satisfaction. Intrathecal opioids are widely used as adjuvants to prolong spinal analgesia, and adjuvants added to a spinal block are associated with a prolonged duration of anaesthesia and improved analgesic effect. [1,2] Multimodal analgesia—combining systemic opioids and NSAIDs, epidural local anaesthetics and/or opioids, peripheral nerve blocks, or other drug combinations—significantly enhances analgesic efficacy, [3,4] which is important as up to 60% of patients undergoing knee replacement surgery report severe postoperative pain, with a further 30% reporting moderate pain. [5] Using adjuvants in a spinal block is a cornerstone of multimodal analgesia, aiming to reduce the total dose of systemic opioids and their associated side effects such as respiratory depression or ileus. [6] Hyperbaric levobupivacaine, an isomer of bupivacaine, is being explored as an alternative to bupivacaine owing to its reduced cardiovascular and CNS toxicity. This study compared the analgesic efficacy and safety of intrathecal morphine and fentanyl as adjuvants to 0.5% hyperbaric levobupivacaine in patients undergoing TKR.

Materials And Methods

- Design: Prospective, randomised, comparative study; 50 ASA I–II patients undergoing elective TKR under spinal anaesthesia.
- Group LM (n=25): 3 mL 0.5% hyperbaric levobupivacaine + 100 µg intrathecal morphine, made up to 3.5 mL with normal saline.
- Group LF (n=25): 3 mL 0.5% hyperbaric levobupivacaine + 25 µg intrathecal fentanyl, made up to 3.5 mL with normal saline.
- Postoperative pain assessed by VAS at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 hours.
- Rescue analgesia: 8 mL 0.125% ropivacaine via epidural catheter, given when VAS > 4.
- Primary outcomes: time to first rescue analgesia; total rescue analgesic requirement over 24 hours.
- Secondary outcomes: sensory/motor block characteristics, haemodynamic parameters, VAS scores, adverse effects.

Results

A total of 50 patients undergoing elective TKR were enrolled and equally allocated to Group LM and Group LF (n=25 each).

Demographic and Baseline Characteristics

Table 1: Demographic and Baseline Characteristics

Parameter	LM (Mean ± SD / n %)	LF (Mean ± SD / n %)	P-value
Age (years)	62.68 ± 8.27	62.44 ± 7.41	0.783
Height (cm)	163.48 ± 7.48	162.84 ± 6.83	0.753
Weight (kg)	66.68 ± 8.26	67.68 ± 7.76	0.661
BMI (kg/m²)	24.96 ± 2.14	25.16 ± 2.75	0.779
Gender	Male: 11 (44%) / Female: 14 (56%)	Male: 10 (40%) / Female: 15 (60%)	0.774
ASA	I: 3 (12%) / II: 22 (88%)	I: 8 (32%) / II: 17 (68%)	0.088

Figure 1: Age distribution between groups.

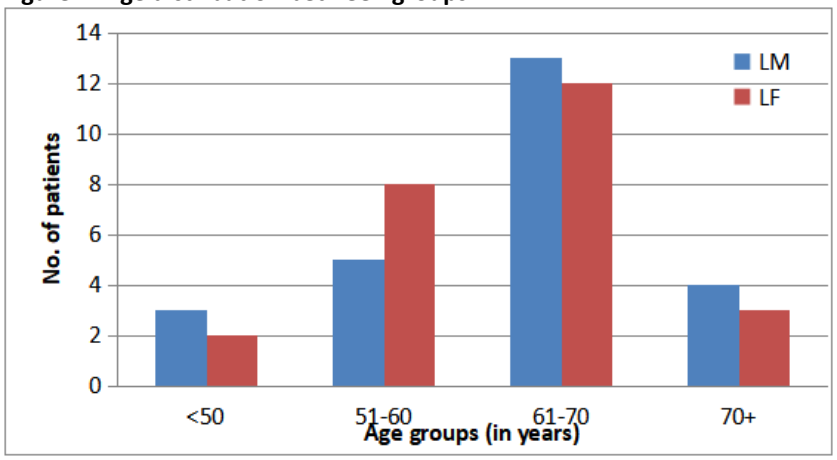


Figure 2: Height, weight and BMI comparison between groups.

