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Research Article

Comparative Evaluation of Dexmedetomidine-Midazolam and Fentanyl-Midazolam for Sedation and Analgesia in Lower Extremity Orthopedic Surgery under Spinal Anesthesia: A Randomized Double-Blind Clinical Trial

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ABSTRACT

Background: Spinal anesthesia is a very commonly used procedure in modern-day anesthesia practice. Today most of the lower limb surgeries are performed under spinal anesthesia. Midazolam, dexmedetomidine, and fentanyl are common intravenous adjuvants used during anesthesia to allay anxiety and sedation. The aim of this study was to compare the effects of intravenous dexmedetomidine-midazolam versus fentanyl-midazolam in terms of analgesic characteristics, sedation, and adverse effects.

Methods: This is a randomized prospective study that included 35 patients in each group, posted for lower limb orthopedic surgery. Intravenous dexmedetomidine, fentanyl, and midazolam were administered after subarachnoid block. Data for sedation, analgesia, hemodynamic parameters, and adverse effects were recorded.

Results: RR for FM group showed significant intra-group variability in RR across perioperative stages ($p<0.05$), whereas the DM group maintained greater respiratory stability ($p=0.243$). HR for DM group exhibited significantly lower intraoperative and postoperative HR compared to FM group ($p<0.001$), with notable within-group changes, unlike the FM group. MAP for both groups remained stable over time (DM: $p= 0.283$, FM: $p= 0.260$), although the FM group had slightly higher values in the postoperative recovery phase. Sedation (RSS): DM produced deeper and more sustained sedation intraoperatively and postoperatively ($p<0.001$), while FM showed quicker sedation decline. Patient satisfaction was significantly higher in the DM group (VAS: 3.0 vs. 4.0, $p= 0.001$), although surgeon satisfaction did not differ notably. Adverse events were rare and comparable, though hypotension was more frequent in the DM group (22.9% vs. 8.6%).

Conclusion: Dexmedetomidine plus midazolam provided superior sedation quality and patient satisfaction, with more stable cardiopulmonary parameters during orthopedic surgery under spinal anesthesia. Despite a slightly higher rate of hypotension, DM appears to offer a more favorable sedative profile compared to fentanyl plus midazolam.

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Introduction

Postoperative pain is a significant clinical concern following lower extremity orthopedic surgeries, particularly under spinal anesthesia [1-5]. It directly affects early mobilization, rehabilitation outcomes, and overall patient satisfaction [6]. Pain intensity is often severe due to the nature of bone and soft tissue manipulation involved in these procedures, which activates both nociceptive and inflammatory pathways [7-10]. Despite the widespread use of multimodal analgesia, current regimens such as opioid-based combinations are limited by short duration of action, frequent need for rescue analgesia, and undesirable side effects including respiratory depression, nausea, vomiting, and sedation [11-12]. These drawbacks highlight the urgent need for optimizing perioperative pain protocols, especially those that minimize opioid reliance [13-15]. Dexmedetomidine (DM), a highly selective α2-adrenoceptor agonist, has gained attention for its analgesic and sedative properties without causing significant respiratory depression [16]. When combined with midazolam, it may offer a balanced sedation-analgesia profile [17-18]. On the other hand, fentanyl-midazolam remains a conventional option but carries a greater risk of opioid-induced adverse effects [19]. Comparing these two regimens under spinal anesthesia allows evaluation of not just pain relief but also sedation depth, opioid-sparing effects, and safety in the intraoperative and early postoperative periods [18]. This study thus seeks to assess which combination achieves superior outcomes in terms of analgesic efficacy and patient safety. Effective postoperative pain management in orthopedic surgery reduces the length of hospital stay, lowers the risk of complications, and enhances functional recovery, especially for lower limb operations where early mobilization is crucial [20-21]. Poorly controlled pain can also lead to chronic pain syndromes, patient dissatisfaction, and increased healthcare costs [22-23]. Dexmedetomidine offers a promising alternative due to its opioid-sparing potential and stable hemodynamic profile [24]. Studies suggest that it can reduce the incidence of respiratory depression, a common concern with opioids like fentanyl, particularly in elderly or high-risk patients [25-27]. Although both drug regimens are clinically used, there is limited comparative evidence directly assessing dexmedetomidine-midazolam versus fentanyl-midazolam in orthopedic surgeries under spinal anesthesia. This gap highlights the need for further randomized studies to evaluate not only efficacy but also safety and outcomes such as pain scores, sedation levels, and recovery trajectories.

