Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Comparison of Analgesic Effect of Fentanyl and Fentanyl with Midazolam as an Adjuvant to Intrathecal Bupivacaine in Lower Limb Surgeries

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Abstract

Introduction: Coadministration of drugs with synergistic effects considered one of the methods to increase the effectiveness of analgesia. The aim of this study is to evaluate the efficacy of midazolam to potentiate the analgesic effect of fentanyl as an adjuvant to bupivacaine.

Materials and Methods: This is a hospital based prospective, randomized, double-blind interventional control study conducted at SMS medical college and hospitals, Jaipur. A total of 90 patients were enrolled in the study. They were allocated into three groups, 30 in each. A total of 3.7 ml study drugs injected in each group. Intraoperative monitoring of hemodynamic parameters, duration of surgery, onset of sensory and motor block, duration of analgesia, sensory and motor block, and incidence of adverse effects was done and compared.

Results: There was no significant difference in mean pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure ($P > 0.05$). The mean duration of surgery in Group A, B, and C was 101.3 ± 13.08, 92.93 ± 15.28, and 95.93 ± 16.03 min, respectively ($P > 0.05$). The mean onset time of sensory block in Group A was 7.29 ± 1.23, in B 4.92 ± 0.60, and in C 4.79 ± 0.91 min ($P < 0.05$). The mean onset time of motor block in Group A was 8.75 ± 0.55, in B 7.79 ± 0.42, and in C 7.57 ± 0.29 min. In Group A, mean time of sensory block was 194.4 ± 6.80, in B 236.60 ± 12.79, and in C 254.30 ± 7.32 min. In Group A, mean duration of motor block was 180.2 ± 5.22, in B 188.7 ± 4.04 and in C 199.6±6.69 min. In Group A, mean duration of analgesia was 215.7 ± 14.6, in B 445.8 ± 18.92, and in C 522.3 ± 16.33 min. The incidence of adverse effects was insignificant.

Conclusion: We conclude that midazolam potentiates the effect of fentanyl in terms of prolonged duration of analgesia and prolonged motor and sensory block when used as an adjuvant of bupivacaine without any significant hemodynamic compromise.

Key words: Adjuvant, Analgesia, Fentanyl, Intrathecal, Midazolam, Prolonged

INTRODUCTION

Perioperative pain management is a topic of concern as postsurgical pain is the most common complication of any surgery. A national survey conducted in the United States depicted, acute post-operative pain continues to be undermanaged with up to 60% of patients experiencing moderate to severe pain at hospital discharge.[1]

Access this article online

www.ijss-sn.com

Month of Submission : 06-2020
Month of Peer Review : 06-2020
Month of Acceptance : 07-2020
Month of Publishing : 07-2020

Optimal perioperative pain management facilitates early post-operative ambulation, rehabilitation, and is considered a prerequisite to enhance recovery. The central neuraxial blockade is one of the most commonly used regional anesthesia for lower limb surgeries.

Anesthesiologists are at the heart of perioperative analgesic management, both as prescribers and administrators. During surgery, pain relief is their main aim.

Intrathecal administration of drugs in combination results in prolonged and better analgesic effect as compare to individual drug administration. In combination drug usage, doses of drugs also reduce which gives another advantage in avoiding their dose-related adverse effects.[2]

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0.5% hyperbaric bupivacaine is the most commonly used drug for spinal anesthesia; however, the most important disadvantage of the single injection is its limited duration.[3]

Opioids like fentanyl are the most common adjuvant drugs for prolongation of intraoperative and post-operative analgesia.[4,5] Midazolam produces a synergistic effect when administered with bupivacaine. Literatures have shown that administration of intrathecal midazolam with local anesthetics prolongs the duration of anesthesia and analgesia.[6-8]

This study was conducted to evaluate the efficacy of intrathecal midazolam to potentiate the analgesic effect of fentanyl as an adjuvant to bupivacaine in lower limb surgeries.