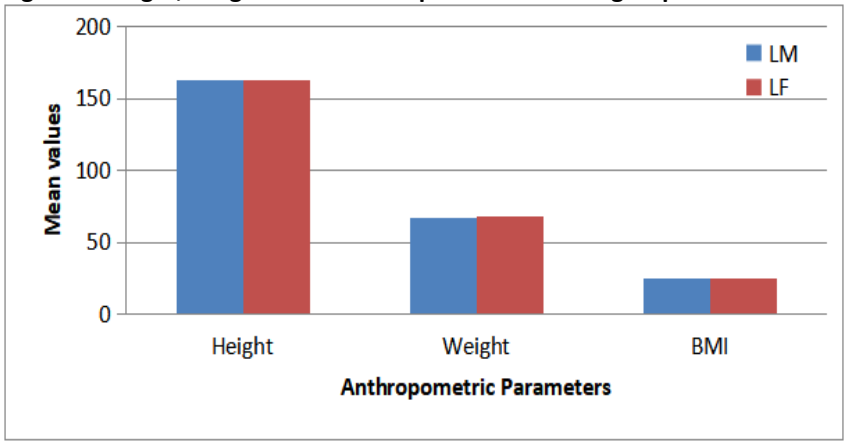


Figure 3: Gender distribution between groups.

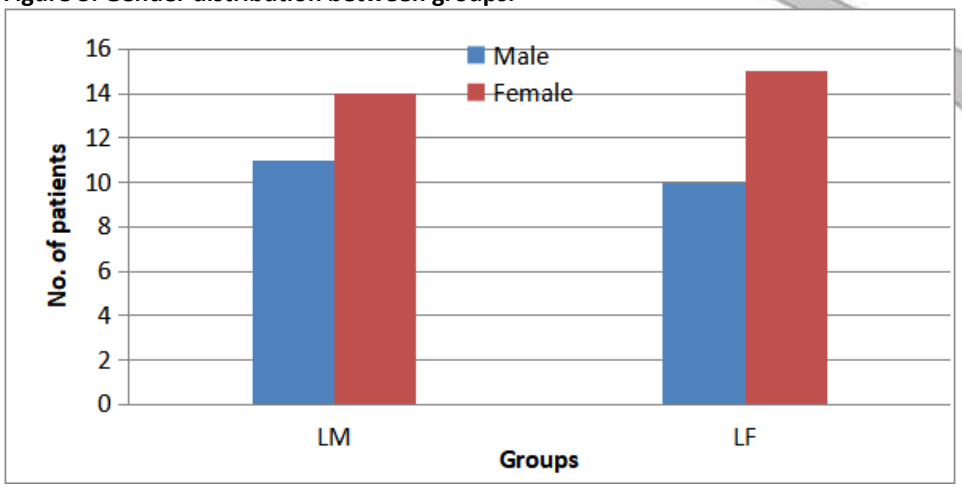
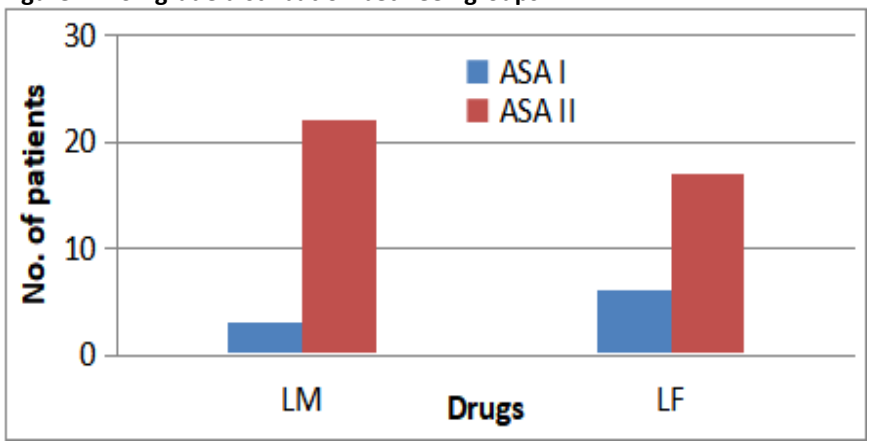


Figure 4: ASA grade distribution between groups.



No statistically significant differences were observed in the baseline characteristics (age, height, weight, BMI, gender and ASA grade) between LM and LF before intervention (all p>0.05).

Intraoperative Vital Parameters

Figure 5: Intraoperative SBP trend.

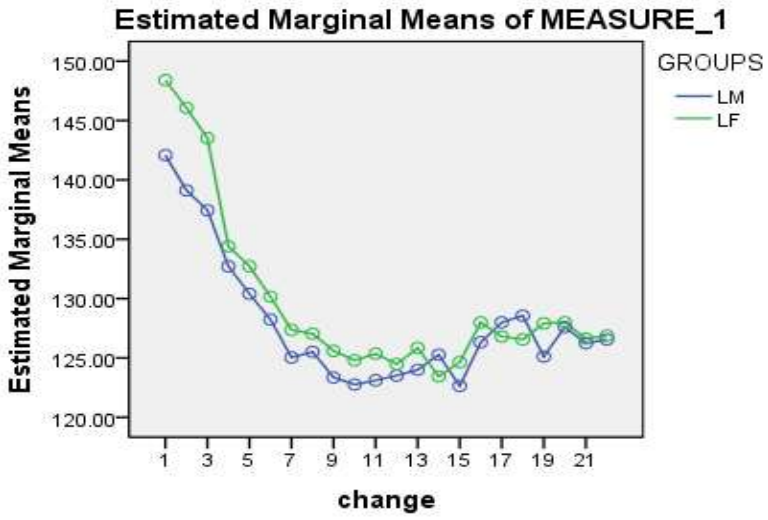


Figure 6: Intraoperative DBP trend.

