

# Dexmedetomidine-As an Adjuvant to Epidural Analgesia: Comparison Between Different Doses

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## Abstract

**Background:** Epidural analgesia offers superior pain relief and early mobilization, especially when a local anesthetic [LA] dose is combined with an adjuvant vs. a LA alone. Our study compares the efficiency of dexmedetomidine (1 and 2 µg/kg) and levobupivacaine, as well as their respective side effects.

**Patients and methods:** This study was conducted on a total of 60 American Society of Anesthesiologists I-II patients who underwent lower limb operations. The patients that received epidural dexmedetomidine (1 µgkg<sup>-1</sup>) plus levobupivacaine were assigned to Group 1 and those that received 2 µgkg<sup>-1</sup> dexmedetomidine plus levobupivacaine to Group 2.

**Results:** Increasing dexmedetomidine dose caused a significant shortening in the onset time of sensory block, time needed for maximum sensory level (p=0.038, 0.016 respectively) and prolonged duration of anesthesia (p=0.022). Postoperatively, a significant decrease in the total dose of levobupivacaine used was observed in Group 2 (p=0.027). In addition, Patients in Group 2 experienced a higher level of sedation (p=0.025) and a better analgesia as observed from time to first top-up dose (p=0.019). However, Bradycardia and hypotension were more pronounced in Group 2 patients (p<0.05).

**Conclusion:** Dexmedetomidine 2 µgkg<sup>-1</sup> as an adjuvant to epidural analgesia prolonged the duration of anesthesia and postoperative analgesia. However, higher doses of epidural dexmedetomidine are cautiously recommended in long surgical operations to avoid its side effects.

**Keywords:** Local anesthetics; Dexmedetomidine; Epidural anesthesia

## Introduction

Epidural anesthesia provides excellent analgesia for patients undergoing lower limb surgery. In addition, its potential reduction in postoperative morbidity and mortality demonstrated by numerous studies is a further credit for this technique [1]. Among many agents used in epidural analgesia, bupivacaine (a long acting amide local anesthetic) has been extensively used in various settings [2]. Levobupivacaine is an S (-) enantiomer of racemic bupivacaine. Affinity of this S (-) isomer to the cardiac sodium channel in the inactive state is lower than that of the R (+) isomer. Levobupivacaine has similar pharmacokinetic characteristics to bupivacaine and is considered a better alternative to bupivacaine, because of its lower side effects on the cardiovascular and central nervous systems [3].

As valuable adjuncts to local anesthetics, α-2 agonists have sedative properties and analgesic actions at peripheral, spinal and supraspinal levels. Dexmedetomidine- a highly selective α-2 agonist has been demonstrated to have a strong synergistic action with local anesthetics [4]. Furthermore, when used through the epidural route, dexmedetomidine has been shown to have numerous beneficial effects. It acts on both pre and post synaptic sympathetic nerve terminals and on the central nervous system, decreasing sympathetic outflow and

norepinephrine release, with consequent sedative, anti-anxiety, analgesic, sympatholytic effects [5]. Dexmedetomidine causes dose-dependent bradycardia, hypotension, so, in this prospective study we have used two different doses that are, 1 and 2 µg/kg along with the local anesthetic agent levobupivacaine to compare their analgesic and anesthetic efficacy as well as their side effects.

## Patients and Methods

After ethical committee approval and informed consent, the current study was conducted at Fayoum University Hospital on 60 adult patients American Society of Anesthesiologists (ASA) Class I or II scheduled to undergo lower limb orthopedic surgery. Exclusion criteria were patients with history of hypersensitivity to any of the drugs used in this study, hematologic disorders, hemostatic abnormalitie, chronic pain syndrome and moe than 100 Kg body weight. The study was designed to be a prospective random double blind study. All patients were anesthetized via epidural route and assigned randomly by a computer randomization program in a double blinded fashion based on a computer generated code to one of the following two treatment groups to receive either 15 ml isobaric levobupivacaine (Chirocaine 0.5%) plus 1 µgkg<sup>-1</sup> dexmedetomidine (100 µg/ml concentration) [Group 1 (n=30)] or 15 ml isobaric levobupivacaine (Chirocaine 0.5%) plus 2 µg/kg dexmedetomidine [Group 2 (n=30)]. The injected dose was calculated according to the body weight and the anesthetic solution was completed to 17 ml using normal saline. All anesthetic

solutions included in this study were prepared by an anesthesiologist unaware of the study design.

