The Egyptian Journal of Hospital Medicine (April 2025) Vol. 99, Page 1771-1777

Comparative study between Epidural Bupivacaine added to Dexmedetomidine versus Bupivacaine with Fentanyl for Postoperative Pain Relief in Lower Limb Orthopedic Surgery: Randomised Controlled Trial

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ABSTRACT

Background: Epidural anesthesia is the best standard for pain relief during and after surgery for lower abdominal and limb procedures. Historically, fentanyl has been used as a supplement for epidural administration, meaning it has been given alongside a smaller quantity of local anaesthetic (LA) to obtain the same level of anaesthesia. When administered via the epidural route, dexmedetomidine, a new member of the alpha-2 agonist class, has several positive effects.

Objectives: This study aimed to evaluate and compare the effectiveness of epidural fentanyl and dexmedetomidine as supplementary agents to epidural bupivacaine in terms of block quality, duration of action, duration of postoperative analgesia, as well as intra-operative and postoperative problems.

Patients and methods: Sixty cases were enrolled in the study with a mean age of 32.58 ± 8.13 years, and were categorised according to their physical status by the American Society of Anesthesiologists (ASA). Patients in classes I and II were divided into two groups of equal size (n=30). Subjects in group I received a spinal injection of 1 g/kg dexmedetomidine and 15 ml of a 0.5% bupivacaine solution. Group II participants were administered a 15 ml solution containing 0.5% bupivacaine along with an epidural injection of fentanyl at a dosage of one μg/kg.

Results: After 5 minutes, group I had a significant increase in mean heart rate (HR) compared to group II. The average start of sensory and motor block, and the duration required to reach the highest level T10, were all significantly decreased in group I compared to group II. After 2 minutes, group I had a much higher mean score on the Bromage scale than group II had. When comparing groups, I and II, group I had much longer postoperative pain relief from their initial rescue analgesic dose.

Conclusion: Based on the findings of our study, it was determined that dexmedetomidine exhibited superior qualities as an epidural adjuvant compared to fentanyl. Specifically, dexmedetomidine demonstrated enhanced hemodynamic stability, prompt onset of action, establishment of sensory anaesthesia, prolonged postoperative analgesia, and reduced consumption of postoperative LA for epidural analgesia (EA).

Keywords: Pain, Epidural space, Epidural anaesthesia, Bupivacaine, Dexmedetomidine, Fentanyl.

INTRODUCTION

Regional anaesthesia is a cost-effective and secure method that offers the benefit of extended pain management after surgery, effectively reducing autonomic, somatic, and endocrine reactions [(1)]. Epidural anaesthesia offers a viable alternative to general anaesthesia, potentially mitigating the occurrence of venous thrombosis, pulmonary embolism, and cardiac problems in patients at high risk. Additionally, it may contribute to a decrease in bleeding, transfusion needs, pneumonia, and respiratory depression [(2)].

Epidural anaesthesia is frequently employed in orthopaedic procedures due to its ease of administration, rapid onset, and favourable anticipated results. Additionally, it facilitates the mitigation of the potential hazards associated with the administration of general anaesthesia [(3)].

Numerous additives have been demonstrated to improve the efficacy of spinal anesthesia, including opioids, which include morphine, fentanyl, nalbuphine, and sufentanil, as well as other medicines like epinephrine, clonidine, neostigmine, adenosine, midazolam, and magnesium sulphate [(4)].

Fentanyl functions as an agonist at μ-opioid receptors, hence augmenting analgesic effects. It possesses a potency that is 100-fold more than that of morphine. The main therapeutic effects of this substance are pain relief and sedation [(5, 6)].

Dexmedetomidine is an adjuvant. The utilisation of alpha 2 agonists in the intensive care unit involves their administration as short-term sedatives and analgesics. These agents are capable of inducing sedation without concurrently inducing respiratory depression. The compound in question is a stereoisomer of medetomidine. The elimination half-life of the substance is two hours (hrs) [(5)].