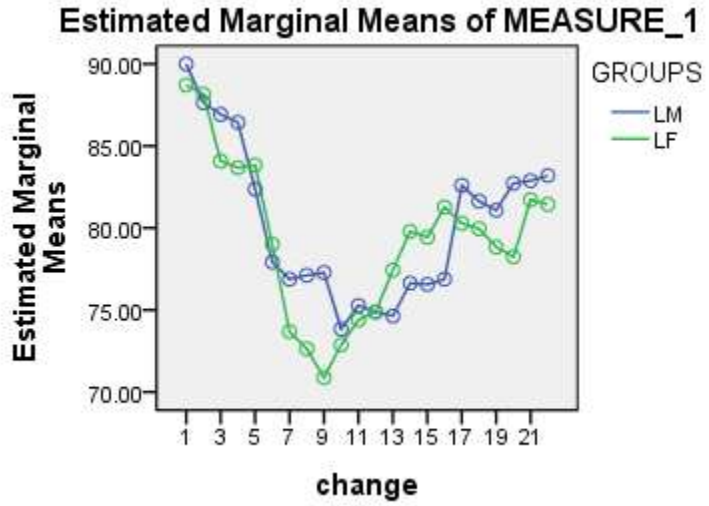


Figure 7: Intraoperative MAP trend.

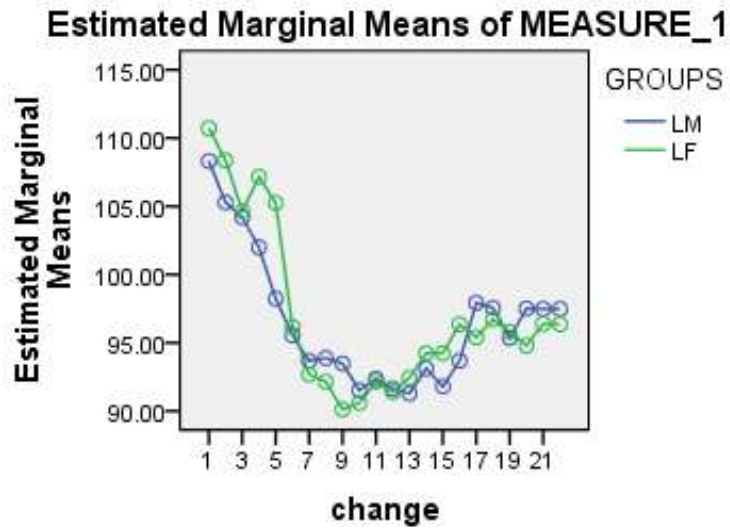
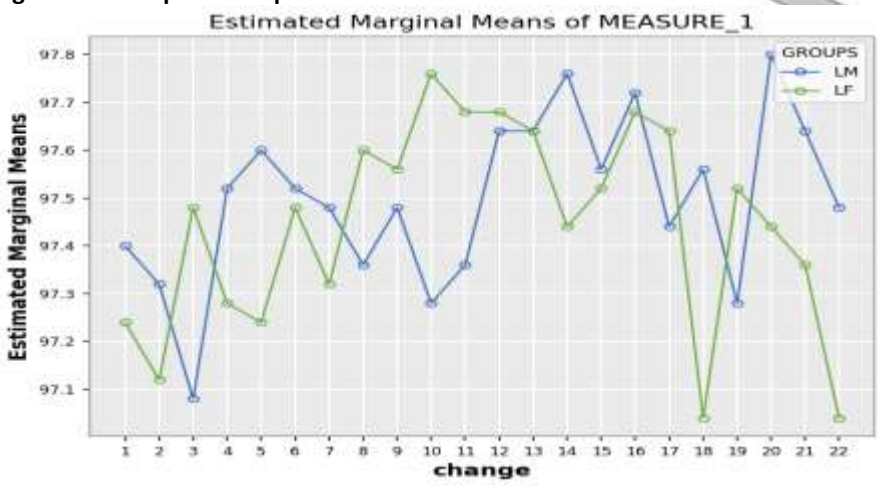


Figure 8: Intraoperative heart rate trend.

