

# Intrathecal Dexmedetomidine and Fentanyl as Adjuvant to Bupivacaine on Duration of Spinal Block in Addicted Patients

Farhad Safari,<sup>1</sup> Reza Aminnejad,<sup>1</sup> Seyed Amir Mohajerani,<sup>1</sup> Farshad Farivar,<sup>1</sup> Kamran Mottaghi,<sup>1</sup> and Hasan Safdari<sup>1,\*</sup>

<sup>1</sup>Department of Anesthesiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

\*Corresponding author: Hasan Safdari, Department of Anesthesiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel/Fax: +98-2155424040, E-mail: dr\_hassansafdari@yahoo.com

Received 2015 June 5; Revised 2015 November 9; Accepted 2015 November 28.

## Abstract

**Background:** Addicted patients have innate tolerance to local anesthetics in both neuraxial and peripheral blocks. Dexmedetomidine (Dex) is a highly selective  $\alpha_2$  adrenergic receptor agonist used as additive to increase quality and duration of peripheral nerve blocks.

**Objectives:** The current study aimed to compare the effect of dexmedetomidine and fentanyl additives on bupivacaine to prolong the duration of block and minimizing side effects.

**Patients and Methods:** Patients were candidates for elective surgery less than three hours of lower abdomen or lower extremities surgeries. Patients were randomly allocated to receive dexmedetomidine 5  $\mu$ g added to 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine (DEX group), or 25  $\mu$ g (0.5 mL) fentanyl added to 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine (F group) or only 12.5 mg of 0.5% hyperbaric bupivacaine. Data were recorded based on sensory block. Motor block was tested using modified Bromage scale every 30 minutes until the end of block. Time to return of sensory block to 4 dermatomes below and time to return of Bromage scale to 0 were recorded. All vital measurements (oxygen saturation, heart rate, electrocardiogram, and non-invasive blood pressure) were performed at 0, 30, 60, 90, 120 and 180 minutes in all three groups of the study. Group DEX received dexmedetomidine additive and group F received fentanyl additive and group C (control) received normal saline.

**Results:** Totally, 84 patients were randomly divided into three groups of 28 patients. Onset of sensory block in DEX group was significantly lower than those of fentanyl ( $P = 0.012$ ) and control groups ( $P = 0.001$ ). Duration of sensory block was significantly longer in DEX group compared to Fentanyl ( $P = 0.043$ ) and control ( $P = 0.016$ ) groups. Duration of motor block in the DEX group was significantly longer than those of the fentanyl ( $P = 0.014$ ) and control groups. Heart rate and mean arterial pressure were significantly higher in the DEX group at 30, 60, 90, 120, and 180 minutes compared to those of the other two groups ( $P < 0.05$ ).

**Conclusions:** Dexmedetomidine added to bupivacaine in spinal anesthesia is more effective to increase duration of block, providing more appropriate sedation and less postoperative pain scale and post-operative nausea and vomiting (PONV) compared to fentanyl additive.

**Keywords:** Dexmedetomidine, Fentanyl, Bupivacaine, Spinal Anesthesia, Addicted Patients, Addiction

## 1. Background

Spinal neuraxial blocks result in sympathetic blockade, sensory analgesia, or anesthesia and motor blockade, depending on the dose, concentration or volume of local anesthetic, after insertion of a needle in subarachnoid space. Despite similarities of various local anesthetics used for spinal anesthesia, there are significant physiologic and pharmacologic differences. Local anesthetics provide longer and better quality of block when used in adjunct to the additive drugs such as opioids. The adjunct drug should be utterly controllable in blocking motor and lacking systemic side effects (1).

Addiction is an increasing problem in modern society and affects patients' management in anesthesia. It is well recognized that the prolonged use of opioids is associat-

ed with a requirement for ever-increasing doses in order to maintain pain relief at an acceptable and consistent level. Addicted patients have innate tolerance to local anesthetics in both neuraxial and peripheral blocks (2). Dexmedetomidine has better effects on sensory and motor block duration and motor block onset in comparison with ketorolac, as lidocaine adjuvants in infraclavicular brachial plexus block (3).

Dexmedetomidine (DEX), a highly selective  $\alpha_2$  adrenergic receptor agonist, is a newly discovered drug that gained much reputation in neuroanesthesia, intensive care unit (ICU) and cardiac anesthesia in recent years (4). DEX has eight times  $\alpha_2/\alpha_1$  activity compared with clonidine (5); therefore, it is considered a full agonist of the

$\alpha_2$  receptor. Compared to clonidine, DEX has proposed unique features to maintain analgesia, anxiolytic and sedative effect without causing major respiratory depression in this sense. Notably, DEX was suggested as an additive to local anesthetics in peripheral and neuraxial blocks (6, 7) in many previous studies. Although available data are insufficient, DEX is a good local anesthetic (LA) adjuvant that can hasten the onset and prolong the duration of sensory and motor blockade when used in intrathecal or epidural block and looks safe (8). Some previous studies showed that  $\alpha_2$  adrenergic receptor agonist prolongs the effects of local anesthetics (9-11), however these results are mixed (12, 13).