Routine preoperative investigations including complete blood picture, liver and renal function tests, and coagulation profile were done. Electrocardiogram (ECG) was done to patients above 30 years. Echocardiography and chest X-ray were done to patients above 60 years. All patients were prehydrated with 10 ml kg<sup>-1</sup> lactated Ringer's solution. Prior to insertion of the epidural needle and catheter (Braun, Melsungen, Germany), the lower back was disinfected with povidone-iodine (10%) and covered with a sterile drape. Lidocaine 2% (3 ml) was used to infiltrate the skin and subcutaneous tissues at the L3-L4 or L4-L5 space, with the patient in the sitting or lateral position. The epidural space was identified by using an 18-gauge Tuohy needle and a midline approach with loss of resistance technique. An epidural catheter was left at 4 cm in the epidural space and fixed. Correct placement of epidural catheter was verified with a test dose of 3 ml epidural lignocaine 2% with adrenaline (1:200,000). After confirmation that negative aspiration yielded no blood or cerebrospinal fluid (CSF) each patient group was injected respectively as follows:

**Group 1** received 15 ml isobaric levobupivacaine (0.5%) plus 1 µg/kg-1 dexmedetomidine slowly administered in the epidural space over a 10 min period in increments to a total volume 17 ml.

**Group 2** received 15 ml isobaric levobupivacaine (0.5%) plus 2 µg/kg-1 dexmedetomidine slowly administered in the epidural space over a 10 min period in increments to a total volume 17 ml.

Heart rate (HR), mean arterial blood pressure (MAP), oxygen saturation % (SpO<sub>2</sub>) and respiratory rate (RR) were measured at the following intervals: baseline (prior to any intervention with patients lying on the operating table), 5, 10, 15, 20, 30, 40, 50, 60, 90 and 120 min following injection of the epidural solution. Sensory blockade was measured by fine pricking using the blunt end of a 27-gauge dental needle at 0, 2, 5, 10, 15, 20, 25, 30, and 60 min post injection and every 30 min thereafter until complete regression of sensory block was observed. Onset time of sensory block at T10, maximum sensory block level, time to maximum sensory block level, time for requirement of first epidural top up dose and the time for two segment regression were recorded.

Motor blockade of the lower extremity was evaluated using the modified Bromage scale every 2 min as follows: (0=No motor block; 1=Inability to raise extended leg, but able to move knees and feet; 2=Inability to raise extended leg or move knee but able to move feet; 3=Complete motor block). Onset time of motor block, time to reach maximal motor block (grade 3 modified Bromage scale), and time for regression to Bromage 1 were also recorded. The total dose of levobupivacaine (0.125% concentration) used in mg/24 hours was recorded. Side effects including hypotension, bradycardia, nausea and vomiting, sedation, respiratory depression, dry mouth and shivering were carefully noted and treated accordingly. Sedation was graded using the following five point scale (1=alert and wide awake; 2=arousable to verbal command; 3=arousable with gentle tactile stimulation; 4=arousable with vigorous shaking; 5=unarousable). Patients were discharged from the operating room to the wards once they showed stable and sustained vital signs and hemodynamic parameters (HR, basal systolic and diastolic blood pressure).

## Statistical Analysis

Based on a pilot study, calculation of sample size was mainly based on difference in the mean value of (time to two segment regression) time to maximum sensory block level (min) between the two groups. Estimation of the sample size was performed using the program GPower3.1. For an effect size of 0.62, assuming a two-sided type I error of 0.05 and a power of 0.80, a sample size of 60 patients (30 patients in each group) would be required.