MATERIALS AND METHODS

After approval from the ethics and research review board of our institute, 90 eligible cases were randomly allocated into three groups using a computerized random number table. Thirty patients enrolled in each group.

1. Group A: Hyperbaric Bupivacaine + Normal Saline
2. Group B: Hyperbaric Bupivacaine + Fentanyl + Normal Saline
3. Group C: Hyperbaric Bupivacaine + Fentanyl + Midazolam.

A total of 3.7 ml drug injected in each group. Drugs were prepared and given by anesthetist other than the anesthetist who observed study variables. Thus, neither the patient nor the anesthetist (observer) was known to the drug used, that is, double-blinding was applied.

Inclusion Criteria

The following criteria were included in the study:

- Patients aged 20–65 years
- Weight – 40–60 kg
- ASA Grade I-II.
- Undergoing lower limb surgeries of duration <120 min.

Exclusion Criteria

The following criteria were excluded from the study:

- Not willing to give consent
- Any deformity or local sepsis in spinal lumbar region
- Severe hypovolemia increased intracranial pressure
- Any bleeding or coagulation abnormalities
- Hb <10 g%
- Pre-existing neurological, cardiovascular, metabolic, hepatic, respiratory, or renal disease
- Hypersensitivity to any of the study drugs
- Severe AS or MS
- In whom spinal anesthesia failed, the desired level of highest sensory block (T5-T6) not achieved and general anesthesia was required.

All patients underwent thorough pre-anesthetic check-up, including history, general physical and systemic examination, vital parameters, and ASA grading.

After written and informed consent, patients were allocated to one of the three groups. Pre-operative baseline readings of NIBP, PR, and saturation were noted. After securing an IV access, all patients irrespective of the group were preloaded with Ringer lactate 15 ml/kg over 10 min. Under all aseptic precautions, spinal anesthesia was performed at the L_3–L_4 interspace, with the patient in sitting position using a 25G Quincke spinal needle. Group A received intrathecal 0.5% hyperbaric bupivacaine 3.0 ml+0.7 ml 0.9% normal saline, Group B 0.5% hyperbaric bupivacaine 3.0 ml+0.5 ml fentanyl 25 μg+0.2 ml of 0.9% normal saline, and Group C 0.5% hyperbaric bupivacaine 3.0 ml+0.5 ml fentanyl 25 μg+0.2 ml midazolam 1 mg. The patient was placed in a supine position immediately after spinal injection. An indwelling urinary catheter was inserted. Intraoperative fluid management was done according to hemodynamic parameters. Vitals were recorded at 5 mins interval for the first 30 mins from the time of injection of the spinal solution and then after every 10 mins for the complete period of surgery.

Intraoperative monitoring of hemodynamic parameters, duration of surgery, onset of sensory and motor block, duration of analgesia, sensory and motor block, and incidence of adverse effects was done and compared.

The level of sensory block was assessed every 2 min after intrathecal injection of the drug by using 20G hypodermic needle (pinprick method) on midclavicular line on both sides until the level had stabilized for four consecutive tests. The onset of sensory block was defined as the time from the intrathecal injection of the drug to the time taken to achieve anesthesia to pinprick at T10 dermatomal level. The duration of sensory block was between the onset of sensory block to two-segment regression time.

The onset of motor block was defined as the time taken for the motor block to reach modified Bromage 3. The degree of motor block was assessed every 2 min until the highest modified Bromage score is achieved. The duration of motor block was the time between onset time and offset time.

The duration of analgesia was the time from the intrathecal injection to the first request of analgesia at VAS 3 was noted.

Post-operative Evaluation

Immediately after operation patients were shifted to recovery room.

1. Vitals – PR, NIBP, and saturation were recorded at a regular interval of 30 min for 8 h
2. Two segment regression time – Time of regression of sensory block by two segments from the highest level attained
3. Duration of analgesia – Analgesia duration was observed and recorded following pain scoring system – visual analog score (VAS). VAS consisted of a 10 cm horizontal paper strip with two endpoints labeled "No Pain" and "Worst pain ever." When patient complaints of pain in ward or recovery room, the patient was asked to mark the strip at a point that corresponds to the level of pain intensity, the patient presently felt. VAS score was serially assessed at half an hour interval starting from 60 min until the patient complains of pain (VAS >3).