## 2. Objectives

The current study aimed to compare the effect of dexmedetomidine and fentanyl additives on bupivacaine to prolong the duration of block and minimizing side effects.

## 3. Patients and Methods

This study was a triple blinded randomized clinical trial (RCT) of 84 patients randomly divided into three groups of 28 patients. This study was performed in Loghman hospital, Tehran, Iran; January 2013 - January 2014.

Inclusion criteria were the American society of anesthesiologists (ASA) class I patients aged 18 to 60-years-old and elective surgery less than three hours for lower abdomen or lower extremities surgeries. Exclusion criteria were history of uncontrolled hypertension, allergy to bupivacaine, fentanyl, or dexmedetomidine, contraindication for spinal anesthesia, or failed spinal.

### 3.1. Patient Selection

Patients were randomly allocated to receive dexmedetomidine (Precedex, Hospira, USA) 5  $\mu$ g diluted in 0.5 mL normal saline added to 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine (Mylan, Italy) (DEX group) or 25  $\mu$ g (0.5 mL) fentanyl (Caspian Tamin, Iran) added to 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine (F group). Control group received 0.5 mL normal saline added to 12.5 mg of 0.5% hyperbaric bupivacaine. Randomization was performed using accidental numbers with concealed allocation. Anesthesiologists administering drugs and anesthesiologists evaluating level and duration of sensory block were blinded to the syringe content.

### 3.2. Ethics Declaration

The study was reviewed and approved by the Shahid Beheshti University of Medical Science Ethics Committee. Information about the study was given comprehensively both orally and in written form to all patients or their accompanying adults. They gave their informed written consents prior to their inclusion in the study according to University Ethical Committee.

### 3.3. Method of Spinal Anesthesia

After entrance to operation room, patients were monitored for all standard procedures including oxygen saturation (pulse oximetry), electrocardiography (ECG), non-invasive blood pressure and heart rate. Then 500 mL Ringer was infused. The patient was positioned in sitting position and spinal anesthesia was performed by midline approach in L3-L4 level with a Quincke 25 G needle. The palpating fingers (usually the index and third fingers) identified the interspinous area by locating the caudad extent of the more cephalad spine and the midline by rolling the fingers in a medial to lateral direction. After inserting the needle into the subarachnoid space and obtaining clear cerebrospinal fluid (CSF), the drug of study was injected after careful aspiration. After injection, patients were immediately aligned into supine position and 5 L/min oxygen was provided through face mask. This moment was assumed as baseline time point and all vital signs were recorded.

### 3.4. Data Entry

Data were recorded based on the sensory block using pin prick sensory test. Motor block was tested using modified Bromage scale every 30 minutes until the end of block. Time to return of sensory block to 4 dermatomes below and time to return of Bromage scale to 0 were recorded.

All vital measurements, including SPO<sub>2</sub>, heart rate (HR), electrocardiography (ECG) and noninvasive blood pressure amplifier (NIBP), were performed at 0, 30, 60, 90, 120 and 180 minutes in all three groups of the study. All data were recorded in a data sheet specified to each patient.

All intra-operative and post-operative adverse effects of spinal anesthesia including post-operative nausea and vomiting (PONV), pruritus and respiratory depression were measured. Post-operative pain score were measured using visual analogue scale (VAS) score scaled from 0 to 10, as 0 being the least and 10 the worst. Post operation pain scales were measured at 1, 3, 6, and 24 hours after injection. In case of VAS  $\geq$  4 the patients received morphine as rescue analgesic until VAS  $\leq$  3. Sedation scale was measured by Ramsay sedation scale at 0, 1, 2 and 3 hours after intrathecal injection during and after anesthesia.

### 3.5. Statistical Analysis

Statistical calculations were conducted using SPSS 20 (Chicago, IL, USA). The parametric variables were presented as Mean  $\pm$  SD and analyzed by the analysis of variance (one-way ANOVA) post-hoc test; non-parametric variables were analyzed by Kruskal-Wallis test. P < 0.05 was considered statistically significant. Sample size was estimated using sample size calculator software with 95% confidence interval, P = 0.05 and power of 80% and differ-

ence between the two groups of 30% in primary outcome based on pilot study.