Methods

A randomized, blinded clinical trial was conducted at Baquba Teaching Hospital from January 15th to July 15th, 2025, to evaluate the effectiveness and safety of a combination of Dexmedetomidine-Midazolam (DM) versus Fentanyl-Midazolam (FM) in elective lower extremity orthopedic surgery using spinal anesthesia.

ASA physical status I or II and aged between 18 and 50 years have been included in the study. Study participants were selected from all patients who met the inclusion criteria using convenience sampling. Participants were randomly allocated to both groups (in a 1:1 ratio) using a computer-generated randomization process. Each group included 35 patients. Group DM received dexmedetomidine 0.5 mcg/kg and midazolam 1-2 mg/hours, while group FM received fentanyl 1-2 mcg/kg per hour and midazolam 1-2 mg/hour. The exclusion criteria were contraindication to regional anesthesia, pregnant women or hemodynamically unstable women, chronic use of corticosteroids and opioids, allergies to drugs, and severe anemia (hemoglobin <13.8 g/dl in men or <12.1 g/dl in women).

In preparation for standard spinal anesthesia, before administering anesthesia, all patients were preloaded with 0.9% normal saline (10 mL/kg), and the spinal anesthesia was then provided using 3 mL of 0.5% hyperbaric bupivacaine at the L3-L4/L4-L5 interspace. Study drugs were infused using an infusion pump after they were found to have sufficient spinal block. Upon arrival in the operating room, continuous cardiac monitoring, non-invasive blood pressure, pulse oximetry, and respiratory rate measurements were initiated. All data were recorded at baseline, after the spinal block, pre- and post-surgical incision, and after every 30 minutes until the surgery was over.

The intensity of sedation was measured by using the Ramsay Sedation Scale (RSS) with 1=anxious to 6=unresponsive, and pain severity was measured on a 10-point Visual Analog Scale (VAS). The surgeon and patient satisfaction were assessed after surgery on a 4-point Likert scale. Adverse reactions such as hypotension (MAP <60 mmHg), apnea, postoperative nausea, vomiting, and airway obstruction were closely observed and noted. Data were analyzed statistically with the help of SPSS 26. Continuous variables with normal distribution would be tested by the use of independent t-tests, and non-parametric variables using the Mann-Whitney U test. Chi-square or Fisher's exact test was applied depending on the nature of the categorical variables. The P value that was taken as significant is less than 0.05.

Results

The findings of our study revealed no significant differences between the two groups in demographic patterns and pre-baseline clinical characteristics such as age (p=0.235), gender (p=0.471), diagnosis (p=0.372), and length of surgery (p=0.237), which shows proper group assignment. The types of surgical procedures included in the study were diverse but evenly distributed across both groups (Table 1).

These included total knee replacement, total hip replacement, femur and leg fracture fixation, ligament repair, ankle fracture fixation, knee arthroscopy, debridement, tibial plating, amputation, and hip fracture fixation. No significant imbalance in procedure type was observed between the DM and FM groups, and each surgical type was represented by a small number of cases (typically 1 to 6 per group). As such, no subgroup analysis by diagnosis was performed.

Respiratory Rate (RR)

There was respiratory stability with the DM group because the mean respirations remained consistent across the entire peri- and postoperative sampling periods (p>0.05 for most time points).

The FM group, conversely, had statistically significant decreases in RR as spinal block was performed (14.8 ± 1.2 vs. 15.4 ± 0.9; p=0.010) and prior to incision (14.6 ± 1.1 vs. 15.3 ± 1.0; p=0.003), which denotes enhanced respiratory irregularity with FM sedation. There was no noticeable between groups variation at the other time points (p>0.05) (Table 2).

