Comparison of Dexmedetomidine Versus Dexamethasone as Adjuvants to IntrathecalBupivacaine in Emergency Orthopedic Lower Limb Operations

Mohamed E. Elshahawy, Hani I. Taman, Mostafa S. Elawady, Ahmed M. Farid*
Anaesthesia and Surgical Intensive Care Department, Faculty of Medicine, Mansoura University, Egypt
***Corresponding author:** Ahmed M. Farid, **Mobile:** (+20)1002356222, **E-Mail:** ahmfarid15@hotmail.com

ABSTRACT

Background: Various adjuvants were added to intrathecal anesthetics to improve quality of the block and postoperative analgesia.

Objective: The aim of the current work was to compare the efficacy of adding dexmedetomidine versus dexamethasone as adjuvants to intrathecal bupivacaine in emergency orthopedic lower limb surgery.

Patients and Methods: This prospective comparative double blinded study included a total of 90 patients with lower limb trauma requiring surgery, attending at Mansoura University emergency Hospital. Cases were randomly divided into three groups; each consisted of 30 cases. **Group A** received dexmedetomidine as an adjuvant tobupivacaine, **Group B** received dexamethasone as anadjuvant, and **Group C** received spinal bupivacaine plus1 cm of normal saline. Sensory and motor blocks as well as post-operative VAS score in addition to need for analgesics were assessed.

Results: Demographic data did not differ between the three study groups ($p > 0.05$).Group A showed a significantly earlier onset of sensory block ($p = 0.005$), motor block ($p = 0.009$), as well as late regression to L1 sensory level ($p < 0.001$). Additionally, longer analgesia ($p < 0.05$) and longer time before the first call for analgesics ($p = 0.005$) was associated with group A. However, complicationsencountered did not differ between the three study groups ($p > 0.05$).

Conclusion: It could be concluded that intrathecal dexmedetomidine is superior to both dexamethasone and bupivacaine alone regarding duration of analgesia and pain severity. Moreover, it has more rapid onset and longer duration of sensory blockade. No significant side effects were noted when compared to the remaining groups.

Keywords: Adjuvants, Intrathecal, Emergency, Orthopedic, Analgesia.

INTRODUCTION

Although lower limb procedures can be conducted under local or general anesthesia, neuraxial blocking is the preferable approach. Spinal blockade is distinguished by its cost-effectiveness, fast start, and ability to achieve deep block with a lesser risk of infection. Nonetheless, because the medications used for this sort of block have a short duration of effect, the patient's experience with post-operative pain is critical. As a result, pain management requires the use of postoperative analgesics [1,2].

Multiple adjuvants have been proposed to extend the duration of action and lessen the negative effects of local anesthetic medicines [3]. Opioids, alpha 2 agonists, steroids, neostigmine, and vasoconstrictors are examples of adjuvants [2, 4].

Clonidine and dexmedetomidine are two 2 agonists that impact 2 receptors pre- and post-synaptically [5]. Dexmedetomidine is a 7-fold more selective alpha•2 receptor agonist than clonidine and works in a similar way to block hyperpolarization activated cation channels. Dexmedetomidine has a long history of usage as an analgesic and anesthetic. It is known for its analgesic, anti-anxiety, neuroprotective, and anesthetic sparing properties [6]. Additionally, it was utilized to prolong analgesia in epidural, subarachnoid, and caudal blocks [7,8]. Intrathecal dexmedetomidine has been demonstrated to have a longer duration of block. It also enhanced postoperative analgesia without causing any major side effects, especially when given at dosages of less than 5g [9].

Dexamethasone is a strong anti-inflammatory drug that has been studied for its function as an adjuvant to local anesthetics in neuraxial and peripheral nerve blocks throughout the last decade [10].

Steroids' methods for potentiating analgesic effects appear to be distinct from its inherent anti-inflammatory activity [11, 12]. There's additional evidence that dexamethasone's analgesic actions are amplified by both local and systemic effects on nerve fibers [13].

Research compared the effects of 8 mg (preservative-free) intrathecal dexamethasone with conventional dosages of 0.5 percent hyperbaric bupivacaine in orthopedic procedures. It has been proven to extend the duration of sensory block in spinal anesthesia without causing any notable side effects [14].