#### 4. Results

Totally, 84 patients were randomly divided into three groups of 28 patients. There was no significant difference in age, gender and body mass index (BMI, kg/m<sup>2</sup>) of patients between the three groups ( $P > 0.05$ ) (Table 1). Duration of surgery was  $150 \pm 44$  minutes in the DEX group,  $152 \pm 41$  minutes in the fentanyl group and  $147 \pm 42$  minutes in the control group. Duration of surgery was not significantly different between the three groups ( $P > 0.05$ ) (Table 1).

Mean of onset of sensory block in the DEX group was  $4.32 \pm 1.6$  minutes,  $6.58 \pm 1.3$  minutes in the F group and  $7.9 \pm 2.3$  minutes in the control group. Onset of sensory block in DEX group was significantly lower than the fentanyl ( $P$

$= 0.012$ ) and control groups ( $P = 0.001$ ) (Figure 1). Besides, onset of sensory block was significantly lower in the fentanyl group than the control ( $P = 0.035$ ) (Marcaïne).

Duration of sensory block was  $185.5 \pm 27.5$  minutes in the DEX group,  $158.5 \pm 29.7$  minutes in the fentanyl group and  $129.3 \pm 25.4$  minutes in the control group. Duration of sensory block was significantly longer in the DEX group compared to the fentanyl ( $P = 0.043$ ) and control ( $P = 0.016$ ) (Figure 2). Duration of sensory block was significantly longer in the fentanyl compared to the control group ( $P = 0.024$ ) (Marcaïne).

Onset of motor block in the DEX group was  $5.46 \pm 2.6$  minutes,  $7.57 \pm 2.3$  minutes in the F group and  $8.69 \pm 2.16$  minutes in the control group. Onset of motor block in the DEX group was significantly lower than those of the fentanyl ( $P = 0.024$ ) and control groups ( $P = 0.022$ ) (Figure 3). Onset of motor block was not significantly lower in the fentanyl group than the control ( $P = 0.073$ ).

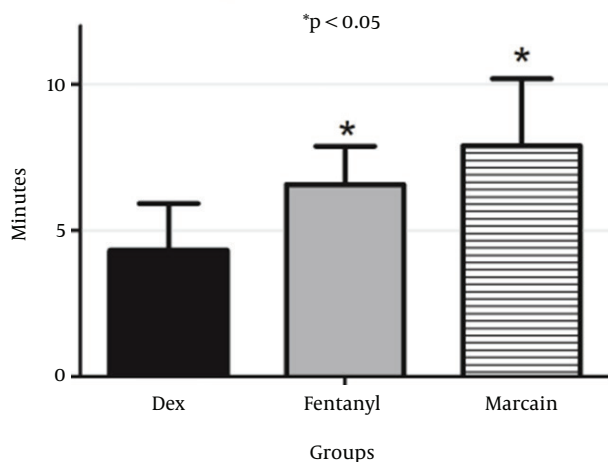
**Table 1.** Demographic Characteristics of Patients in the Three Groups of Study<sup>a</sup>

Variable	DEX	Fentanyl	Marcaïne <sup>b</sup>
Age, y	45.7 ± 11.3	44.5 ± 15.8	46.9 ± 13.6
Weight, kg	65.7 ± 13.8	69.8 ± 16.3	64.7 ± 17.8
BMI, kg/m <sup>2</sup>	22.4 ± 3.8	23.8 ± 4.4	21.6 ± 3.9
Duration of surgery, min	150 ± 44	152 ± 41	147 ± 42

<sup>a</sup> $p > 0.05$

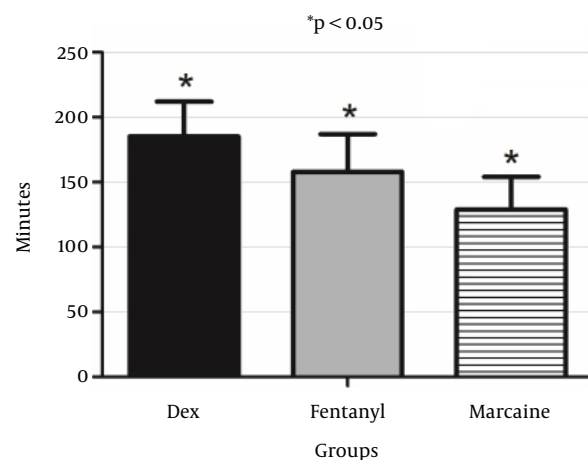
<sup>b</sup>Bupivacaine is the control group.