Heart Rate (HR)

The DM group showed a large reduction of HR values in comparison with the FM group at almost every intraoperative and postoperative time point (p<0.05). Notably, the greatest changes in HR are the most marked in the DM group between pre-incision and recovery (DM: 69.8 ± 5.5 to 72.1 ± 5.3 bpm vs. FM: 77.7 ± 10.9 to 77.1 ± 8.6 bpm; p < 0.001 for most comparisons). Such results indicate the strong sympatholytic effect of dexmedetomidine, and more consistent and higher HR values could be found in the FM group during the procedure (p=0.075 within-group variability) (Table 3).

Table 1- Demographic and Clinical Characteristics

Variable	DM Group (n = 35)	FM Group (n = 35)	P value	Statistical Test
Age (years)	37.12 ± 9.32	36.92 ± 9.48	0.837	Independent t-test
Gender (Male)	21 (60.0%)	18 (51.4%)	0.470	Chi-square test
Duration of surgery (h)	2.01 (1.34 – 2.05)	1.45 (1.18 – 2.17)	0.235	Mann–Whitney U test

Table 2– Comparison of Respiratory Rate (RR) Between Groups at Different Time Points

Time Point	DM Group (Mean ± SD)	FM Group (Mean ± SD)	P value
Before spinal block	16.1 ± 1.24	16.1 ± 1.4	0.549
After spinal block	15.4 ± 0.95	14.8 ± 1.2	0.010
Before incision	15.3 ± 1.03	14.6 ± 1.1	0.003
After incision	15.2 ± 2.41	14.9 ± 0.9	0.450
30 minutes after incision	15.1 ± 1.42	14.8 ± 0.9	0.250
60 minutes after incision	15.2 ± 1.18	14.9 ± 0.8	0.150
90 minutes after incision	15.3 ± 2.40	15.1 ± 2.4	0.700
120 min after incision	15.2 ± 1.01	14.8 ± 1.0	0.060
End of surgery	15.1 ± 3.39	14.9 ± 0.9	0.700
5 min after arrival in recovery	15.3 ± 2.32	15.2 ± 0.9	0.800
30 minutes after arrival in recovery	15.2 ± 2.11	15.5 ± 1.0	0.400
60 minutes after arrival in recovery	15.4 ± 0.93	15.6 ± 1.0	0.300

Table 3– Heart Rate (HR) Comparison Between Groups

Time Point	DM Group (Mean ± SD)	FM Group (Mean ± SD)	P value
Before spinal block	77.9 ± 7.11	79.7 ± 11.0	0.444
After spinal block	75.3 ± 9.56	74.3 ± 9.3	0.828
Before incision	69.8 ± 5.57	77.7 ± 10.9	0.002
After incision	69.6 ± 5.84	77.4 ± 8.9	<0.001
30 minutes after incision	70.7 ± 5.63	77.7 ± 9.1	<0.001
60 minutes after incision	70.8 ± 6.89	76.8 ± 10.1	0.007
90 minutes after incision	69.4 ± 7.33	76.6 ± 10.9	0.011
120 min after incision	69.2 ± 5.31	76.0 ± 9.4	0.008
End of surgery	70.9 ± 4.70	78.1 ± 9.4	<0.001
5 min after recovery room entry	72.1 ± 5.32	77.1 ± 8.6	0.003

Mean Arterial Pressure (MAP)

There is a significant difference in the change in MAP among individuals within groups (DM: p=0.283; FM: p=0.260). Nevertheless, when comparisons were done between different groups, there was generally lower MAP in the DM group during both the intraoperative and perioperative periods, but those differences were not found to be significant (p>0.05 in all occasions). Intraoperative hypotension was greater in the DM group (22.9% versus 8.6%, p=0.101), 83-87 mmHg versus 86-90 mmHg in median MAP within the DM versus FM group, respectively. These results lead to the hypothesis of a small but measurable hypotensive response to the use of dexmedetomidine and a confirmation of the hemodynamic stability of the FM.