The duration of effective analgesia was measured as time from the intrathecal drug administration to the patient's VAS score = 3 either in the recovery room or ward and was recorded in minutes. The patient's VAS = 3 and administration of rescue analgesia constituted the endpoint of the study. Intramuscular diclofenac was given as a rescue analgesic. The patient was kept under observation for a period of 24 h for routine post-operative monitoring.

Statistical analysis of the data was done with software – (Statistical Package for the Social Science) version 20.0.0 (SPSS Inc., Chicago, Illinois, USA). For a significant difference in the proportion of cases, a Chi-square test was applied. For significance, *P*-value was calculated. The continuous variables were analyzed by applying a one-way ANOVA test and *post hoc* test Tukey for intergroup comparison.

RESULTS

A total of 90 cases were enrolled in the study and divided into three groups. There was no drop-out.

Demographic Data

The mean age in Group A, B, and C was 43.13 ± 7.80 years, 44.23 ± 4.22 years, and 41.40 ± 5.28 years, respectively. Mean weight in Group A, B, and C was 61.33 ± 7.26 kg, 62.20 ± 6.72 kg, and 63.80 ± 7.37 kg, respectively. Mean height in Group A, B, and C was 163.70 ± 7.77 cm, 163.53 ± 7.52 cm, and 163.23 ± 7.90 cm, respectively. Among 90 patients, 67 were female and 23 were male.

Physical status of the patient was judged using ASA grading. Group A had 24 patients of ASA Grade I (80%) and 6 patients of Grade II (12.5%). Group B had 27 patients of ASA Grade I (90%) and 3 of Grade II (30%). Group C had 25 of ASA Grade I (83.33%) and 5 of Grade II (16.67%).

Hemodynamic Parameters

We observed pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at various time intervals. There was no statistically significant difference at different time intervals ($P > 0.05$). We also noted the intraoperative mean arterial pressure (MAP) which was statistically non-significant.

Duration of Surgery

The mean duration of surgery in Group A, B, and C was 101.3 ± 13.08 min, 92.93 ± 15.28 min, and 95.93 ± 16.03 min, respectively. There was no statistically significant difference ($P > 0.05$).

Onset of Sensory Block

The mean onset time of sensory block in Group A was 7.29 ± 1.23 min, in B 4.92 ± 0.60, and in C 4.79 ± 0.91 min. The difference was statistically significant ($P < 0.05$) [Figure 1].

The mean onset of sensory block was higher in Group A as compared to Group B and C. *Post hoc* Tukey test revealed that the mean onset of sensory block was statistically not significant between Group B and C ($P > 0.05$).

Onset of Motor Block

Mean onset time of motor block in Group A was 8.75 ± 0.55 min, in B 7.79 ± 0.42, and in C 7.57 ± 0.29 min. The mean onset of motor block was higher in Group A as compared to Group B and C [Figure 2]. This difference showed statistical significance ($P = 0.000$). *Post hoc* Tukey test revealed that mean onset of motor block was statistically non-significant between Group B and C.