**Figure 1.** Onset of Sensory Block After Intrathecal Injection of Dexmedetomidine (DEX), or Fentanyl (F) and Marcaïne (M), Marcaïne (Bupivacaine)



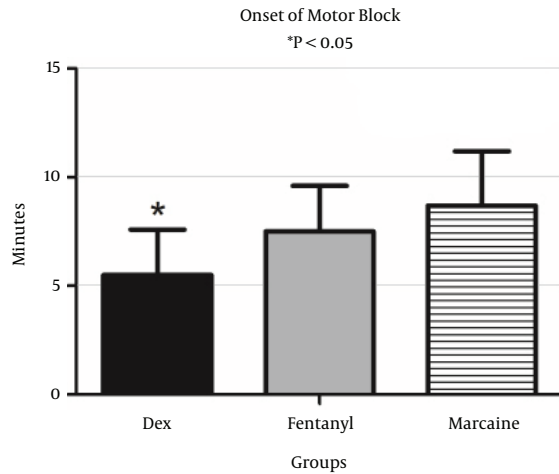
P value for DEX versus F and M groups is less than 0.05.

**Figure 2.** Duration of Sensory Block After Intrathecal Injection of Dexmedetomidine (DEX), Fentanyl (F) and Marcaïne (M)



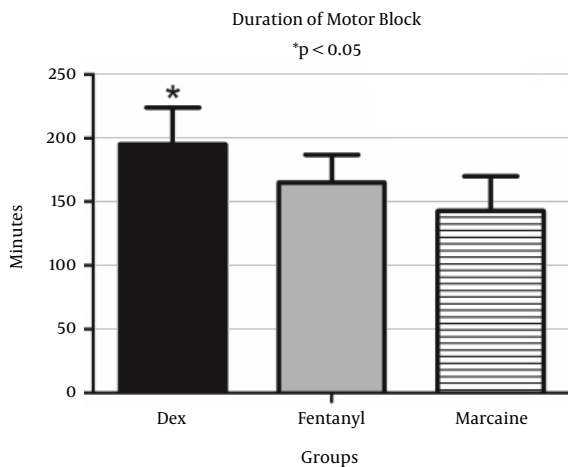
P value for DEX versus F and M groups is less than 0.05.

**Figure 3.** Onset of Motor Block After Intrathecal Injection of Dexmedetomidine (DEX), or Fentanyl (F) and Marcaine (M)



Onset of motor block was significantly lower in the fentanyl and Marcaine groups; P value for DEX versus F and M groups is less than 0.05.

**Figure 4.** Duration of motor block after intrathecal injection of dexmedetomidine (DEX), fentanyl (F) and Marcaine (M)

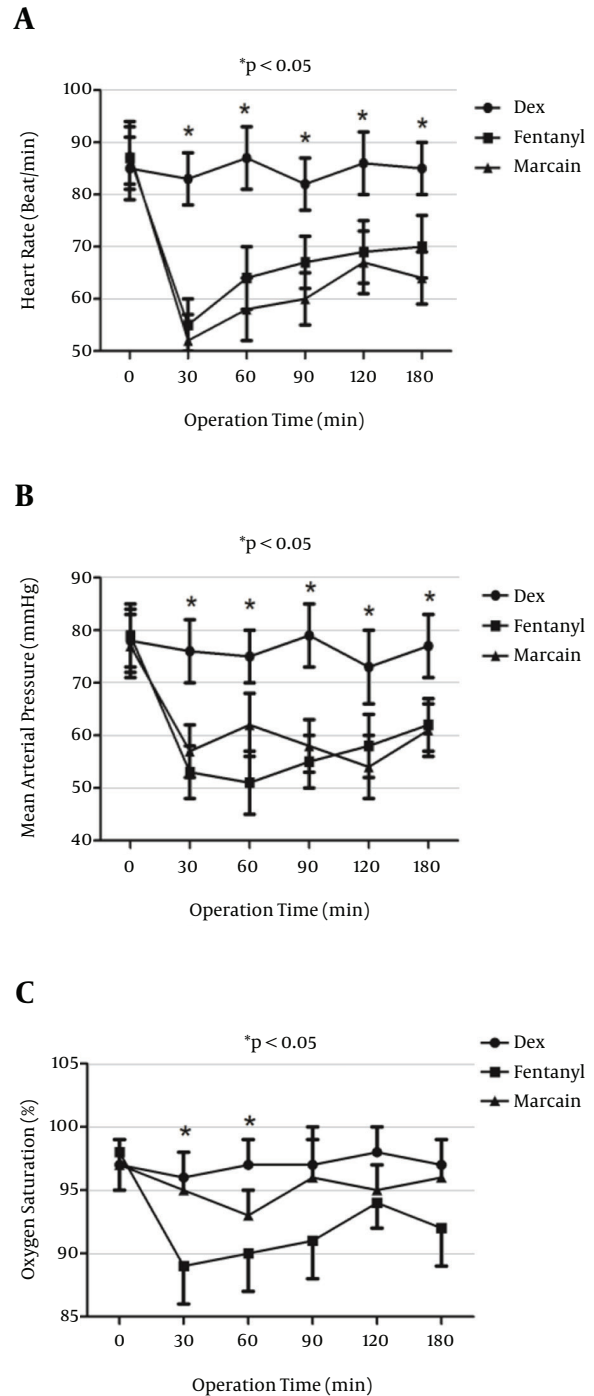


Bupivacaine, as the control group; DEX was significantly higher than fentanyl and Marcaine groups.