The potential cause for the extended duration of the motor effect could be attributed to the direct hindrance of excitatory amino acid release from spinal interneurons. The sedative action is elicited through the activation of alpha 2 adrenergic receptors. The alpha 2 adreno receptors do not exert a significant influence on the respiratory system, hence resulting in negligible impact on respiratory function [(5, 7)].

The aim of this research was to assess the effects of adding epidural fentanyl or dexmedetomidine to epidural bupivacaine, and to compare those effects to those of just using epidural bupivacaine alone in terms of block efficacy, duration of action, duration of post-operative analgesia, and intra- and post-operative adverse events.

Received: 18/11/2024
Accepted: 17/01/2025

PATIENTS AND METHODS

Sixty patients between the ages of 20 and 70 with ASA physical status classes I and II were enrolled in this study at Sohag University Hospital. They were divided into 2 equal groups (n=30).

Group D: The subject was administered 15 ml solution containing 0.5% bupivacaine and 1 μg/kg dose of dexmedetomidine through epidural route.

Group F: Received an epidural injection of 1 g/kg fentanyl and 15 ml of 0.5% bupivacaine.

Inclusion criteria: Patients who fall under ASA physical status classes I and II. Making the necessary preparations for elective surgery involving the lower leg in the field of orthopaedics. Patients within the age range of 20 to 70 years.

Exclusion criteria: Patient refuse to participate. Patients with severe, untreated cases of cardiac diseases, impairment of renal or hepatic function, chronic pulmonary diseases, and diabetics. Neuromuscular disorders. Infection at site of technique. Bleeding disorder. Prior surgical experience with any of the study medicines that resulted in an allergic reaction.

Methods: Prior to undergoing surgery, patients underwent a preanesthetic check and had all necessary investigations conducted. The patients were provided with written consent forms and were duly informed before participating in the study. The individuals were instructed to observe a period of fasting, abstaining from solid food for duration of 8 hrs and limiting intake to clear liquids for 2 hrs before to the surgical procedure.

Upon entering the operating theatre, non-invasive monitoring including a pulse oximeter, non-invasive blood pressure (BP) (NIBP) monitor, and electrocardiogram (ECG) were affixed to the patient, and initial measurements of vital signs were documented. The medical team established intravenous (IV) access and initiated the administration of IV fluid. After taking strict aseptic procedures, an 18G Tuohy's needle was inserted into the epidural space between the L2 and L3 vertebrae while the subjects were seated. The loss of resistance method was used to confirm the presence of the epidural space. The next step involved inserting and securing an epidural catheter 3–4 centimetres into the epidural space. Then, 3 millilitres (0.2% lidocaine) were given as a test dose. Patients were randomly divided into two groups of similar size:

- Group D was administered a 15 ml solution containing 0.5% bupivacaine and 1 μg/kg of dexmedetomidine by spinal injection.
- In this study, group F was administered a 15 ml solution containing 0.5% bupivacaine along with an epidural injection of 1 μg/kg of fentanyl.

Observation:

1) **Hemodynamics:** After the first 15 minutes, vital signs like pulse, BP, oxygen saturation, and breathing rate were recorded every 15 min for the next hour. After that, readings were obtained every 30 minutes for the next 3 hrs, then every hour for the next 3 hrs, and so on, until the end of the 6th hour.
2) The initiation of sensory blockage was evaluated using the pin prick technique.
3) The time at which the sensory level at T10 began was recorded.
4) The duration required to attain a modified Bromage scale grade-III was measured as the time to commencement of complete motor blockage.
5) The duration of motor block refers to the time needed to transition from a modified Bromage scale grade III to grade zero.
6) Pain levels were evaluated on an hourly basis use the visual analogue scale (VAS), with a range of zero representing the absence of pain and ten indicating the most severe pain.
7) The duration of efficient analgesia was documented.
8) Complications including attacks of intraoperative hypotension, bradycardia, desaturation and vomiting.