This study was aimed to compare the efficacy of adding dexmedetomidine compared with dexamethasone to intrathecal bupivacaine regarding duration of anesthesia and post-operative analgesia for emergency lower limb orthopedic operations.

PATIENTS AND METHODS

This prospective comparative double blinded study included a total of 90 patients with lower limb trauma requiring surgery, attending at Mansoura University emergency Hospital. Cases were randomly divided into three groups; each consisted of 30 cases.

Group A received dexmedetomidine as an adjuvant to bupivacaine, **Group B** received dexamethasone as anadjuvant, and **Group C** received spinal bupivacaine plus1 cm of normal saline.

***Ethical Consideration*:**

An approval from Institutional Review Board (IRB-MFM) of Mansoura University, Faculty of

Received: 09/12/2021
Accepted: 08/02/2022

Medicine with code number (R/16.12.32, March 2017) was obtained. Every patient signed an informed written consent for acceptance of participation in the study. Ethics guidelines for human experimentation were adhered to in line with the Helsinki Declaration of the World Medical Association.

Inclusion criteria: Age range between 20 and 60 years, scheduled for orthopedic lower limb surgery with ASA scores 1 and 11.

Exclusion criteria: Patients outside the previously mentioned range, presence of any contraindication for regional anesthesia, history of allergyto one of the study medications, and cases with severe cardiac, renal, or hepatic illness.

Patient preparation:

Before surgery, the patients were transferred to the operation theater, and they were connected to all noninvasive monitors. Pulse, non-invasive arterial blood pressure (BP) as well as oxygen saturation were noted for every patient. Moreover,electrocardiography monitoring was enabled. All cases were preloaded with 10 ml/kg Ringer's lactate.

Procedure:

Under strict aseptic precaution, 25-gauge spinal needle was inserted in L3-L4 interspinal space with patient in sitting position using a midline approach. After confirmation with free flow of cerebrospinal fluid, patients allocated to Group A were injected by bupivacaine 0.5% heavy × 3.0 ml + 1 ml of preservative free normalsaline containing 5 µg dexmedetomidine. Patients allocated to Group B received injection bupivacaine 0.5% heavy × 3.0 ml + 1 ml fentanyl equivalent to 4 mg. In addition, Patients in group C received bupivacaine 0.5% heavy × 3.0 ml + 1 ml of normal saline.

Intraoperative complaints were managed by increments of fentanyl 25 µg,midazolam 1–2 mg, and propofol 50 mg in consequence as required. General anesthesia was applied using a laryngeal mask and sevoflurane inhalation if the patient still cannot tolerate pain, and these patients excluded from the study.

Outcome measures:

VAS score was the primary outcome and it was measured at different time points (2h, 4h, 6h, 8h, 10h, 12h, and 24 hours postoperatively). The secondary outcome included the effect of these adjuvants on sensory and motor blockade. If the postoperative VAS was higher than 3, it was treated by analgesics according to the WHO analgesic ladder.

Bromage scale (0–3)[15]: 0: The patient is able to move the hip, knee and ankle. 1: The patient is unable to move the hip, but can move knee and ankle. 2: The patient is unable to move the hip and knee but can move the ankle.3: The patient cannot move the hip, knee and ankle.

Complications:

Hypotension was defined as a mean arterial blood pressure (MAP) < 60 mmHg, and it was managed by bolus doses of ephedrine 5 mg, fluids and blood transfusion as indicated. Bradycardia was defined as heart rate (HR) < 60 b/min, and it was managed by atropine 0.5 mg increments. Desaturation was defined as SaO2 <90% and managed by an oxygen face mask. Vomiting was treated with metoclopramide 10 mg or granisetron 1 mg if persistent.

Statistical analysis

Data were analyzed by SPSS software version 24. Qualitative data were expressed as number and percentage within group. Quantitively data were tested fornormality using Kolmogorov Smirnov test and they were expressed as mean±standard deviation or median and range. Comparison between the quantitative data ofthree study groups was carried out by one-way ANOVA test. Qualitative data werecompared between the three groups using Chi square test. P value < 0.05 was considered significant in all used tests.