Duration of motor block was  $196.5 \pm 24.5$  minutes in the DEX group,  $165.5 \pm 22.7$  minutes in the F group and  $143.9 \pm 22.1$  minutes in the control group. Duration of motor block in the DEX group was significantly longer than those of the fentanyl ( $P = 0.014$ ) and control groups ( $P = 0.005$ ) (Figure 4). Duration of motor block was not significantly lower in the fentanyl group than the control ( $P = 0.081$ ).

Heart rate was depicted in the three groups of the study during operation. Heart rate was significantly higher in the DEX group at 30, 60, 90, 120, and 180 minutes compared to the other two groups ( $P < 0.05$ ) (Figure 5). Mean blood pressure was also significantly higher in the DEX group compared to the fentanyl and control groups at 30, 60, 90, 120 and 180 minutes compared to the fentanyl

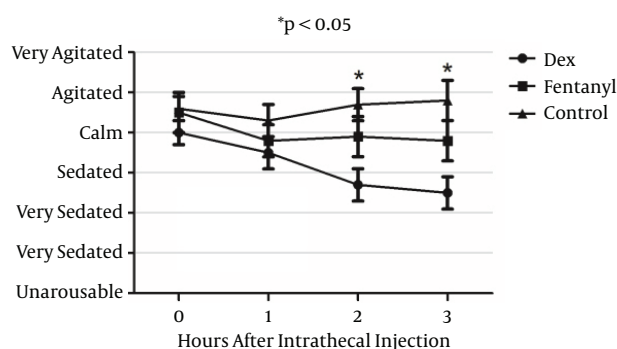
**Figure 5.** Heart Rate and Mean Arterial Blood Pressure (MAP) and Arterial Oxygen Saturation (%) of Patients After Intrathecal Injection of Dexmedetomidine (DEX), Fentanyl (F) and Marcaine (M), Bupivacaine The Control Group



P value for DEX versus F and M groups is less than 0.05.

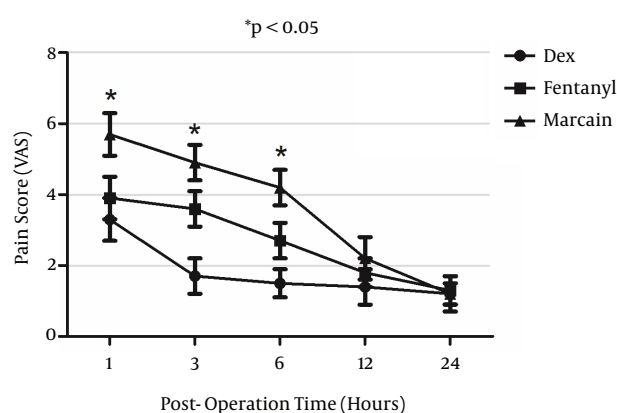
and control groups ( $P < 0.05$ ) (Figure 5). Arterial oxygen saturation was significantly higher in the DEX group as compared to the fentanyl and control groups at 30 and 60 minutes ( $P < 0.05$ ).

**Figure 6.** Sedation scale (Ramsey scale) of Patients in Post-Operation Time After Intrathecal Injection of Dexmedetomidine (DEX), Fentanyl (F) and Marcaine (M) Bupivacaine The Control Group



P value for DEX versus F and M groups is less than 0.05.

**Figure 7.** Pain Score Visual Analogue Scale (VAS) of Patients in Post-Operation Time After Intrathecal Injection of Dexmedetomidine (DEX), Fentanyl (F) and Marcaine (M) Bupivacaine as The Control Group



P value for DEX versus F and M groups is less than 0.05.

Sedation scale was measured using Ramsay sedation score at zero, one, two and three hours after intrathecal injection. Sedation score was significantly better in the DEX group compared to the fentanyl and control groups ( $P < 0.05$ ) in two and three hours but not in zero and one hours ( $P > 0.05$ ) (Figure 6).

Post-operative pain score was measured using visual analogue scale (VAS) at one, three, six and 24 hours after surgery. VAS scores in the DEX group at three and six hours post operation time were significantly lower than those of the fentanyl group ( $P < 0.05$ ); Besides, at one, three and six hours, VAS scores in the DEX group were significantly lower than those of the control group ( $P < 0.05$ ). VAS scores in the Fentanyl group at one, three and six hours were significantly lower than those of the control group ( $P < 0.05$ ) (Figure 7).