Results are expressed in terms of means ± standard deviation (SD), median, 25th and 75th percentiles or number and percent. Comparison between categorical data was performed using Chi square test. Comparison between different variables in the two studied groups was performed using either unpaired t test or Mann-Whitney test whenever it was appropriate. Comparison relative to baseline within the same group was performed using repeated measures ANOVA followed by Bonferroni test with corrected p value = 0.431. The data were considered significant if p value was ≤ 0.05.

All statistical calculations were done using computer program SPSS (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL) software for Windows (Version 16.0).

## Results

Table 1 shows the demographic data of patients of the current study. No statistically significant difference was noted between both groups as regards age, sex, BMI, ASA type and duration of surgery.

	Group 1 (n=30)	Group 2 (n=30)
Age (years)	33.45 ± 10.15	34.26 ± 11.24
Gender (Male/Female)	17/13	15/15
BMI	27.59 ± 3.02	28.67 ± 2.92
ASA class I/II	18/12	19/11
Duration of operation (minutes)	148.0 ± 12.36	150.26 ± 14.97

Group 1: 1 µg/kg dexmedetomidine, Group 2: 2 µg/kg dexmedetomidine.  
Values are expressed with mean ± SD or numbers, BMI: Body mass index, ASA: American Society of Anesthesiologist.

**Table 1:** Demographic data of the studied patients.

The onset time of sensory block at T10 was significantly shorter in Group 2 as compared to Group 1, increasing the dose having led to a moderate decrease in the onset time (7.82 ± 2.33 and 9.12 ± 2.42 minutes respectively, p=0.038). Patients in Group 2 achieved a higher maximum sensory block level compared to group 1 (median and 25-75% were T5/T6 (T4/T5- T6/T7) vs. T7/T8 (T6/7-T8/T9) respectively, P=0.001).

The time needed to reach the maximum sensory level was significantly shorter in Group 2 than Group 1 (respectively 13.26 ± 4.22 min vs. 16.1 ± 4.68 min, P=0.0165) (Table 2). Postoperatively, there was a significant delay in the time for two segment regression (138.39 ± 8.26 vs. 133.6 ± 7.49; P=0.022) and there was a significant decrease in the total dose of levobupivacaine used /24 hours in Group 2 than Group 1 (respectively 66.47 ± 15.39 mg/24 hr vs. 78.32 ± 24.12mg/24 hr, P=0.027) (Table 3).

In addition, a significantly delayed in the time to first top-up dose of levobupivacaine was observed in Group 2 compared to Group 1 (respectively  $354.72 \pm 26.79$  mins vs.  $339.51 \pm 21.67$  mins;  $P=0.019$ ). The mean time to reach maximal motor block was markedly shortened in Group 2 vs. Group 1 (respectively  $17.70 \pm 4.84$  min vs.  $21.50 \pm 4.65$  min;  $P=0.003$ ), similarly there was a significant delay in the time regression to Bromage I in Group 2 vs. Group 1 (respectively  $253.17 \pm 9.16$  min vs.  $244.92 \pm 18.24$  min;  $P =0.308$ ) (Tables 2 and 3).

	Group 1 (n=30)	Group 2 (n=30)	P value
Onset time of sensory block (min)	$9.12 \pm 2.42$	$7.82 \pm 2.33$	0.0383*
Maximum sensory block level (median)	T7-T8	T5-T6	0.001*
Maximum sensory block level (25-75%)	(T6/T7-T8/T9)	(T4/T5-T6/T7)	-
Time to maximum sensory level (min)	$16.1 \pm 4.68$	$13.26 \pm 4.22$	0.0165*
Time to reach maximal motor block (min)	$21.50 \pm 4.65$	$17.70 \pm 4.84$	0.003*
Group 1: 1 µg/kg dexmedetomidine, Group 2: 2 µg/kg dexmedetomidine Data are expressed with mean ± SD *p<0.05=significant			