RESULTS

Regarding demographics, there were no significant differences between the three study groups when it comes to age, sex, or BMI (p > 0.05) (Table 1).

Table (1): Baseline findings.

	Group A (n = 30)	Group B (n = 30)	Group C(n = 30)	P value
Age (years)	34.86 ± 11.68	36.27 ± 14.59	41.00 ± 12.82	0.170
Gender				
-Male	21 (70%)	19 (63.33%)	18 (60%)	
-Female	9 (30%)	11 (36.67%)	12 (40%)	0.274
BMI (kg/m^2)	22.23 ± 3.32	25.22 ± 3.45	25.74 ± 7.59	0.248

When compared to groups B and C, group A reported a faster start of sensory blocking at the T 10 level (p = 0.005) and a shorter duration to reach maximal sensory intensity. In addition, Group B had a faster start of sensory block and a shorter time to reach maximal block than Group C. Despite this, there was no significant difference in the highest sensory level attained across the three groups. When compared to the other groups, Group A had a considerably longer duration for sensory block regression down to the L1 dermatome (p 0.001), and the same when comparing Group B to Group C. (Table 2).

Table (2): Sensory block characteristics.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value
Mean onset time of sensory blockade at T10 (min)	4.44±0.81	6.82±0.56*	8.44±1.46†‡	0.005
Maximumsensory level achieved	T5 (5-6)	T6 (5-6)	T6 (5-6)	0.824
Time to achieve maximum sensory level (min)	9.80±0.62	12.69±0.72*	15.06±1.82†‡	0.001
Mean time to regression to L1 dermatome (min)	295.08±39.77	208.80±42.76*	191.69±27.08‡	0.001

*P<0.05 when group B compared to group A. †P<0.05 when group C compared to group A.
‡P<0.05 when group C compared to group B.

When compared to the other groups, group A had a significantly earlier start of motor block (p = 0.003). The three research groups had the same maximum Bromage score. When compared to the other two groups, group A had a substantially longer total time of motor blockage (p 0.001) (Table 3).

Table (3): Motor block characteristics.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value
Mean onset time of motor block (min)	9.33±0.61	12.09±2.03*	13.36±3.16†	0.003
Maximum Bromage scale	3	3	3	1
Total durationof motor block (min)	229.2±35.4	181.3±22.5*	167.89±29.05†	<0.001

*P<0.05 when group B compared to group A. †P<0.05 when group C compared to group A.
‡P<0.05 when group C compared to group B.

Although postoperative pain scores did not differ between the three study groups during the early 8 hours after operation (p > 0.05). However, 10-. 12-, and 24-hour VAS scores were significantly lower for group A when compared to group B and C (Table 4).

Table (4): Post-operative VAS scores.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value
2h	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	1
4h	2 (1 – 3)	2 (1 – 4)	2 (2 – 4)	0.245
6h	3 (2 – 4)	3 (3 – 4)	3 (3 – 4)	0.226
8h	3 (3 - 4)	4 (3 – 4)	4 (3 – 4)	0.156
10h	3 (3 – 4)	4 (3 – 5)*	5 (4 – 6)†	0.039
12h	3 (3 – 4)	4 (4 – 5)*	5 (4 – 6)†	0.018
24h	4 (3 – 4)	5 (4 – 6)*	6 (4 – 7)†	0.008

*P<0.05 when group B compared to group A. †P<0.05 when group C compared to group A.
‡P<0.05 when group C compared to group B.

Adverse effects including bradycardia, hypotension, as well as nausea and vomiting did not differ between the three study groups (Table 5).

Table (5): Adverse effects.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value
Bradycardia	3 (10%)	2 (6.67%)	3 (10%)	0.756
Hypotension	2 (6.67%)	3 (10%)	3 (10%)	0.698
Nausea and vomiting	2 (6.67%)	2 (6.67%)	2 (6.67%)	1

*P<0.05 when group B compared to group A. †P<0.05 when group C compared to group A.
‡P<0.05 when group C compared to group B.