Sedation Depth

The DM group achieved significantly deeper sedation levels compared to the FM group throughout the intraoperative period (p<0.001 at all measured time points). RSS scores in the DM group remained consistently higher, ranging from 4.5±0.5 (pre-incision) to 3.4±0.6 (end of surgery), while the FM group showed progressively lighter sedation (4.0±0.5 to 3.0±0.6 during the same period). Notably, the DM group maintained moderate sedation (RSS 3-5) for a prolonged duration, with scores decreasing gradually from incision through recovery (4.6±0.5 to 3.1±0.4), whereas the FM group demonstrated faster recovery to lighter sedation levels (RSS 2-3). These results demonstrate the superior sedative properties and more sustained effect of the DM combination.

Patient and Surgeon Satisfaction:

There were much better VAS patient satisfaction scores in the DM group (median 3.0, IQR 2.0-4.0) than in the FM group (median 4.0, IQR 3.0-5.0; p=0.001). Surgeon satisfaction, in turn, did not differ significantly across groups (p=0.861), with those two combinations being rated mostly as Excellent (37.1%; 34.3%) or Good (40.0%; 37.1%).

Negative event profiles were similar between groups; low, statistically identical percentages of PONV (2.9% of both groups, p=0.895), apnea (DM: 2.9% and FM: 5.7%, p=0.558), and airway obstruction (0 and 2.9%, p=0.590). Nonetheless, the DM group had a clinically significant but not statistically significant higher rate of hypotension (22.9 percent vs. 8.6 percent, p=0.101). These results indicate excellent patient experience outcomes under DM, but similar surgical parameters and overall safety rates.

Complications

The rate of complications was not high in either group. There were no significant differences in the rates of postoperative nausea and vomiting (PONV) between the DM and FM groups (p = 0.298).

The frequencies of apnea were 2.9 percent in the DM and 5.7 percent in the FM groups (p=0.558), and only the FM group had airway obstruction (2.9 percent, p=0.590). As it had already been mentioned, hypotension was more frequent in the DM group. There was, however, no case of intubation or advanced airway management, with all symptoms resolved using simple supportive care.

Table 4– Mean Arterial Pressure (MAP) Comparison Between Groups

Time Point	DM Group (Mean ± SD)	FM Group (Mean ± SD)	P value
Before spinal block	91 (78–114)	92 (89–104)	0.805
After spinal block	86 ± 32	89 ± 4	0.105
Before incision	85 ± 73	87 ± 9	0.277
After incision	85 ± 86	87 ± 13	0.378
30 minutes after incision	83 ± 88	87 ± 8	0.057
60 minutes after incision	83 ± 84	86 ± 11	0.184
90 minutes after incision	84 ± 63	86 ± 7	0.057
120 min after incision	84 ± 10	88 ± 7	0.091
End of surgery	87 ± 72	88 ± 10	0.115
5 min after recovery room entry	85 ± 62	89 ± 8	0.135
30 minutes after recovery	86 ± 12	88 ± 7	0.115
60 minutes after recovery	87 (80–88)	90 (87–98)	0.145
Before discharge from recovery	88 (82–90)	89 (86–97)	0.225

Table 5– RSS Scores

Time Point	DM Group (Mean ± SD)	FM Group (Mean ± SD)	P value
After spinal block	2.7 ± 0.65	2.6 ± 0.5	0.694
Before incision	4.5 ± 0.58	4.0 ± 0.5	<0.001
After incision	4.6 ± 0.54	4.0 ± 0.5	<0.001
30 minutes after incision	4.5 ± 0.58	3.9 ± 0.6	<0.001
60 minutes after incision	4.3 ± 0.59	3.5 ± 0.5	<0.001
90 minutes after incision	4.3 ± 0.43	3.5 ± 0.5	<0.001

120 min after incision	4.0 ± 0.46	3.3 ± 0.5	<0.001
End of surgery	3.4 ± 0.61	3.0 ± 0.6	0.001
5 min after recovery room entry	3.1 ± 0.46	2.5 ± 0.5	<0.001