Figure 9: Intraoperative SpO2 trend.



Vitals were compared between the intrathecal morphine group (LM) and the intrathecal fentanyl group (LF) at multiple time intervals following spinal anaesthesia for total knee replacement surgery. SBP did not demonstrate statistically significant between-group differences at the assessed time points, with p values ranging from 0.163 to 0.911. DBP showed no statistically significant difference between the groups, with p values ranging from 0.068 to 1.000. MAP values also showed no statistically significant between-group differences at the assessed time points, with p values ranging from 0.147 to 0.955. HR demonstrated no statistically significant between-group differences across the assessed time points, with p values ranging from 0.099 to 0.980. SpO_2 remained statistically similar between the groups, with p values ranging from 0.068 to 1.000. Overall, no statistically significant differences were observed in the intraoperative vital parameters assessed between the two groups.

Sensory and Motor Block Characteristics

Table 2: Sensory and Motor Block Characteristics

Parameter	LM (Mean ± SD)	LF (Mean ± SD)	P-value
SENSORY AND MOTOR BLOCK CHARACTERISTICS			
Onset of Sensory Block at T10 (min)	7.36 ± 1.04	3.00 ± 0.71	<0.001
Time to Highest Sensory Level (min)	14.56 ± 0.87	13.16 ± 0.85	<0.001
Time for Two-Segment Regression (min)	101.04 ± 1.67	87.76 ± 1.56	<0.001
Onset of Motor Block (min)	8.32 ± 1.31	3.64 ± 0.64	<0.001
Time to Complete Motor Block (min)	16.76 ± 1.61	14.76 ± 1.16	<0.001
HIGHEST LEVEL OF SENSORY BLOCK			
T6	16 (64%)	17 (68%)	>0.05
T8	9 (36%)	8 (32%)	>0.05
DURATION OF SENSORY AND MOTOR BLOCK			
Duration of Sensory Block (min)	286.72 ± 5.33	201.12 ± 17.13	<0.001
Duration of Motor Block (min)	202.48 ± 4.47	167.32 ± 19.48	<0.001

Figure 10: Time for two-segment regression of sensory level.

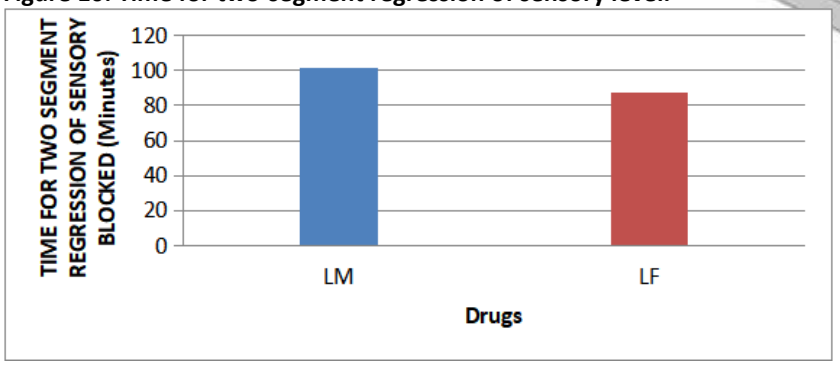
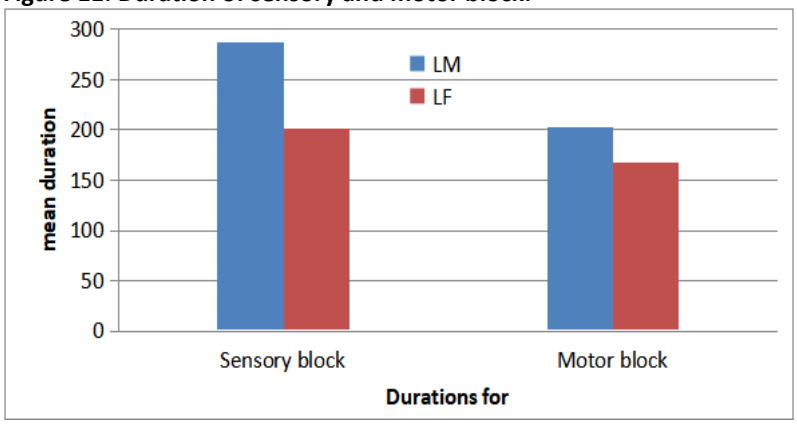


Figure 11: Duration of sensory and motor block.



Fentanyl produced significantly faster onset of both sensory and motor block ($p<0.001$), whereas morphine produced significantly longer duration of both sensory and motor block ($p<0.001$). The highest sensory level reached (T6 vs T8) was distributed almost identically between groups, with no significant difference ($p>0.05$).