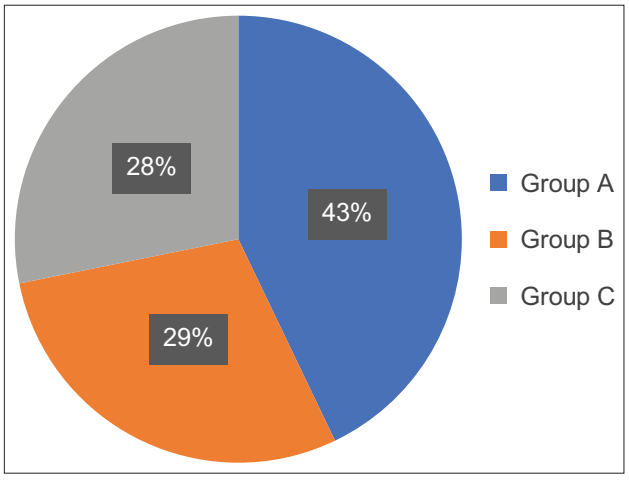

Figure 1: Comparison of onset of sensory block among study groups

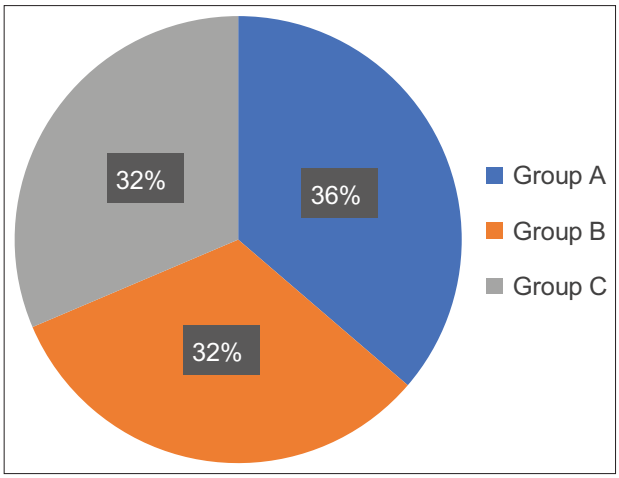

Figure 2: Comparison of onset of motor block among study groups

Duration of Sensory Block

In Group A, mean duration of sensory block by two-segment regression was 194.4 ± 6.80 min, in B 236.60 ± 12.79, and in C 254.30 ± 7.32 min. It was more in Group C as compared to Group A and B. Statistically significant difference was noted ($P = 0.000$). *Post hoc* Turkey test revealed that there was a statistically significant difference among the groups.

Duration of Motor Block

In Group A, mean duration of motor block was 180.2 ± 5.22 min, in B 188.7 ± 4.04, and in C 199.6 ± 6.69 min. There was a significant difference among the groups ($P < 0.05$). The mean duration of motor block was higher in Group C as compared to A and B. *Post hoc* Tukey test compared the *P*-value between the groups showed a statistically significant difference among all groups.

Duration of Analgesia

In Group A, mean duration of analgesia was 215.7 ± 14.6 min, in B 445.8 ± 18.92, and in C 522.3 ± 16.33 min. There was a statistically significant difference between Group A and B (P = 0.000), Group A and C (P = 0.000), and Group B and C (P = 0.000). This difference was statistically significant ($P < 0.001$). Group C had the longest duration of analgesia as compared to Group A and B.

Incidence of Side Effects

We observed various side effects intraoperatively and in the early post-operative period such as hypotension, bradycardia, nausea, and vomiting in all three groups. The incidence of hypotension was 20%, 13.33%, and 26.67% in Group A, B, and C, respectively. The incidence of bradycardia was 6.67%, 0%, and 10.0% in Group A, B, and C, respectively. The incidence of nausea and vomiting was 13.33%, 13.33%, and 13.33% in Group A, B, and C, respectively. There were no associated complications in 60.00%, 80.00%, and 50.00% cases of Group A, B, and C, respectively. We revealed that there was no statistical significance in their incidence.

Table 1 is showing a comparison of various study factors mentioned above among Group A, B, and C along with their P-values to describe their statistical significance.

DISCUSSION

The chore of medicine is to preserve and restore patient's health and to minimize their suffering. To achieve these goals, intellection about pain is a must because pain is universally understood as a distressing feeling, especially in post-operative period.

Spinal anesthesia is the most commonly used technique for lower limb surgeries. However, post-operative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action, and thus early rescue analgesic is needed in the post-operative period. However, a combination of drugs with synergistic effects can enhance the anticipated impacts, and the patient may suffer from fewer side effects due to insignificant concentrations of each drug.