**Table 2.** Morphine Requirement in the Groups of Study

Time, h	DEX	Fentanyl	Bupivacaine <sup>a</sup>	P value
0	2.1 ± 2.34	6.6 ± 3.2	6.4 ± 0.86	< 0.05 <sup>b</sup>
1	2.6 ± 2.23	6.1 ± 2.2	5.95 ± 1.51	< 0.05 <sup>c</sup>
12	2.3 ± 2.12	3.5 ± 2.6	3.75 ± 2.5	> 0.05
<b>Total 24</b>	9.1 ± 2.5	16.3 ± 3.2	18.3 ± 3.9	< 0.05 <sup>d</sup>

<sup>a</sup>Bupivacaine is the control group.

<sup>b</sup>ANOVA post-hoc test: DEX vs. Fentanyl:  $P = 0.02$ ; DEX vs. Marcaine:  $P = 0.001$ .

<sup>c</sup>ANOVA post hoc-test: DEX vs. Fentanyl:  $P = 0.003$ ; DEX vs. Marcaine:  $P = 0.015$ .

<sup>d</sup>ANOVA post-hoc test: DEX vs. Fentanyl:  $P = 0.001$ ; DEX vs. Marcaine:  $P = 0.002$ .

Total morphine requirement dose in the DEX group was significantly lower than those of the fentanyl and control groups at zero and one hour (Table 2). However, at 12 hour post-operation morphine requirement was not significantly lower in the DEX group compared to fentanyl and control groups ( $P > 0.05$ ) (Table 2). Total morphine dose in 24 hours was significantly lower in the DEX group as compared to fentanyl and control groups ( $P < 0.05$ ) (Table 2).

Incidence of post-operative nausea and vomiting (PONV) in the DEX, fentanyl and control groups were 14.5%, 38.5% and 22.5%, respectively (Mann-Whitney). PONV was significantly lower in the DEX group compared to fentanyl ( $P = 0.03$ ) and control groups ( $P = 0.022$ ) (Table 2).

## 5. Discussion

The current study attempted to compare dexmedetomidine (DEX) and fentanyl as the appropriate adjunct drugs for spinal block in addicted patients. Addicted patients may need higher doses of bupivacaine in combination with an adjunct drug. The results showed that an adjunct dose of dexmedetomidine significantly enhanced onset and duration of block, stabilized vital signs and provided more appropriate sedation; besides it decreased post operation pain, post operation morphine requirement and the incidence of PONV compared to addition of fentanyl to bupivacaine or bupivacaine alone.

The current study results showed a substantial effect of DEX adjunct to bupivacaine in shortening the onset of block and increasing the duration of block compared to those of the fentanyl additive or bupivacaine alone. Although the exact mechanism of DEX additive is not clear in intrathecal injection, however its strong and significant effect on improving the quality and quantity of spinal block in addicted patients suggests a direct anesthetic action of this drug. Zhang et al. attempted to find intrathecal action site for DEX (14), they suggested a direct action for DEX on motor neurons or posterior horn neurons or their synapses in spinothalamic pathway (15). The second theory was that DEX increases duration



of block through indirect action. It means that  $\alpha_2$  agonist activation affect other receptors inside spinal canal such as Na-K exchange channels and acetylcholine receptors (16, 17). Another mechanism also suggested for DEX including antinociception and vasoconstriction (18). Significant effect of DEX on shortening onset and increasing duration of neuraxial block could be the same as its effect on increasing peripheral nerve block duration. On the other hand, intrathecal additives of opioids gained much popularity (19), due to their significant effects on increasing the duration of blocks in addicted patients. However, the current study showed superiority of intrathecal DEX to fentanyl when used in addicted patients, consistent with other studies (20).

Pain and sedation scales were improved in the DEX patients compared to those of fentanyl and control groups. Patients in the DEX group were mostly calm and sedated even better than the ones in the fentanyl group. Sedative effects of systemic DEX were proved in many previous studies, but the current study showed significant sedative effects of DEX when used in intrathecal injections. Better sedation scale could be the result of both anxiolytic and analgesic effects of intrathecal DEX simultaneously. Sedative effects of intrathecal DEX could be mediated by interacting with its receptors in locus coeruleus through circulation of cerebrospinal fluid (CSF) (21).