Adverse Effects

Table 3: Adverse Effects

Adverse Effect	LM Group (n=25)	LF Group (n=25)	P value
Nausea & Vomiting	7 (28%)	4 (16%)	0.504
Pruritus	2 (8%)	0 (0%)	0.490

Figure 12: Hour-wise incidence of nausea and vomiting.

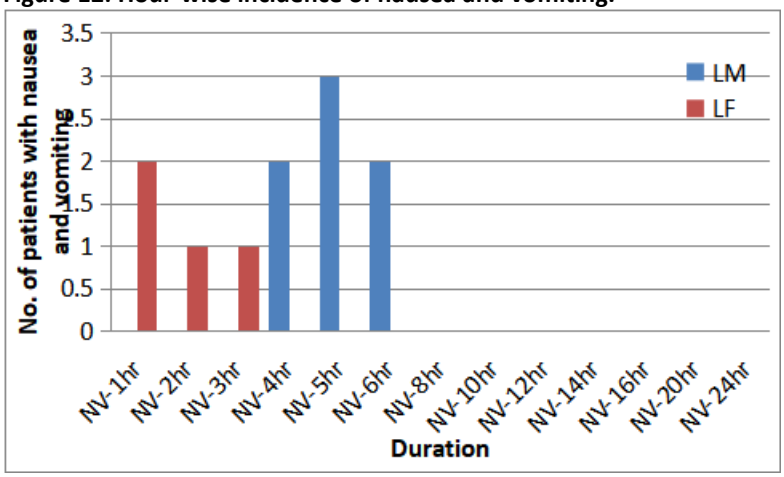
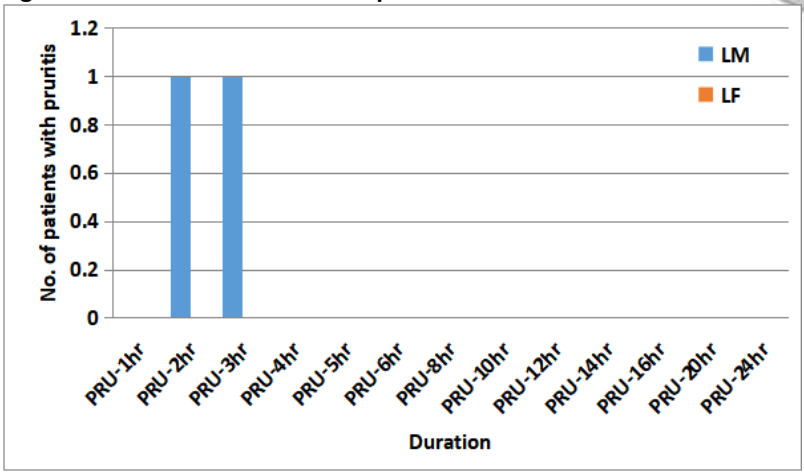


Figure 13: Hour-wise incidence of pruritus.



Nausea/vomiting occurred in 28% (LM) vs 16% (LF) and pruritus in 8% (LM) vs 0% (LF); no statistically significant difference in adverse effects was observed between the groups ($p>0.05$).

Postoperative Pain Score and Rescue Analgesia

Table 4: Postoperative Pain Score and Rescue Analgesia

Time	LM Pain	LF Pain	P (Pain)	LM Rescue (n)	LF Rescue (n)	P (Rescue)
1st Hour	0.00 ± 0.00	0.20 ± 0.58	0.0811	0	0	—
2nd Hour	0.00 ± 0.00	1.20 ± 1.58	<0.001	0	2	0.2347
3rd Hour	0.00 ± 0.00	2.32 ± 1.75	<0.001	0	7	0.02
4th Hour	0.80 ± 0.96	2.84 ± 1.18	<0.001	0	9	0.002
5th Hour	1.36 ± 1.60	3.32 ± 1.11	<0.001	5	15	0.009
6th Hour	1.52 ± 1.64	3.48 ± 0.96	<0.001	5	15	0.004
8th Hour	1.80 ± 0.96	3.32 ± 1.18	<0.001	2	10	0.018
10th Hour	2.12 ± 1.09	3.44 ± 1.00	<0.001	3	11	0.0083
12th Hour	1.84 ±	3.44 ±	<0.001	2	11	0.008

Time	LM Pain	LF Pain	P (Pain)	LM Rescue (n)	LF Rescue (n)	P (Rescue)
	0.90	1.39				
14th Hour	2.28 ± 1.02	3.68 ± 1.38	<0.001	3	13	0.0054
16th Hour	2.88 ± 1.33	3.84 ± 1.25	0.0148	7	16	0.045
20th Hour	2.68 ± 1.11	4.52 ± 1.12	<0.001	8	17	0.023
24th Hour	2.40 ± 1.12	4.72 ± 0.89	<0.001	4	23	<0.001

Figure 14: Postoperative VAS pain score trend over 24 hours.