Intrathecal adjuvants are added to improve the quality of neuraxial blockade and prolong the duration of analgesia. Used intrathecally, fentanyl improves the quality of spinal blockade as compared to plain bupivacaine and confers a longer duration of post-operative analgesia. Intrathecal midazolam as an adjuvant can be used to improve post-operative analgesia.

Demographic Data

Regarding the age of patients, our study concurs with the study of Gupta *et al.*[9] where the mean age of patients was 40 ± 2.5, 39.1 ± 10.2, and 42.9 ± 12.6 years which is comparable with Group A, B, and C of our study, respectively. The mean weight of patients in the present study was comparable with the study of Gupta *et al.*[9] where it was 46.8 ± 8.7, 50.9 ± 8.0, and 58.7 ± 10.6 kg respective to our study groups.

Similarly, the mean height of the population of Group A, B, and C of our study was comparable with the study of Gupta *et al.*[9] where it was 161.1 ± 1.5, 161.0 ± 1.4, and 162.2 ± 1.1 cm respective with our study groups. To the best of our knowledge, no study described ASA physical status of the study population.

Hemodynamic Parameters

Our results concur with the study of Gupta *et al.*,[9] who observed that changes in PR, SBP, and DBP between

Table 1: *P*-value of comparison of various study factors among groups

Factors compared among groups	*P*-value		
	Group A versus B	Group A versus C	Group B versus C
Onset of sensory block	0.000	0.000	0.506
Onset of motor block	0.000	0.000	0.526
Duration of sensory block	0.000	0.000	0.000
Duration of motor block	0.000	0.000	0.000
Duration of analgesia	0.000	0.000	0.000

the groups and within the groups were not statistically significant with $P = 0.735$, $P = 0.148$, and 0.171, respectively. Shah *et al.*[10] observed no significant decrease in MAP when midazolam was used as an adjuvant with bupivacaine.

Onset of Sensory Block

Gupta *et al.*[9] observed that there was a statistically significant difference in time of onset of the sensory block between Groups B (bupivacaine) and BF (bupivacaine plus fentanyl) ($P = 0.000$) as well as between Groups B and BFM (bupivacaine + fentanyl + midazolam) ($P = 0.000$). There was no clinically or statistically significant difference in the time for onset of the sensory block between Groups BF and BFM ($P = 0.054$). Usmani *et al.*[11] observed a significant difference in time of onset of the sensory block when fentanyl was combined with bupivacaine. When midazolam was added to the bupivacaine, Agrawal *et al.*[12] observed no significant difference in onset of sensory blockade time.

Onset of Motor Block

Gupta *et al.*[9] concluded that there was a statistically significant difference in time of onset of the motor block between Groups B and BF ($P = 0.000$) as well as between Groups B and BFM ($P = 0.000$). There was no clinically or statistically significant difference in the time for onset of the motor block between Groups BF and BFM ($P = 0.054$). Usmani *et al.*[11] observed a significant difference in time of onset of motor block when fentanyl was combined with bupivacaine. When midazolam was added to the bupivacaine, Agrawal *et al.*[12] observed no significant difference in onset of motor blockade.

Duration of Surgery

A study almost similar to the present study done by Gupta *et al.*[9] and they observed duration of surgery was 128.8 ± 39.7, 125.6 ± 38.3, and 124.2 ± 35.8 min in their groups respective to our study groups.

Duration of Sensory Block

Gupta *et al.*[9] quoted that there was a statistically significant difference in duration of the sensory block between Groups B and BF, Groups B and BFM, and Groups BF and BFM. Bharti *et al.*[13] observed that the duration of sensory blockade was prolonged when midazolam is added to bupivacaine. Khanna and Singh[14] observed a significant increase in the duration of the sensory block with fentanyl when added to bupivacaine. Similarly, Tucker *et al.*[15] observed prolongation of the duration of the sensory block when midazolam added to fentanyl in labor analgesia.