**Table 2:** Intraoperative sensory and motor block variables.

	Group 1 (n=30)	Group 2 (n=30)	P value
Two-segment regression (mins.)	$133.6 \pm 7.49$	$138.39 \pm 8.26$	0.022*
Time to regression to Bromage I (mins.)	$244.92 \pm 18.24$	$253.17 \pm 9.16$	0.308
Time to first top-up dose (mins.)	$339.51 \pm 21.67$	$354.72 \pm 26.79$	0.019*
Total dose of levobupivacaine (mg/24 h)	$78.32 \pm 24.12$	$66.47 \pm 15.39$	0.027*
Group 1: 1 µg/kg dexmedetomidine, Group 2: 2 µg/kg dexmedetomidine Data are expressed with mean ± SD *p<0.05=significant			

**Table 3:** Post-block sensory and motor variables.

In both Group 1 and 2, a lower HR compared to baseline was observed throughout the study. Also, a significant drop in MAP was observed compared to baseline values in group 1 and 2 starting from 5 min and 15 min respectively till the end of the study. Lower HR and MAP values were found in Group 2 compared to Group 1 in variable degrees. The recorded differences were statistically significant. In group 2, an increased dose of dexmedetomidine led to a decrease in HR at 15, 20 and 30 minutes ( $P=0.04$ ,  $0.0003$ ,  $0.013$  respectively) and a decrease in the MAP was recorded at 10, 15, 20, 30, 40, 50, 60 and at 120 min ( $p<0.05$ ) (Tables 4 and 5).

Time (mins)	Group (1) (n=30)	Group 2 (n=30)	P
0 min	$85 \pm 5.932$	$82 \pm 6.565$	0.068
5 min	$85 \pm 7.156a$	$86 \pm 8.902a$	0.633
10 min	$80 \pm 6.420a$	$79 \pm 8.765a$	0.616
15 min	$76 \pm 6.357a$	$71 \pm 11.390a$	0.040*
20 min	$72 \pm 5.270a$	$63 \pm 11.852a$	0.0003*
30 min	$61 \pm 4.718a$	$55 \pm 11.914a$	0.013*
40 min	$58 \pm 6.327a$	$53 \pm 12.762a$	0.059
50 min	$55 \pm 6.357a$	$54 \pm 11.918a$	0.687
60 min	$59 \pm 7.634a$	$56 \pm 8.766a$	0.163
90 min	$64 \pm 6.357a$	$61 \pm 9.259a$	0.149
120 min	$70 \pm 6.565a$	$68 \pm 9.235a$	0.338
Group 1: 1 µg/kg dexmedetomidine , Group (2): 2 µg/kg dexmedetomidine Data are expressed with mean ± SD. *p< 0.05 relative to group 2. <sup>a</sup> p<0.05 relative to zero minute (baseline) within the same group			

**Table 4:** Mean heart rate changes in the Studied Groups.

Time (min)	Group 1 (n=30)	Group 2 (n=30)	p value
0	$98 \pm 8.029$	$97 \pm 6.632$	0.601
5	$96 \pm 7.220 a$	$95 \pm 5.702$	0.5539
10	$97 \pm 7.970 a$	$92 \pm 5.702$	0.0070*
15	$95 \pm 8.108 a$	$88 \pm 6.313 a$	0.0004*
20	$90 \pm 8.071 a$	$79 \pm 7.109 a$	0.0001*
30	$81 \pm 8.012 a$	$75 \pm 6.116 a$	0.002*
40	$78 \pm 5.791 a$	$73 \pm 6.310 a$	0.0022*
50	$78 \pm 7.225 a$	$75 \pm 6.117 a$	0.0054*
60	$84 \pm 5.725 a$	$79 \pm 6.942 a$	0.0035*
90	$86 \pm 5.418 a$	$83 \pm 6.667 a$	0.0607
120	$91 \pm 6.055 a$	$86 \pm 6.869 a$	0.0041*
Group 1: 1 µg/kg dexmedetomidine , Group (2): 2 µg/kg dexmedetomidine *p< 0.05 relative to group 2. <sup>a</sup> p< 0.05 relative to zero minute (baseline) within the same group.			