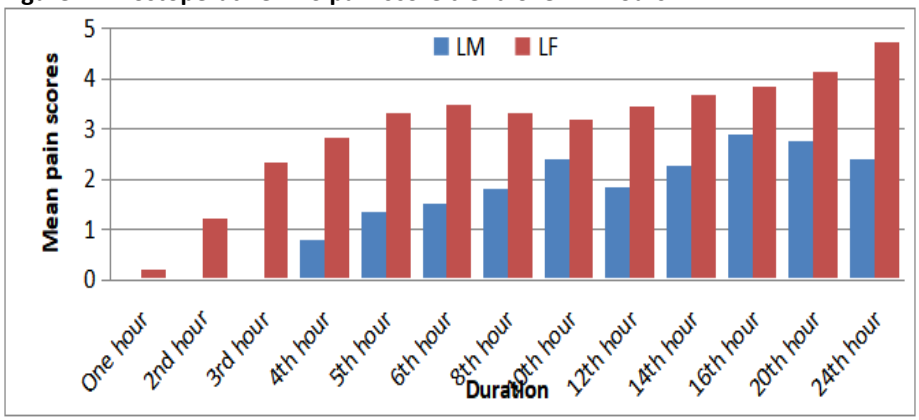


Table 5: Rescue Analgesia Summary

Parameter	LM (Mean ± SD)	LF (Mean ± SD)	P-value
Time to 1st Rescue Analgesia (h)	5.56 ± 0.71	3.88 ± 0.88	<0.001
Total Rescue Doses in First 24 h	1.52 ± 1.05	5.64 ± 1.41	<0.001

Figure 15: Mean time to first rescue analgesia.

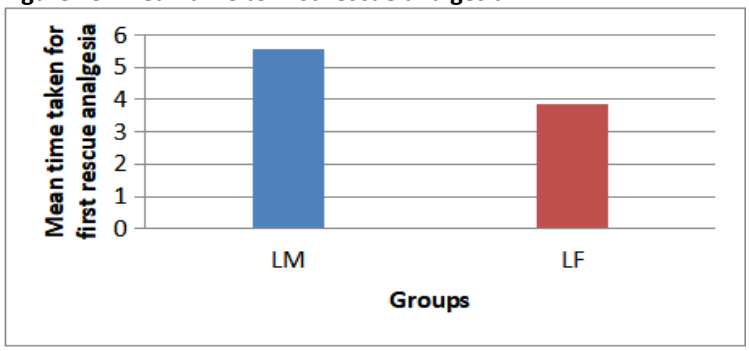
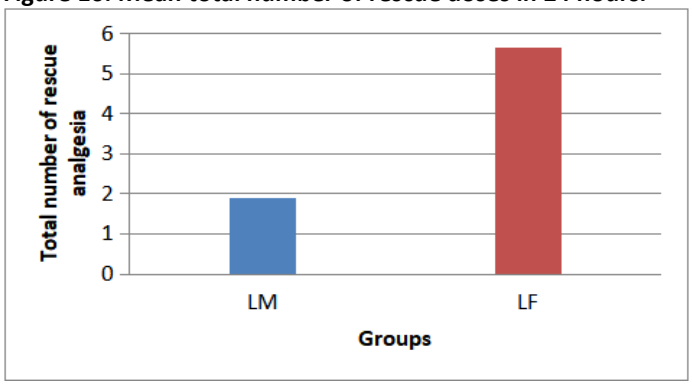


Figure 16: Mean total number of rescue doses in 24 hours.



Postoperative pain was assessed at predefined intervals over 24 hours, with mean ± SD compared between groups.
Pain scores were significantly lower in Group LM than Group LF from the 2nd to 24th hour (p value<0.05).
No patient required rescue analgesia during the 1st postoperative hour, indicating adequate initial analgesia in both groups.
Significant differences in rescue analgesic requirements were observed at multiple time points throughout 24 hours.

Postoperative Vital Parameters

Figure 17: Postoperative SBP trend.

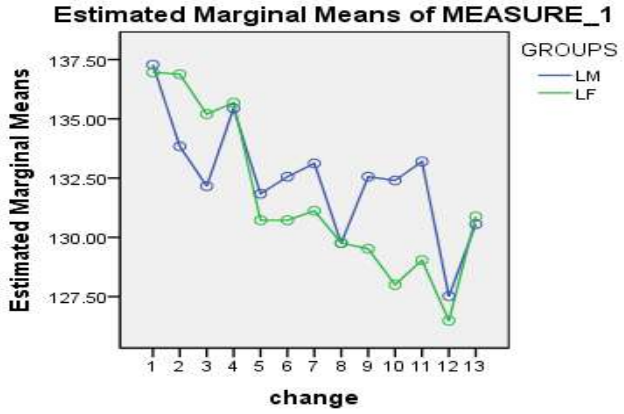


Figure 18: Postoperative DBP trend.