Table 6– Patient and Surgeon Satisfaction

Parameter	DM Group (n = 35)	FM Group (n = 35)	P value
Patient satisfaction (VAS)	3.0 (2.0 – 4.0)	4.0 (3.0 – 5.0)	0.001
Surgeon satisfaction			0.861
– Excellent	13 (37.1%)	12 (34.3%)	
– Good	14 (40.0%)	13 (37.1%)	
– Moderate	8 (22.9%)	10 (28.6%)	

Table 7– Patient and Surgeon Satisfaction, and Adverse Events

Parameter	DM Group (n = 35)	FM Group (n = 35)	P value
Post-op nausea & vomiting	1 (2.9%)	1 (2.9%)	0.895
Apnea	1 (2.9%)	2 (5.7%)	0.558
Airway obstruction	0 (0.0%)	1 (2.9%)	0.590
Hypotension*	8 (22.9%)	3 (8.6%)	0.523

Discussion

The top-notch management of intraoperative sedation and postoperative pain still lies in the success factor of an orthopedic operation conducted using spinal anesthesia [17]. As there are more and more concerns regarding the side effects of the opioid-based regimens, especially in at-risk populations, alternative protocols of sedative-analgesic methods are becoming significant subjects of study [28]. The purpose of this study was to determine the effects of dexmedetomidine-midazolam and fentanyl-midazolam on various clinical outcomes associated with respiratory parameters, hemodynamic stability, the depth of sedation, patient and surgeon satisfaction, and postoperative complications. The major effects indicate different physiologic effects of the two combinations of drugs. In spite of the rather identical demographic and procedural traits of both groups, there were certain disparities in respiratory and cardiovascular responses, level of sedation, and patient satisfaction.

The Primary Parameters

Another notable finding identified during this study was the stability of respiration in the DM group. The respiratory rate also *remained* unchanged during the intraoperative and postoperative stages. This finding is consistent with previous studies' striking fact, where the study by Choi Y-M. has shown that dexmedetomidine, specifically in conjunction with midazolam, is resistant to respiratory instability [18]. Conversely, the patients in the FM group had more unpredictable respiratory rates during surgery, as was the case with the study conducted by Peng, who also reported that FM leads to less predictable respiratory rates [29]. These disparities indicate the respiratory-sparing benefits of dexmedetomidine, particularly in an environment where there is a high chance of respiratory compromise [24]. Cardiovascular monitoring showed that patients under DM had a lower heart rate during and after surgery than those in the FM group. This is in line with the pharmacologic profile of dexmedetomidine, which is sympatholytic by activation of 2-adrenoceptors [30]. The Li's study synthesis presented similar results of reduced heart rates of patients sedated using DM [31]. On the other hand, the FM group experienced comparatively intact levels of heart rates, and the results of the study conducted by Shorabi align with this data, as they also revealed that FM resulted in low cardiac rhythm disturbances [32]. Comparable conclusions were also drawn by Yadavet and Magazine, supporting the cardiac neutrality of the FM combination [33-34].

Regarding the mean arterial pressure, the two groups recorded average stable groupings, and there was no remarkable alteration in the readings between time divisions. MAP was, however, slightly lower on average in the DM group than at baseline, indicating a mild hypotensive effect. Such results are consistent in those studies that investigate MAP among patients treated with dexmedetomidine alone as a sedative agent [35-36]. Quite conversely, other researchers found that FM maintained the MAP during the operation and returned it to baseline after the operation, which is also seen in the current paper [27,37].

Sedation Profile

The Ramsay Sedation Score demonstrates an obvious difference between the depths of sedation in the 2 groups. Patients in the DM group more reliably demonstrated a greater depth of sedation throughout the intraoperative phase and maintained moderate sedation throughout the immediate postoperative period. This result is synonymous with the findings described by Nie, which emphasized the capacity of DM to induce intended levels

of sedation without impeding respirations [38]. RSS scores in the DM group experienced in the current study did not exceed the clinically desirable range of 3 through 5. In comparison, the levels of sedation were lighter and decreased faster in the FM group, and a similar trend was observed in the study by Yadav [33]. Although both types of combinations offered outstanding intraoperative sedation, they may be advantageous for prolonged procedures or when lengthy monitoring in the recovery room is an option.