Post-operative call for analgesics took longer time for group A compared to other study groups (p = 0.005) and in group B when compared to C group (Table 6).

Table (6): post-operative call for analgesics.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value
Time to firstcall for analgesics (hours)	4.93 ± 1.86	2.86 ± 0.79*	2.41 ± 0.78†‡	0.001

DISCUSSION

Surgery is frequently associated with a high rate of pain. Previous research found that in industrialized nations, 41-61% of patients have moderate or severe postoperative pain [16].

Adjuvant to local anesthetics is a rapidly changing and interesting field of anesthesia, with new technologies promising to increase patient pleasure and safety. While opioids are still the most widely used local anesthetic adjuvants in clinical practice, alpha•2 receptor antagonists, particularly dexmedetomidine, have been found to augment the efficacy of local anesthetics while maintaining a safe profile [10].

Our study included 90 cases who were divided into three groups each included 30 cases. The first group received dexmedetomidine as an adjuvant, the second one received dexamethasone as an adjuvant, and the last group received bupivacaine alone. Age and sex distribution did not differ significantly between thethree study groups ($p > 0.05$).

Another study examined the effectiveness of adding dexmedetomidine to bupivacaine against dexamethasone to extend the duration of spinal anesthesia and analgesia during lower abdominal surgeries. A total of 60 cases were studied, with one group receiving dexmedetomidine as an adjuvant, another receiving dexamethasone as an adjuvant, and the third group receiving simply bupivacaine without any adjuvants. There was no significant difference between the three groups in terms of baseline variables (age and sex) ($p > 0.05$) in that research [17].

In our study, mean time of onset of sensory blockade in the dexmedetomidine group was 4.52 minutes and it was significantly shorter than the other two groups ($p= 0.005$). Moreover, time elapsed till reaching the maximum level of sensory blockade was 9.95 minutes ($p = 0.001$). In addition, mean time to regression to L1 dermatome was 302.44 minutes ($p < 0.001$).

Another study discovered that the time it took for sensory block to begin was 4.85 minutes, which was considerably less than the Mg sulphate group ($p <0.001$). The average time it took to attain the maximal sensory level was 10.03 minutes ($p <0.001$). Furthermore, the dexmedetomidine group's mean time for regression to the L1 dermatome was substantially longer (290.3 minutes – $p< 0.001$) [18].

Regarding motor block in our study, mean onset of block was achieved after 9.35 minutes in the dexmedetomidine group ($p = 0.009$). Furthermore, total durationof motor block was significantly longer for the same group ($p < 0.001$).

Makhni *et al.* [18] found that, the average onset of motor block was 9.02 minutes, which was substantially longer than the Mg sulphate group (p 0.001). The average duration of the motor block was 224.2 minutes ($P <0.05$).

The current study found that dexmedetomidine was associated with faster onset of both sensory and motor blockade. Moreover, it was associated with prolonged post-operative analgesia compared to dexamethasone and bupivacaine alone. Addition of dexamethasone was better than bupivacaine alone regarding the same perspectives. However, it was inferior to dexmedetomidine.

Because dexmedetomidine is a highly selective agonist of the 2-adrenergic receptor, it can extend sensory and motor blockage. Sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing characteristics are also present [19]. It also has the benefit of not causing respiratory depression [20]. It stimulates 2-adrenergic receptors in the superficial dorsal horn neurons in the spinal cord [21]. It inhibits pain transmission directly by inhibiting the release of pronociceptive transmitters, substance P, and glutamate from primary afferent terminals, as well as hyperpolarizing spinal interneurons through G-protein-mediated potassium channel activation [22].

The possible explanation of the effect of adding dexmedetomidine to intrathecal bupivacaine lies in its synergistic effect being selective α2-adrenergic receptor agonist, which binds to the presynaptic C-fibers and postsynaptic dorsal horn neurons. Thus, it produces analgesia by depressing the release of C-fiber transmitters, hyperpolarization of postsynaptic dorsal horn neurons, whereas bupivacaine as a local anesthetic act by blocking sodium channels [23].