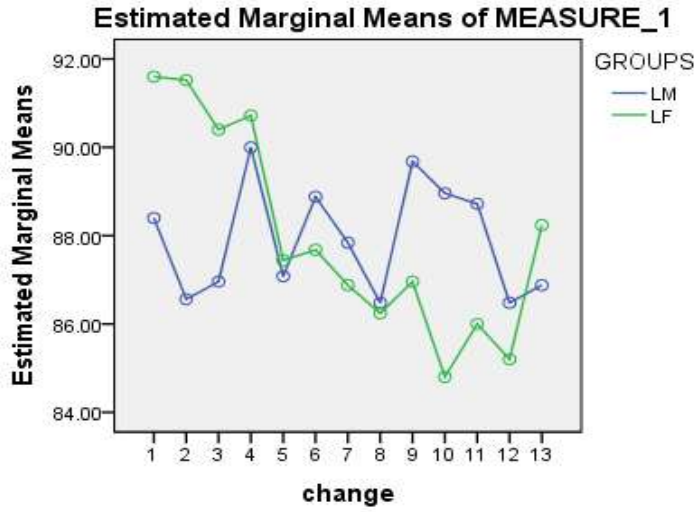


Figure 19: Postoperative MAP trend.

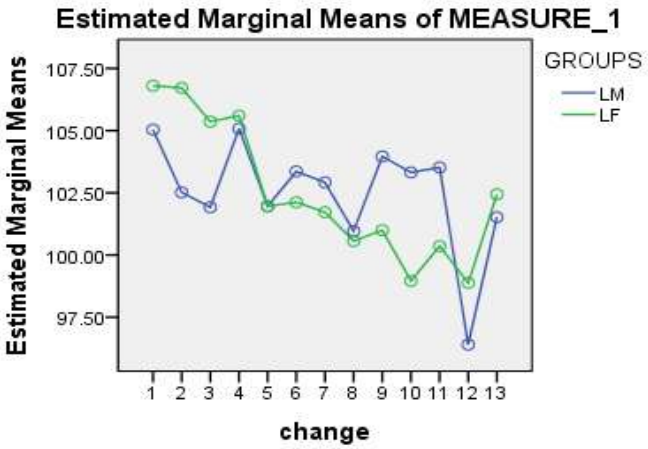


Figure 20: Postoperative heart rate trend.

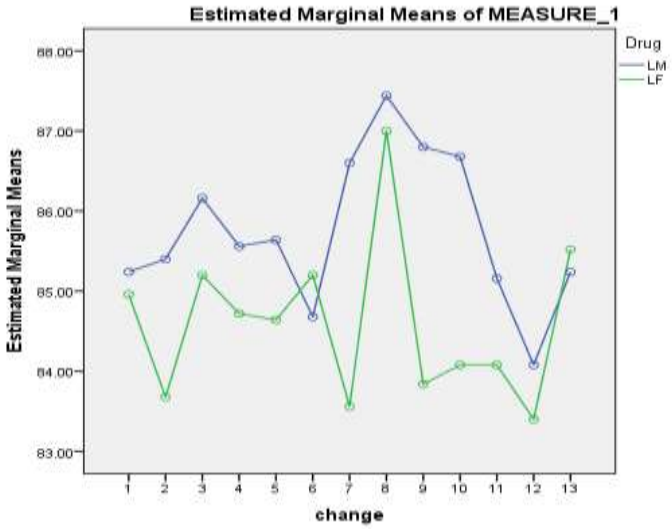
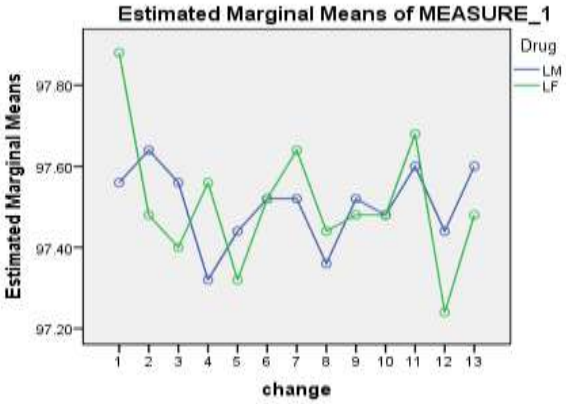


Figure 21: Postoperative SpO2 trend.