Opium sparing effect is of particular importance in addicted patients due to less withdrawal symptoms and side effects. Besides, patients in the DEX group showed lower pain scores which could result in less withdrawal and agitation symptoms after surgery, consistent with other studies (22, 23). Opium sparing effects of dexmedetomidine was also one of the important aspects of the current study. Opium addicted patients have tolerance and dependence to opium. Morphine doses were significantly lower in the DEX group compared to midazolam group. In addition,  $\alpha_2$  agonists such as clonidine and DEX are useful to alleviate withdrawal symptoms in addicts and controlling postoperative pain when added to morphine pumps (24).

Patients' hemodynamics remained more stable in the DEX group compared to those of the midazolam group, which gives advantage to DEX in these patients. DEX has sympatholytic effects (25) and hypothetically could depress blood pressure and heart rate. However, patients in the DEX group had significantly higher blood pressure and heart rate, which was consistent with other studies (26). This is of particular importance while systemic DEX could induce profound hypotension and bradycardia. The current study used adjusted intrathecal dose of DEX which could be a complete different entity. In addition, oxygen saturation and respiratory rate were higher in the DEX group compared to the fentanyl and control groups, as expected.

One other interesting result of the study showed that DEX decreased PONV incidence as compared to intrathecal fentanyl. This is of particular importance in both ad-

dicted and non-addicted patients. Intrathecal fentanyl induces PONV as a major side effect in many patients (27).

No adverse neurologic problems were observed in any of the patients; however longer follow-ups and experimental studies could determine all adverse neurologic deficits. Future studies are needed to further explore the exact mechanism of intrathecal fentanyl and dexmedetomidine site of action and neurologic pathway, particularly in addicted patients.

In conclusion, dexmedetomidine added to bupivacaine in spinal anesthesia was more effective to increase the duration of block, provide more appropriate sedation and less postoperative pain scale and PONV compared to fentanyl additive.

## Footnote

**Authors' Contribution:**Suggested the study design: Farhad Safari; performed data collection: Hasan Safdari and Farshad Farivar; performed data analysis: Kamran Mottaghi; interpretation and statistics: Reza Aminnejad; performed critical revision and manuscript approval: Seyed Amir Mohajerani.

## References

- Rodriguez J, Barcena M, Lagunilla J, Alvarez J. Increased success rate with infraclavicular brachial plexus block using a dual-injection technique. *J Clin Anesth.* 2004;**16**(4):251-6. doi: 10.1016/j.jclinane.2003.08.006. [PubMed: 15261314]
- Narita M, Imai S, Nakamura A, Ozeki A, Asato M, Rahmadi M, et al. Possible involvement of prolonging spinal micro-opioid receptor desensitization in the development of antihyperalgesic tolerance to micro-opioids under a neuropathic pain-like state. *Addict Biol.* 2013;**18**(4):614-22. doi: 10.1111/j.1369-1600.2011.00354.x. [PubMed: 21812868]
- Mirkheshti A, Saadatniaki A, Salimi A, Manafi Rasi A, Memary E, Yahyaei H. Effects of dexmedetomidine versus ketorolac as local anesthetic adjuvants on the onset and duration of infraclavicular brachial plexus block. *Anesth Pain Med.* 2014;**4**(3):e17620. doi: 10.5812/aapm.17620. [PubMed: 25237638]
- Ishikawa S, Kugawa S, Neya K, Suzuki Y, Kawasaki A, Hayama T, et al. Hemodynamic effects of dexmedetomidine in patients after cardiac surgery. *Minerva Chir.* 2006;**61**(3):215-9. [PubMed: 16858303]
- Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *Eur J Pharmacol.* 1988;**150**(1-2):9-14. [PubMed: 2900154]
- Agarwal S, Aggarwal R, Gupta P. Dexmedetomidine prolongs the effect of bupivacaine in supraclavicular brachial plexus block. *J Anaesthesiol Clin Pharmacol.* 2014;**30**(1):36-40. doi: 10.4103/0970-9185.125701. [PubMed: 24574591]
- Esmooglu A, Mizrak A, Akin A, Turk Y, Boyaci A. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. *Eur J Anaesthesiol.* 2005;**22**(6):447-51. [PubMed: 15991508]
- Solanki SL, Goyal VK. Neuraxial dexmedetomidine: wonder drug or simply harmful. *Anesth Pain Med.* 2015;**5**(2):e22651. doi: 10.5812/aapm.22651. [PubMed: 25866711]
- Chin KJ, Singh M, Velayutham V, Chee V. Infraclavicular brachial plexus block for regional anaesthesia of the lower arm. *Cochrane Database Syst Rev.* 2010(2):CD005487. doi: 10.1002/14651858.CD005487.pub2. [PubMed: 20166075]
- Iskandar H, Guillaume E, Dixmerias F, Binje B, Rakotondriamihary S, Thiebaut R, et al. The enhancement of sensory blockade by clonidine selectively added to mepivacaine after midhumeral block. *Anesth Analg.* 2001;**93**(3):771-5. [PubMed: 11524354]