The study results went in line with the study conducted by **Shukla *et al.*** [24] who compared dexmedetomidine versus magnesium sulfate added to intrathecal bupivacaine and found that dexmedetomidine shortened the onset and prolonged theduration of spinal anesthesia. Also, **Solanki *et al.*** [25] study proved superiority of intrathecal dexmedetomidine in comparison with clonidine and fentanyl. It provided prolonged motor and sensory block and reduced demand of additional analgesics.

The current study results were in agreement with the two studies comparing clonidine and dexmedetomidine in different doses (5 and 3 μg,

respectively) as adjuncts to bupivacaine. Both found the duration of sensory and motor block to be prolonged with dexmedetomidine compared with clonidine. Postoperative analgesiawas comparable in these two groups and superior compared with bupivacaine alone [26, 27].

Makhni *et al.* [18] study found that dexmedetomidine was associated with faster sensory and motor blocks. In addition, the total duration of analgesia was significantly betterwhen compared to Mg sulphate group.

Almost all of the previously mentioned studies as well as the current study confirmed safety and hemodynamic stability of dexmedetomidine, whether administered intravenously or intrathecally as an adjuvant to spinal bupivacaine anesthesia.

In our study, the detected complications (bradycardia, hypotension, as well as nausea and vomiting) did not differ significantly between the three groups. Moreover, they occurred with a low incidence as no one of such complications occurred in more than 10% of cases in each group. In addition, these complications were properly managed as discussed in patients and methods.

On the contrary, in this study, dexamethasone was found to prolong the sensory blockade and prolong the time to first call for analgesia when added to intrathecal bupivacaine compared with bupivacaine alone.

Intrathecal dexamethasone as an analgesic could be explained by influencing prostaglandin production. Corticosteroids are capable of reducing prostaglandin synthesis by inhibition of phospholipase A2 through the production of calcium-dependent phospholipid-binding proteins called annexins, and by the inhibition of cyclooxygenases during inflammation [28].

The results of the current study regarding dexamethasone went in line with astudy conducted by **Bani-Hashem *et al.*** [14] who reported an increase in the duration of sensory block associated with the addition of intrathecal dexamethasone.

CONCLUSION

It could be concluded that intrathecal dexmedetomidine is superior to both dexamethasone andbupivacaine alone regarding duration of analgesia and pain severity. Moreover, it has more rapid onset and longer duration of sensory blockade. No significant side effects were noted when compared to the remaining groups.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Boussofara M, Carlès M, Raucoules-Aimé M *et al.* (2006):** Effects of intrathecal midazolam on postoperative analgesia when added to a bupivacaine-clonidine mixture. Reg Anesth Pain Med., 31(6):501-05.
2. **Elia N, Culebras X, Mazza C *et al.* (2008):**Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. Regional Anesthesia and Pain Medicine, 33(2): 159-167.
3. **Faiz S, Rahimzadeh P, Sakhaei M *et al.* (2012):** Anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities surgeries. Journal of Research in Medical Sciences: the Official Journal of Isfahan University of Medical Sciences, 17(10): 918-24.
4. **Rahimzadeh P, Faiz S, Imani F *et al.* (2018):** Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. BMC Anesthesiology, 18(1): 62-66.
5. **Shah A, Patel I, Gandhi R (2013):** Haemodynamic effects of intrathecal dexmedetomidine added to ropivacaine intraoperatively and for postoperative analgesia. Int J Basic Clin Pharmacol., 2(1): 26-29.
6. **Panzer O, Moitra V, Sladen R (2011):** Pharmacology of sedative- analgesic agents: dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Anesthesiology Clinics, 29(4): 587-605.
7. **Bekker A, Sturaitis M, Bloom M *et al.* (2008):** The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. Anesthesia & Analgesia, 107(4): 1340-1347.
8. **Sudheesh K, Harsoor S (2011):** Dexmedetomidine in anaesthesia practice: A wonder drug? Indian Journal of Anaesthesia, 55(4): 323-27.
9. **Niu X, Ding X, Guo T *et al.* (2013):** Effects of Intravenous and Intrathecal Dexmedetomidine in Spinal Anesthesia: A Meta-Analysis. CNS Neuroscience & Therapeutics, 19(11): 897-904.
10. **Swain A, Nag D, Sahu S *et al.* (2017):** Adjuvants to local anesthetics: Current understanding and future trends. World Journal of Clinical Cases, 5(8): 307-11.
11. **McCormack K (1994):** The spinal actions of nonsteroidal anti-inflammatory drugs and the dissociation between their anti-inflammatory and analgesic effects. Drugs, 47(5): 28-45.
12. **Ahlgren S, Wang J, Levine J (1996):** C-fiber mechanical stimulus–response functions are different in inflammatory versus neuropathichyperalgesia in the rat. Neuroscience, 76(1): 285-290.
13. **Kopacz D, Lacouture P, Wu D *et al.* (2003):** The dose response and effects of dexamethasone on bupivacaine microcapsules for intercostal blockade (T9 to T11) in healthy volunteers. Anesth Analg., 96(2):576-82.
14. **Bani-Hashem N, Hassan-Nasab B, Pour E *et al.* (2011):** Addition of intrathecal Dexamethasone to Bupivacaine for spinal anesthesia in orthopedic surgery. Saudi Journal of Anaesthesia, 5(4): 382-86.
15. **Bromage P (1965):** A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiologica Scandinavica, 9: 55-69.
16. **Sommer M, De Rijke J, Van Kleef M *et al.* (2008):** The prevalence of postoperative pain in a sample of