**Table 5:** Mean arterial blood pressure changes (mmHg) in the studied groups.

The sedation score was significantly higher in Group 2 median 25-75% quartiles 3.0 (2.0-3.0) vs. 2.0 (2.0-3.0) in Group 1 ( $P=0.025$ ). Regarding other side effects, increasing the dexmedetomidine dose led to increased risk for nausea (RR 4.5; 95% CI (1.059-19.1115) , no significant increase in the risk of vomiting, dry mouth , shivering or respiratory depression was found between both groups (Tables 6 and 7).

	Group 1	Group 2	RR	95% CI
Nausea [n(%)]	2 (6.6%)	9 (30.0%)	4.5	1.059-19.1115
Vomiting [n(%)]	1 (3.3%)	7 (23.3%)	7	0.913-53.476
Shivering [n(%)]	4 (13.3%)	1 (3.3%)	4	0.474-33.73
Respiratory depression [n(%)]	0 (0%)	1 (3.3%)	0.3	0.0141-7.870
Dry mouth [n(%)]	3 (10%)	7 (23.3%)	2.33	0.665-8.179

Group 1: 1 µg/kg dexmedetomidine, Group 2: 2 µg/kg dexmedetomidine; RR: relative risk; CI: Confidence interval.

**Table 6:** Side effects in both groups.

	Group 1 (n=30)	Group 2 (n=30)	p value
Sedation score	2.0 (2.0-3.0)	3.0 (2.0-3.0)	0.025*

Group 1: 1 µg/kg dexmedetomidine , Group 2: 2 µg/kg dexmedetomidine  
Data are expressed with median and its 25-75% quartiles  
\*p<0.05=significant.

**Table 7:** Sedation scores among the studied groups.

## Discussion

Epidural analgesia offers superior pain relief and early mobilization, especially when a local anesthetic [LA] dose is combined with an adjuvant *vs.* a LA alone [6].

The search for adjuvants for local anesthetics to improve quality of regional anesthesia is an ongoing process. In current anesthetic practice, alpha 2 adrenoceptor agonists are preferred for their sympatholytic, sedative, analgesic and anesthetic-sparing effects. Clonidine has been used extensively for this purpose. Dexmedetomidine is a more selective alpha 2 agonist with a greater selectivity for  $\alpha$ -2 receptors than  $\alpha$ -1 receptor [7]. In the current study, we directly compared the effects of epidurally administered different doses of dexmedetomidine [Group 1 1 µgkg<sup>-1</sup> and Group 2 2 µgkg<sup>-1</sup>] on the intra- and post-operative sensory and motor variables. Moreover, we aimed to study the side effects of giving an increased dexmedetomidine dose. In the present work, the demographic profile did not show any significant difference between both groups on statistical comparison.

Intraoperatively, Group 2 had a significantly shorter onset time of sensory block, shorter time needed for maximum sensory level and achieving a higher maximum sensory block level compared to Group 1. The post-block sensory study revealed a better anesthetic effect when using a higher dose of dexmedetomidine where the two-segment regression time was found to be significantly longer and a lower total dose of levobupivacaine was used. Group 2 showed a significantly shortened onset time of sensory block, time needed for maximum sensory level and prolonged duration of anesthesia. Postoperatively, the total dose of levobupivacaine used was significantly lower, patients experienced a higher level of sedation and postoperative analgesia. In addition, the time to first top-up dose was significantly delayed with a higher dose of dexmedetomidine, a good evidence of the analgesic effect of increasing the drug dose.

As regards motor variables, higher doses of dexmedetomidine shorten the mean time to reach maximal motor block. Regarding the hemodynamic changes, significant bradycardia was observed in both groups. Bradycardia was more pronounced in Group 2 patients at 15 and 30 min. Similarly, there was a more significant drop in the mean arterial pressure in Group 2 compared to Group 1. The maximal recorded drop reached 78 mmHg in Group 1 and 73 mmHg in Group 2. In both groups, atropine and ephedrine were used as needed and patients remained hemodynamically stable. The side effect profile of both groups exhibited a significantly higher incidence of sedation in Group 2 compared to Group 1. Increasing dexmedetomidine dose to 2 µg/kg increased the risk for nausea. Vomiting and dry mouth were experienced in both groups with no increase in its relative risk. Similarly, there was no increase in risk of shivering, or respiratory depression.