Postoperative HR, SBP, DBP, MAP, and SpO_2 were assessed at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 24 h. SBP showed no statistically significant between-group differences at any assessed time point, with p values ranging from 0.092 to 1.000. DBP similarly showed no statistically significant differences, with p values ranging from 0.089 to 0.922. MAP values did not differ significantly between the groups, with p values ranging from 0.082 to 1.000. HR showed no statistically significant between-group differences throughout the 24-h postoperative period, with p values ranging from

0.055 to 0.846. SpO_2 also showed no statistically significant differences between the groups, with p values ranging from 0.122 to 1.000. Thus, none of the postoperative vital parameters demonstrated a statistically significant between-group difference during the 24-h observation period.

Discussion

Spinal anaesthesia is widely used for TKR, and hyperbaric levobupivacaine is increasingly used in place of bupivacaine owing to its lower cardiovascular and CNS toxicity. Intrathecal opioid adjuvants prolong analgesia and are a cornerstone of multimodal analgesia, reducing systemic opioid requirements and related side effects. Rathmell et al. [7] found that 0.2–0.3 mg intrathecal morphine gave more effective analgesia than 0.1 mg after hip/knee arthroplasty. Similarly, intrathecal morphine (0.4 mg) has been shown to produce a long duration of analgesia, [8] and intrathecal morphine (4 µg/kg) has been reported to significantly reduce postoperative analgesic requirement in the first 48 hours after radical prostatectomy. [9] Karaman et al. [10] reported that 0.1 mg intrathecal morphine gave longer analgesia than 25 µg fentanyl after total hip replacement — consistent with our finding of significantly lower VAS scores and delayed rescue analgesia with morphine.

Our results align with Kılıçkaya et al. [11], who reported that intrathecal morphine gives superior, longer-lasting analgesia than fentanyl in TKR when combined with hyperbaric bupivacaine — attributed to morphine's hydrophilicity prolonging spinal bioavailability, versus fentanyl's lipophilic, shorter action. Time to first rescue analgesia was significantly longer with morphine (5.56 ± 0.71 h vs 3.88 ± 0.88 h; $p<0.001$), and total rescue doses over 24 hours were fewer (1.52 ± 1.05 vs 5.64 ± 1.41; $p<0.001$).

Regarding side effects, Agrawal et al. [12] reported that adding fentanyl to bupivacaine reduces the incidence of nausea, vomiting and shivering, whereas Shim et al. [13] found greater postoperative nausea and vomiting with 0.2 mg intrathecal morphine; in our study (0.1 mg dose) nausea/vomiting was numerically higher in the morphine group but not statistically significant. Pruritus was seen in 2 morphine patients and none in the fentanyl group, again without statistical significance — consistent with Rathmell et al.'s [7] observation that pruritus becomes dose-dependent above 0.2 mg, and with Yang et al., [14] who found that intrathecal morphine (0.15 mg) with ropivacaine significantly increased pruritus (35.9% vs 2.6% in controls; $p<0.001$). Consistent with Gehling and Tryba's [15] finding that doses below 0.3 mg maintain a safety profile similar to placebo, no respiratory depression was observed in our cohort. Our findings also parallel Gulec et al. [16], who found that 0.1 mg intrathecal morphine gave more prolonged analgesia and delayed rescue requirement than 25 µg fentanyl in inguinal hernia repair.

Summary

This study evaluated 50 patients undergoing elective total knee replacement to compare intrathecal morphine (Group LM) versus intrathecal fentanyl (Group LF) as adjuvants to 0.5% hyperbaric levobupivacaine. Both groups were well matched for age, BMI and ASA grade, and maintained stable heart rate, blood pressure and SpO2 throughout the perioperative period, with no significant haemodynamic differences between adjuvants.

Postoperative analgesia was the most distinct difference between groups: Group LF had a faster onset of block, but Group LM provided superior, more prolonged postoperative analgesia. By 24 hours, rescue analgesia had been administered to 4 patients (16%) in the intrathecal morphine group and 23 patients (92%) in the intrathecal fentanyl group, with a statistically significant difference between the groups ($p<0.001$). While intrathecal fentanyl facilitates a faster surgical block, intrathecal morphine is significantly more effective for long-term postoperative pain management after total knee replacement.

Conclusion

Intrathecal morphine and fentanyl produced similar baseline characteristics, haemodynamic stability and adverse-effect profiles. Intrathecal fentanyl gave faster onset of sensory/motor block, but intrathecal morphine provided significantly superior and more prolonged postoperative analgesia — longer time to first rescue analgesia, lower VAS scores, and fewer rescue doses, particularly in the later postoperative period. Intrathecal morphine (100 µg) therefore appears to be a more suitable adjuvant to 0.5% hyperbaric levobupivacaine for TKR when sustained postoperative analgesia is the primary clinical goal.

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