1490 surgical inpatients. European Journal of Anaesthesiology, 25(4): 267-274.

17. **Elzayyat N, Nagy H, Girgis K (2014):** Comparing the effect of adding dexmedetomidine versus dexamethasone on prolonging the duration of intrathecal bupivacaine in lower abdominal operations. Ain Shams Journal of Anaesthesiology, 7(3): 388-93.
18. **Makhni R, Attri J, Jain P *et al.* (2017):** Comparison of dexmedetomidine and magnesium sulfate as adjuvants with ropivacaine for spinal anesthesia in infraumbilical surgeries and postoperative analgesia. Anesthesia, Essays and Researches, 11(1): 206-211.
19. **Khan Z, Ferguson C, Jones R (1999):** Alpha-2 and imidazoline receptor agonistsTheir pharmacology and therapeutic role. Anaesthesia, 54(2): 146-165.
20. **Carollo D, Nossaman B, Ramadhyani U (2008):** Dexmedetomidine: a review of clinical applications. Current Opinion in Anesthesiology, 21(4): 457-461.
21. **Ishii H, Kohno T, Yamakura T *et al.* (2008):** Action of dexmedetomidine on the substantia gelatinosa neurons of the rat spinal cord. European Journal of Neuroscience, 27(12): 3182-3190.
22. **Stone L, Broberger C, Vulchanova L *et al.* (1998):** Differential distribution of α2A and α2C adrenergic receptor immunoreactivity in the rat spinal cord. Journal of Neuroscience, 18(15): 5928-5937.
23. **Kanazi G, Aouad M, Jabbour-Khoury S *et al.* (2006):** Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiologica Scandinavica, 50(2): 222-227.
24. **Shukla D, Verma A, Agarwal A *et al.* (2011):** Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. Journal of Anaesthesiology, Clinical Pharmacology, 27(4): 495.
25. **Solanki S, Bharti N, Batra Y *et al.* (2013):** The analgesic effect of intrathecal dexmedetomidine or clonidine, with bupivacaine, in trauma patients undergoing lower limb surgery: a randomised, double-blind study. Anaesthesia and Intensive Care, 41(1): 51-56.
26. **Al-Mustafa M, Badran I, Abu-Ali H *et al.* (2009):** Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East J Anesthesiol., 20(2): 225-231.
27. **Kaya F, Yavascaoglu B, Turker G *et al.* (2010):** Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Canadian Journal of Anesthesia, 57(1): 39-45.
28. **Yao X, Cowan M, Gladwin M *et al.* (1999):** Dexamethasone alters arachidonate release from human epithelial cells by induction of p11 protein synthesis and inhibition of phospholipase A2 activity. Journal of Biological Chemistry, 274(24): 17202-17208.