Ethical approval:

This study has been approved by the Sohag Faculty of Medicine's Ethics Committee. Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

SPSS version 25.0 was used for the statistical analysis. The Shapiro-Wilks normality test was employed to evaluate the distribution of quantitative data in order to determine the appropriate form of statistical testing, whether it is parametric or nonparametric. The parametric variables, such as age, were represented by their mean and SD. These variables were subjected to analysis of variance (ANOVA) using the F test, comparing three groups. Post hoc testing was conducted using the least significant difference (LSD) method. Non-parametric variables, such as the Visual Analogue Scale (VAS), were represented by their median and interquartile range (IQR). The statistical analysis involved the application of the Kruskal-Wallis test to compare these variables among three groups. Additionally, the Mann-Whitney test was employed to conduct pairwise comparisons between each group. Categorical data, such as sex, were represented as frequencies and percentages and were analyzed using the Chi-square test. A p-value of ≤ 0.05 was deemed to be statistically significant.

RESULTS

Table (1) showed that there was no discernible difference in age or sex between the two research groups.

Table (1): Demographic data of both study group (n=60)

Demographic data	**Study group** (n=60)
Age (years)	32.58 ± 8.13 (18-70)
Males Females	34 (56.7%) 26 (43.3%)

After five minutes, the average heart rate (HR) in group (D) was higher compared to group (F) by a significant margin (P 0.014). Table (2) showed that after 1.5 hrs, two hrs, 2.5 hrs, three hrs, four hrs, five hrs, and six hrs, the average HR in group (D) was significantly decreased compared to group (F) (p values of 0.019, 0.001, and 0.0001 respectively).

Table (2): Comparing between two groups based on HR by ANOVA test

Heart rate (HR)	**Group D(n=30)**		**Group F(n=30)**		**P.value**
	Mean	**SD**	**Mean**	**SD**	
Baseline	101.72	11.91	98.21	7.23	0.067
5 min	100.53	9.81	95.40	5.28	0.014*
10 min	96.50	6.57	93.90	4.41	0.077
15 min	95.40	7.69	93.10	4.24	0.157
30 min	91.87	7.61	92.70	4.23	0.603
45 min	91.40	6.95	92.70	3.71	0.370
60 min	91.63	8.39	93.70	3.75	0.223
1.5 hour	92.20	8.42	96.43	4.66	0.019*
2 hour	93.93	11.78	103.20	10.38	0.002*
2.5 hour	91.93	9.08	103.53	5.11	< 0.001*
3 hour	89.77	7.42	112.97	8.21	< 0.001*
4 hour	89.73	7.29	101.40	8.42	< 0.001*
5 hour	91.73	5.76	97.67	2.39	< 0.001*
6 hour	100.83	7.83	114.07	6.48	< 0.001*

***** P <0.05 is considered significant * P < 0.001 is considered highly significant

After 15 minutes, the mean blood pressure (MBP) in group (D) had decreased significantly compared to group (F) (P 0.

018) in terms of blood pressure. In contrast, the average blood pressure in group (D) increased significantly when compared to group (F) at 60 min, 1.5 hrs, 2 hrs, 3 hrs, 4 hrs, 5 hrs, and 6 hrs, with p-values of 0.014, 0.028, and 0.03 respectively (Table 3).

Table (3): Comparing mean blood pressure (MBP) between two groups by ANOVA test

Blood pressure	**Group D**		**Group F**		**P.value**
	Mean	**SD**	**Mean**	**SD**	
Baseline	78.70	7.45	76.37	6.21	0.240
5 min	75.60	5.40	74.20	2.99	0.220
10 min	73.27	4.20	74.23	3.01	0.310
15 min	73.57	3.47	75.37	2.10	0.018*
30 min	73.03	3.65	73.93	1.87	0.235
45 min	73.77	4.69	72.40	3.10	0.189
60 min	74.37	6.35	71.33	4.70	0.040*
1.5 hour	74.63	7.96	70	6.02	0.014*
2 hour	72.83	8.14	67.93	8.41	0.026*
3 hour	73.70	4.34	71.23	4.12	0.028*
4 hour	74.43	4.29	73.97	1.58	0.579
5 hour	74.03	4.59	73.47	1.19	0.516
6 hour	74.70	4.09	72.90	1.72	0.030*

***** P < 0.05 is considered significant

When comparing groups D and F, after 2 hrs there was a significant decrease in the mean VAS score in group D (P 0.001). In contrast, after 3 and 4 hrs, the average VAS score in group (D) increased significantly compared to group (F) (P 0.001) (Table 4).