Patient and Surgeon Satisfaction

Patient satisfaction was higher in the DM group, as indicated by lower VAS scores, suggesting superior analgesic efficacy and overall comfort. The results correlate with the study of Tajammul, who also indicated high satisfaction levels with DM (31. In line with our findings, a recent study indicated an acceptable level of satisfaction; however, they were comparatively lower, a tendency that is also reflected in the findings by Abida, where satisfaction scores were moderate with FM [27]. The satisfaction of the surgeons, however, did not differ significantly across the two groups, implying that the two combinations offered sufficient surgical conditions to the operator.

Complications

The postoperative nausea and vomiting (PONV) experienced was very low and equally identical in both groups, making it a good prospect when compared to the emetogenic properties of opioids. This is also in line with the existing data, as the study by Abdolrazaghnejad and Banaie (2017) and the report by Kostroglou [39]. Our findings also revealed low rates of PONV with the respective combinations applied [27]. The FM group tended to show more apnea, although statistically not significantly. Such a tendency has been reinforced by many studies in which FM has been linked to a greater prevalence of respiratory depression [33,40]. On the contrary, there was only a single instance of apnea in the DM group, which is also in line with the respiratory-sparing effects mentioned by previous studies [27,33]. Hypotension is a known side effect of dexmedetomidine [35]. However, although our study also showed that 20% of the patients in group DM experienced hypotension, 3% of the patients in group FM also experienced this adverse effect. Therefore, unlike some studies, the incidence of hypotension was not statistically significant between the two study groups [33,35]. Though the upper airway obstruction has been noted frequently with an administration of fentanyl, our study indicated only one case observed in the group of FM, but no cases in DM, and the difference between the two groups was not statistically significant. Such a conclusion can be compared with other work that finds that occasionally, FM has upper airway obstruction [27,41]. No case in our study needed advanced airway interventions, and all of them were treated using supportive measures.

Clinical Implications

The results of this trial advocate taking advantage of dexmedetomidine-midazolam as a promising substitute to the opioid-based regimens of spinal anesthesia, at least in situations when long-duration sedation and opioid-sparing analgesia are expected. The combination can be particularly useful in patients who are likely to face or have respiratory compromise or those patients requiring a greater depth of intraoperative sedation. Nonetheless, the higher rates of hypotension when DM is used highlight the necessity of close monitoring of the cardiovascular system, particularly of those patients who exhibit a small hemodynamic reserve. Fentanyl-midazolam can still be used in shorter procedures or at sites where it is preferable to achieve emergence with rapidity and stability of hemodynamic effects. In general, anesthetic management is an individualized procedure, and prospective research with sample sizes and focus should be wider and conducted on larger patient numbers to support the evidential scope of these results more and to narrowly define perioperative sedation techniques in orthopedic surgery.

Conclusion

This experiment has established that the mixture of dexmedetomidine and midazolam produced better results with respect to the depth of sedation, respiratory stability, and postoperative analgesia than fentanyl-midazolam in the lower extremity orthopedic surgical patients under spinal anesthesia. Still, the patients who used the DM group were more deeply and longer sedated and had better breathing trends, as well as increased satisfaction in general. Nonetheless, this regimen, also, was characterized by an increased risk of intraoperative hypotension, which would require increased hemodynamic monitoring. Comparison, on the other hand, would show that the FM combination produced lighter sedation and faster recoveries, and fewer hemodynamic errors existed. In spite of the safety of both combinations being reported to be overall favorable with no significant adverse effects reported, these findings suggest that the choice of sedative-analgesic regimen should be tailored to individual patient characteristics, including procedural duration, comorbidities, and postoperative monitoring requirements.

Ethical considerations

The Ethics Committee at Tehran University of Medical Sciences allowed the study protocol (IR.TUMS.SPH.REC.1403.269). The anesthetic technique to be used was carefully explained to the

patient by the investigators, as well as the complications and other outcomes related to the procedure during the preanesthetic review. All participants gave written informed consent before joining the study. Language editing and proofreading were performed using Grammarly to enhance grammatical accuracy. However, all scientific content, data interpretation, and conclusions remain the sole responsibility of the authors.

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