11. Casati A, Magistris L, Beccaria P, Cappelleri G, Aldegheri G, Fanelli G. Improving postoperative analgesia after axillary brachial plexus anesthesia with 0.75% ropivacaine. A double-blind evaluation of adding clonidine. *Minerva Anesthesiol.* 2001;**67**(5):407-12. [PubMed: 11382830]
12. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study. *Br J Anaesth.* 2005;**94**(1):112-6. doi: 10.1093/bja/aei009. [PubMed: 15516351]
13. Sariguney D, Mahli A, Coskun D. The extent of blockade following axillary and infraclavicular approaches of brachial plexus block in uremic patients. *J Clin Med Res.* 2012;**4**(1):26-32. doi: 10.4021/jocmr723w. [PubMed: 22383924]
14. Zhang H, Zhou F, Li C, Kong M, Liu H, Zhang P, et al. Molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and its neurotoxicity evaluation: an in vivo and in vitro experimental study. *PLoS One.* 2013;**8**(2):e55556. doi: 10.1371/journal.pone.0055556. [PubMed: 23409000]
15. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. *J Anaesthesiol Clin Pharmacol.* 2013;**29**(4):496-502. doi: 10.4103/0970-9185.119151. [PubMed: 24249987]
16. Chen BS, Peng H, Wu SN. Dexmedetomidine, an alpha2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current. *Br J Anaesth.* 2009;**103**(2):244-54. doi: 10.1093/bja/aep107. [PubMed: 19542547]
17. Oda A, Iida H, Tanahashi S, Osawa Y, Yamaguchi S, Dohi S. Effects of alpha2-adrenoceptor agonists on tetrodotoxin-resistant Na<sup>+</sup> channels in rat dorsal root ganglion neurons. *Eur J Anaesthesiol.* 2007;**24**(11):934-41. doi: 10.1017/S0265021507000543. [PubMed: 17568475]
18. Sezer Z, Sezer G, Tekol Y. Ephedrine enhances the antinociceptive effect of dexmedetomidine in mice. *Neuro Endocrinol Lett.* 2011;**32**(4):552-6. [PubMed: 21876510]
19. Gupta S, Sampley S, Kathuria S, Katyal S. Intrathecal sufentanil or fentanyl as adjuvants to low dose bupivacaine in endoscopic urological procedures. *J Anaesthesiol Clin Pharmacol.* 2013;**29**(4):509-15. doi: 10.4103/0970-9185.119158. [PubMed: 24249989]
20. Mohamed AA, Fares KM, Mohamed SA. Efficacy of intrathecally administered dexmedetomidine versus dexmedetomidine with fentanyl in patients undergoing major abdominal cancer surgery. *Pain Physician.* 2012;**15**(4):339-48. [PubMed: 22828688]
21. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. *Minerva Anesthesiol.* 2014;**80**(1):96-112. [PubMed: 23839318]
22. Trevor S, Upadya M, Sinha C, Kaur M. A comparison of midazolam and clonidine as an oral premedication in pediatric patients. *Saudi J Anaesth.* 2012;**6**(1):8-11. doi: 10.4103/1658-354X.93045. [PubMed: 22412769]
23. Tazeroualti N, De Groote F, De Hert S, De Ville A, Dierick A, Van der Linden P. Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. a prospective, randomized, controlled trial. *Br J Anaesth.* 2007;**98**(5):667-71. doi: 10.1093/bja/aem071. [PubMed: 17416907]
24. Imani F, Rahimzadeh P, Faiz SH. Comparison of the efficacy of adding clonidine, chlorpromazine, promethazine, and midazolam to morphine pumps in postoperative pain control of addicted patients. *Anesth Pain Med.* 2011;**1**(1):10-4. doi: 10.5812/kowsar.22287523.1336. [PubMed: 25729649]
25. Heinmiller LJ, Nelson LB, Goldberg MB, Thode AR. Clonidine premedication versus placebo: effects on postoperative agitation and recovery time in children undergoing strabismus surgery. *J Pediatr Ophthalmol Strabismus.* 2013;**50**(3):150-4. doi: 10.3928/01913913-20130205-02. [PubMed: 23394604]
26. Niu XY, Ding XB, Guo T, Chen MH, Fu SK, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: a meta-analysis. *CNS Neurosci Ther.* 2013;**19**(11):897-904. doi: 10.1111/cns.12172. [PubMed: 24118775]
27. Kim JE, Kim NY, Lee HS, Kil HK. Effects of intrathecal dexmedetomidine on low-dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostatectomy. *Biol Pharm Bull.* 2013;**36**(6):959-65. [PubMed: 23727917]