Table (4): Comparing VAS Score 6 hrs postoperative between two groups by ANOVA test

VAS score 6 hour postoperative	Group D(n=30)		Group F(n=30)		P.value
	Mean	SD	Mean	SD	
1hour	0.00	0.00	0.00	0.00	---
2 hour	0.00	0.00	2.43	0.50	< 0.001*
3 hour	0.63	0.55	3.83	0.37	< 0.001*
4 hour	1.77	0.67	0.67	1.51	0.001*
5 hour	2.77	0.62	2.67	0.75	0.580
6 hour	3.97	0.18	3.83	0.37	0.088

***** P < 0.05 is considered significant

When comparing groups (D) and (F) on the basis of additional anaesthetic criteria, table (5) displayed a significant (P 0.001) decrease in the average start of sensory and motor block and the time taken to achieve the highest level T10 in group (D).

Table (5): Comparing of onset of sensory block, motor block and time to reach highest level between two groups by ANOVA test

Anesthetic criteria	Group D (n=30)		Group F (n=30)		P. value
	Mean	SD	Mean	SD	
Onset of sensory block (min)	1.02	0.09	1.22	0.25	< 0.001*
Onset of motor block (min)	2.02	0.09	2.22	0.25	< 0.001*
Time to reach highest level T10 (min)	3.15	0.35	4.13	0.22	< 0.001*

* P < 0.05 is considered significant

Mean post-operative hrs until the first dose of rescue analgesia was administered were significantly longer in group (D) than in group (F) (P 0.001) (Table 6).

Table (6): Comparing postoperative first dose rescue analgesia between two groups by ANOVA test

1st dose rescue of analgesia in hrs	Group D(n=30)		Group F(n=30)		P. value
	Mean	SD	Mean	SD	
1st dose analgesia	6.20	0.42	3.17	0.37	< 0.001*

***** P < 0.05is considered significant

As can be shown in table (7), there was insignificant difference in the prevalence of adverse events between groups D and F. The p-values for this comparison ranged from 0.136 to 0.137, and from 0.137 to 0.139.

Table (7): Side effects in both studied groups

		Group D (n = 30)	Group F (n = 30)	P value
Side effects Hypotention	Yes	5 (16.7%)	10 (33.3%)	0.136
	No	25 (83.3%)	20 (66.7%)	
Itching	Yes	3	5	0.137
	No	27	25	
Vomiting	Yes	2	6	0.139
	No	28	24	

DISCUSSION

Epidural anaesthesia is widely employed as the primary method for producing surgical anaesthesia and providing postoperative pain control in lower abdomen and limb procedures. The management of pain following surgery is considered a critical aspect within the field of anaesthesia [8].

The optimal characteristic sought in contemporary orthopaedic surgery is the early initiation of postoperative mobilisation and rehabilitation, while minimising pain and discomfort. In order to attain this desired outcome, significant quantities of local anaesthetics were employed, hence augmenting the potential risks associated with local anaesthetic toxicity and hemodynamic instability [9].

Fentanyl is a potent mu opioid agonist, hence augmenting analgesic effects. Notably, it exhibits a potency that is one hundred times more than that of morphine. Dexmedetomidine is a pharmacologically powerful and specifically targeted agonist of the α-2-adrenoceptor. The observed ratio of α-2/α-1 activity is relatively high (1620:1) [10].

The enhanced selectivity of dexmedetomidine towards the α-2 receptor results in its heightened efficacy as a sedative, anxiolytic, analgesic, antihypertensive, and sympatholytic agent, while minimising the undesired cardiovascular effects associated with α-1 receptor activation. The implementation of this intervention enhances the overall standard of perioperative anaesthesia and analgesia [11].