Bajwa et al. studied the effect of clonidine and dexmedetomidine on patients undergoing surgery under epidural analgesia. They noticed an increase in time to two-segment regression, sensory and motor block duration and an increase in time to first request of analgesia and better sedation in the dexmedetomidine 1.5 µgkg<sup>-1</sup> Group [8].

Sinha et al. studied the effect of dexmedetomidine 1 µgkg<sup>-1</sup> on paravertebral block using ropivacaine and noticed significant increase in duration of sensory and motor block as well as sedation levels. The authors also reported bradycardia and hypotension in the dexmedetomidine group [9].

Zeng et al. studied the effect of adding of dexmedetomidine 0.5 µgkg<sup>-1</sup> to 0.75% levobupivacaine epidurally in patients undergoing nephrectomy. The duration of sensory and motor blockade was prolonged in the dexmedetomidine group compared to placebo [10]. Bajwa et al. also found the early onset of analgesia and motor blockade in epidural dexmedetomidine when used with ropivacaine [8].

Fukushima et al. were the first to report the use of epidural dexmedetomidine in patients undergoing surgery under general anesthesia. They found that an epidural injection of dexmedetomidine 2 µgkg<sup>-1</sup> resulted in depression of the total electroencephalogram pattern. At 10 minutes, decreased blood pressure (80/65 mmHg), and heart rate (50-70 beats/min), were observed (P<0.05). Dexmedetomidine reduced analgesic drug requirements by 70% for 24 hours, and analgesia lasted 4-6 hours postoperatively [11], a result comparable to those of the current study, where the mean time at first top up dose was 354.72 ± 26.79 min.

Jain et al. studied the synergistic effect of dexmedetomidine with 0.5% bupivacaine, and observed that epidural dexmedetomidine 2

$\mu\text{gkg}^{-1}$  enhances motor and sensory blockade, and prolongs analgesia duration [12].

The analgesic effect of dexmedetomidine is induced by stimulation at the spinal cord level. At the dorsal root neuron, alpha-2 agonists inhibit the release of substance P in the nociceptive pathway. By inhibiting the release of norepinephrine, the alpha-2 receptors located at the nerve endings play a possible role in analgesia. Despite evidence of supraspinal and peripheral actions of dexmedetomidine, the spinal mechanism tends to be considered the main mechanism responsible for its potent analgesic effects [12].

Although the prolonged duration of sensory blockade with dexmedetomidine can improve postoperative pain management, delayed recovery of motor function may have its disadvantages and may be inappropriate in day care surgeries [13]. The decrease in the heart rate caused by alpha-two agonists can be explained by their central action, mediated by a decrease in sympathetic outflow and potentiation of norepinephrine release. The sedative effects observed in Group 2 are mediated by activation of presynaptic alpha-2 adrenoreceptors in the locus coeruleus, inhibiting norepinephrine release. Adenylate cyclase inhibition may also play a role in the hypnotic response of dexmedetomidine [14].

In the current study, dexmedetomidine  $2 \mu\text{gkg}^{-1}$  as an adjuvant to epidural analgesia significantly prolonged the duration of anesthesia and provided excellent sedation and postoperative analgesia. On the other hand, the hemodynamic profile study showed a significantly higher incidence of hypotension and bradycardia compared with dexmedetomidine  $1 \mu\text{gkg}^{-1}$ . In addition, the frequency of nausea and vomiting incidence was higher with the  $2 \mu\text{gkg}^{-1}$  dose.

Therefore, this study provides an evidence that higher doses of epidural dexmedetomidine are cautiously recommended in long surgical procedures to avoid delayed motor recovery and unwanted side effects.

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