However, some studies do not favor it. Roussel and Heindel[16] did not observe significant prolongation of the sensory block when fentanyl was added to bupivacaine. Bhattacharya *et al.*[17] also observed no significant prolongation of the sensory block when midazolam added to bupivacaine.

Duration of Motor Block

Our results concur with the study of Gupta *et al.*[9] where there was a statistically significant difference in duration of the motor block between Groups B and BF, Groups B and BFM, and Groups BF and BFM. Bharti *et al.*[13] observed that the duration of motor blockade was prolonged when midazolam is added to bupivacaine. Grewal *et al.*[18] also observed significant prolongation of the motor block by adding fentanyl to bupivacaine. Some study results are against to it. Roussel and Heindel[16] did not observe significant prolongation of the motor block when fentanyl added to bupivacaine.

Mean Duration of Analgesia

Gupta *et al.*[9] observed that mean duration of analgesia in Group B was 211.60 ± 16.12 min, in Group BF 420.80 ± 32.39 min, and in Group BFM 470.68 ± 37.51 min. There was a statistically significant difference in duration of analgesia between Groups B and BF ($P = 0.000$), between Groups B and BFM ($P = 0.000$), and between Groups BF and BFM ($P = 0.000$). Our study results favor these observations.

Various studies have observed the prolongation of analgesia with the addition of midazolam or fentanyl. Tucker *et al.*[15] observed prolongation of the duration of analgesia in labor when a combination of intrathecal midazolam and fentanyl was used for labor analgesia. Shah *et al.*[10] also observed prolongation of the duration of analgesia with the addition of 2 mg intrathecal midazolam to 15 mg bupivacaine and 0.15 mg buprenorphine. Most of the studies done so far have used intrathecal bupivacaine combined with either fentanyl[14,19,20] or midazolam.[6,12,21,22] All have shown a significant increase in the duration of analgesia.

Incidence of Side Effects

In a study conducted by Gupta *et al.*,[9] the incidence of side effects was 28% in Group BFM and 28% in Group BF, whereas it was 12% in Group B. The incidence of

bradycardia was maximum in Group BF while that of hypotension was same in Groups BF and BFM. In all three groups, the incidence of side effects was not found to be significant.

Martyr and Clark[23] found the incidence of hypotension as a common complication when intrathecal fentanyl was added to bupivacaine in elderly patients, but the incidence and severity of hypotension were not significant. Grewal *et al.*[18] and Ben-David *et al.*[20] found an increased incidence of hypotension by adding fentanyl to bupivacaine. Bhattacharya *et al.*[17] did not found any significant change in blood pressure when intrathecal midazolam was added to bupivacaine.

Rudra and Rudra[24] observed that when the two groups, one with a combination of intrathecal bupivacaine (0.5%) 10 mg with fentanyl 12.5 mcg and other with bupivacaine (0.5%) 10 mg and midazolam 2 mg were compared, the incidence of nausea and vomiting was found to be less in the group with a combination of bupivacaine with fentanyl than the group with bupivacaine and midazolam.

Shah *et al.*[10] also observed that when bupivacaine + buprenorphine was compared with intrathecal bupivacaine + buprenorphine + midazolam, incidences of nausea, vomiting, and bradycardia were the same in both the groups. These results were not found to be significant.

CONCLUSION

The present study concludes that midazolam potentiates the effect of fentanyl in terms of prolonged duration of analgesia and prolonged motor and sensory block when used as an adjuvant of bupivacaine without any significant hemodynamic compromise in lower limb surgeries.

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How to cite this article: Kuldeep S, Singh M, Chauhan S, Sharma S. Comparison of Analgesic Effect of Fentanyl and Fentanyl with Midazolam as an Adjuvant to Intrathecal Bupivacaine in Lower Limb Surgeries. Int J Sci Stud 2020;8(4):72-77.

Source of Support: Nil, **Conflicts of Interest:** None declared.