We aimed to assess the effects of adding epidural fentanyl or dexmedetomidine to epidural bupivacaine, and to compare those effects to those of bupivacaine alone in terms of block efficacy, duration of action, duration of postoperative analgesia, and intra- and postoperative adverse events.

Sixty adult patients, ranging in age from 20 to 70 years old and classed as ASA classes I and II, were divided into two groups (n=30). Epidural injections of 1 g/kg dexmedetomidine were given to individuals in group D, and they were also given 15 ml of a 0.5% bupivacaine solution. Participants in group F received an epidural injection of 1 g/kg fentanyl and 15 ml of a 0.5% bupivacaine solution.

In terms of hemodynamics, there was a significant increase in the mean HR observed in group D after a 5-minute interval, compared to group F. Additionally, there was a statistically significant reduction in the mean HR observed in group D after 1.5 hrs, two hrs, 2.5 hrs, three hrs, four hrs, five hrs, and six hrs, compared to group F. In contrast, a statistically significant reduction in the average BP was observed in group D after duration of 15 minutes, as compared to group F. In contrast, a statistically significant increase in the average BP was observed in group D at 60 minutes, 1.5 hrs, two hrs, three hrs, four hrs, five hrs, and six hrs, compared to group F. In agreement with our results, **Soliman and Eltaweel** [12] the dexmedetomidine group exhibited a substantial reduction in HR.

Also, **Prakash *et al.*** [13] employed the aforementioned method. The utilisation of a reduced concentration of bupivacaine has been employed for the purpose of delivering analgesia during the perioperative period. The purpose of this study was to conduct a comparison between the administration of low concentration bupivacaine (0.25%) as a standalone treatment and its combination with fentanyl (17μg/kg) or dexmedetomidine (1μg/kg) in the context of epidural anesthesia for cases undergoing percutaneous nephrolithotomy (PCNL). The researchers observed a notable disparity in heart rate between the placebo, fentanyl, and dexmedetomidine groups. Specifically, the dexmedetomidine group had the lowest average values in comparison to the other two groups. **Gupta *et al.*** [14] discovered in his investigation that dexmedetomidine provides superior hemodynamic stability in comparison with fentanyl, aligning with the results obtained in our own study. On the contrary, **Sarkar *et al.*** [15] in his study total of 70 patients (35 in each group) with ASA classes I and II and planned for lower limb orthopaedic procedures under epidural blockade were divided into the two groups (Age from 20 to 60 years old). Group I received one g/kg of fentanyl after a 15 ml spinal injection of 0.5% bupivacaine, while group II received one g/kg of dexmedetomidine. At no point during the monitoring periods did the two groups show significant differences in their heart rates or mean arterial blood pressures.

Also, in **Elfawal *et al.*** [16] study, participants were divided into three groups: Group L (healthy controls), group LD, and group LF. Group L received a dose of 0.75 ml/kg of levobupivacaine 0.25% (dissolved in NaCl 0.9%). Group LD received the same dose of levobupivacaine 0.25% along with dexmedetomidine at a concentration of 1 μg/kg. Lastly, group LF that received the same dose of levobupivacaine 0.25% along with fentanyl at a concentration of 1 μg/kg. The researchers provided evidence to support the claim that the intraoperative hemodynamic profile exhibited similarities across all groups. **Kaur *et al.*** [17] indicated that both fentanyl and dexmedetomidine exhibit similar effects when administered in conjunction with 0.75% ropivacaine, as observed by hemodynamic alterations. Also, **Hanoura *et al.*** [18] revealed that there was insignificant difference observed in terms of hemodynamic stability between the groups administered with fentanyl and dexmedetomidine.

In terms of respiratory metrics, there was no statistically significant difference in the mean respiratory rate observed between group D and group F. In contrast, **Akin *et al.*** [19] demonstrated significant respiratory depression and hypoxia in dexmedetomidine group.

When comparing groups A, B, C, and F on the VAS, after 2 hrs, group D had a significantly lower mean VAS score than group F (P 0.05). In agreement with our results, **Gousheh *et al.* [20]** in their study the participants were assigned to receive one of two treatment options: Lumbar epidural bupivacaine + morphine (BM) (consisting of 12 mL of bupivacaine 0.5% and 2 mg of morphine) or bupivacaine and dexmedetomidine (BD) (consisting of 12 mL of bupivacaine 0.5% and a dose of dexmedetomidine at 1 µg/kg). The researchers provided evidence that the group receiving BD had significantly lower VAS ratings ($P < 0.0001$) and a longer duration till the 1st analgesic call compared with the group receiving BM. On the contrary, **Taher-Baneh *et al.* [21]** with a total of 90 cases undergoing elective calf operation who were assigned to three separate groups, the rate of spinal anaesthesia in each of the three groups was administered as one mL of bupivacaine 0.5% (equivalent to 5mg). In the bupivacaine dexmedetomidine group, 5µg of dexmedetomidine was added. In the bupivacaine fentanyl group, 25µg of fentanyl was added. In the bupivacaine saline group, 0.5 mL of saline was added. The study findings indicated that the VAS scores were considerably lower in the two groups treated with bupivacaine fentanyl (1.4) and bupivacaine dexmedetomidine (1.3) compared to the bupivacaine saline (1.6) group, within 24 hrs post-surgery. However, fentanyl was more efficacious than dexmedetomidine. Also, **Dilesh *et al.* [22]** discovered the VAS obtained at the point of maximum analgesia demonstrated a significant decrease in the fentanyl group as compared to the dexmedetomidine group. This finding indicates that fentanyl induced a considerably greater analgesic depth compared with dexmedetomidine.

In relation to the initiation of block, there was a significant decrease in the average commencement of sensory and motor blockade, and the time consumed to attain the greatest level T10, in group D compared to group F ($P < 0.05$). In agreement with our results, **Bajwa *et al.* [23]** assigned the patients into two groups, namely combined ropivacaine and dexmedetomidine (RD) and combined ropivacaine and fentanyl (RF) (n=50). Intravenous administration of ropivacaine, at a concentration of 0.75% and a volume of 15 ml, was performed epidurally in both experimental groups. Additionally, the RD group received an adjunct of one µg/kg of dexmedetomidine, while the RF group received one µg/kg of fentanyl. The RD group had a considerably earlier onset of sensory analgesia at T10 (7.12±2.44 versus 9.14±2.94) and total motor blockage (18.16 ± 4.52 versus 22.98 ± 4.78) compared to healthy controls. On the other hand, **Dilesh *et al.* [22]** found that consumption of fentanyl has been observed to result in a shorter onset time compared to dexmedetomidine.

Regarding the timing of the first administration of rescue analgesia, there was a significant increase in the average number of postoperative hrs before the first dosage of rescue analgesia in group D compared to group F ($P < 0.05$). In agreement with our results, **Bajwa *et al.* [23]** revealed a considerable prolongation of postoperative analgesia in the RD group (366.62±24.42). As a result, there was a lower intake of LA (76.82±14.28 versus 104.35±18.96) throughout epidural top-ups in the postoperative period. This comes in disagreement with **Taher-Baneh *et al.* [21]** who revealed that the duration of motor and sensory block was considerably greater in the dependent limb in the BF group (96 and 169 minutes) compared to the BD group (92 and 166 minutes) and the BS group (84 and 157 minutes).

In terms of the development of unfavourable symptoms like low blood pressure, itching, nausea, and throwing up within the sample population, neither study group differed from the other statistically. In agreement with our results, **Dilesh *et al.* [22]** found that there was insignificant distinction between the groups administered with dexmedetomidine and fentanyl in terms of hypotension. This comes in disagreement with **Ayoub and Hakim [8]** who observed that patients belonging to group D exhibited a considerably greater risk of bradycardia and hypotension compared with those in group F.

CONCLUSION

Dexmedetomidine appears to present a more favorable option in comparison with fentanyl as an epidural adjuvant secondary to its ability to offer comparable stable hemodynamics, prompt onset, and establishment of sensory anesthesia, extended postoperative analgesia, as well as reduced consumption of post-operative local anesthetics for EA.

No funding.

No conflict of interest.

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