ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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# Comparing Effects of Midazolam and Dexmedetomidine Sedation on Ultrasound Guided Infraclavicular Nerve Block for Upper Extremity Orthopedic Surgeries

## Ultrasonografi Kılavuzluğunda İnfraklaviküler Blok ile Üst Ekstremite Ortopedi Cerrahisi Geçiren Hastalarda Midazolam ve Deksmedetomidin ile Sedasyonun Periferik Sinir Bloğu Üzerine Etkilerinin Karşılaştırılması

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**ABSTRACT Objective:** Sedation is an important step of regional anesthesia, the effects of sedative agents on nerve block characteristics are often subjects of scientific researches. In our study, we aimed to compare the effects of dexmedetomidine and midazolam sedation on sensory and motor onset and termination time after infraclavicular nerve block. **Material and Methods:** After local ethics committee approval and patients written informed consents were obtained, 60 patients between the ages of 18-65 years, with an American Society of Anesthesiologists (ASA) classification I-II who received infraclavicular nerve block randomized into two groups. Group D received 0.8 μg/kg bolus continued with 0.2-0.7 μg/kg/h of maintenance dose of dexmedetomidine group M received 0.05mg/kg bolus continued with 0.02-0.2 mg/kg/h of maintenance dose of midazolam. The patient's demographic data heart rate pulse, mean arterial pressure, sensory and motor block onset and termination time were analyzed. **Results:** Heart rate and mean arterial pressure were lower in dexmedetomidine group. Sensory (Group D: 8.6±2.4 Group M: 16.2±1.8) and motor block onset time (Group D: 14.2±1.6, Group M: 21.4±2.3) was shorter in dexmedetomidine group. Sensory (Group D: 715.4±41.1 min Group M: 518.1±44.2 min) and motor block termination time (Group D: 613.6±38.1 min Group M: 421.3±37.2 min) were longer in dexmedetomidine group. **Conclusion:** The use of dexmedetomidine for sedation on patients who received ultrasound-guided infraclavicular block for upper extremity surgeries resulted earlier onset time to sensory and motor block and prolonged sensory and motor block termination time.

**Keywords:** Dexmedetomidine; midazolam; infraclavicular nerve block

**ÖZET Amaç:** Rejyonel anestezinin önemli bir basamağı olan sedasyon amacıyla kullanılan sedatif ajanların sinir bloğu karakteristiğine etkileri sıklıkla bilimsel araştırmalara konu olmaktadır. Çalışmamızda, deksmedetomidin ve midazolam ile sedasyonun infraklaviküler sinir bloğu başlama ve sonlanma zamanına etkilerini karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Yerel etik kurul onayı ve yazılı bilgilendirilmiş onam formu alındıktan sonra, 18-65 yaş aralığında, Amerikan Anesteziyologlar Birliği (ASA) I-II grubu İnfraklaviküler blok yapılacak 60 hasta randomize edilerek iki gruba ayrıldı. Grup D'ye sedasyon amacıyla 0,8 μg/kg deksmedetomidin bolus sonrasında 0,2-0,7 μg/kg/saat idame tedavi verildi, Grup M'ye 0,05 mg/kg midazolam bolus sonrasında 0,02-0,2 mg/kg/saat idame tedavi verildi. Hastaların demografik verileri, kalp tepe atımı, ortalama arteriyel basınç, duyusal ve motor blok başlama ve sonlanma zamanı analiz edildi. **Bulgular:** Grupların demografik verileri benzerdir, kalp tepe atımı ve ortalama arteriyel basınç deksmedetomidin grubunda daha düşük bulundu. Duyusal (Grup D: 8,6±2,4 dk, Grup M: 16,2±1,8 dk) ve motor blok başlama zamanı (Grup D: 14,2±1,6 dk, Grup M: 21,4±2,3 dk) Deksmedetomidin grubunda midazolam grubuna göre daha kısa, duyusal (Grup D: 715,4±41,1 dk, Grup M: 518,1±44,2 dk) ve motor blok sonlanma zamanı (Grup D: 613,6±38,1 dk, Grup M: 421,3±37,2 dk) ise daha uzun olarak bulundu. **Sonuç:** Ultrasonografi kılavuzluğunda infraklaviküler blok yapılmış hastalarda sedasyon amacıyla deksmedetomidin kullanılması midazolama kıyasla, blok başlama süresini kısaltıp, blok sonlanma süresini uzatmaktadır.



**Anahtar Kelimeler:** Deksmedetomidin; midazolam; infraklaviküler sinir bloğu

Regional anesthesia methods are becoming more common every day as they cause earlier mobilization, higher analgesia quality, shorter hospital stay, lower postoperative nausea and vomiting compared to general anesthesia. Infraclavicular brachial plexus block is used as an anesthetic method to provide postoperative analgesia in addition to general anesthesia in patients undergoing upper extremity surgery.[1] With the use of ultrasound in anesthesia practice, as it could decreases the number of complications, decreases the number of interventions and volume of regional anesthetics, ultrasound-guided peripheral nerve blocks are becoming more and more common. One of the most important steps of regional anesthesia is adequate sedation. Patient positions and applications given during orthopedic surgery may be uncomfortable for the patient. Adequate sedation is essential to prevent complications caused by sympathetic nervous system activation due to fear and excitement. Benzodiazepines and alpha adrenergic receptor agonists are the most commonly used drug groups for sedation. Of these, the most commonly used benzodiazepine group is midazolam, and the alpha receptor agonists group is clonidine. The using of dexmedetomidine is increasing, since it is a more selective alpha 2 receptor agonist than clonidine.[2]

Dexmedetomidine is a selective alpha 2 adrenergic receptor agonist with sympatholytic and analgesic properties, which has been used for sedation as patients receiving mechanical ventilation support in intensive care units.[3] Over time, its use in operating rooms has been increased due to the reduction of the need for narcotic analgesics and its positive effects on peripheral nerve blocks. There are several studies concerning perineural use of dexmedetomidine which indicates prolonged nerve block time and shortened block initiation time.[4] The aim of our study is to analyze the effect of intravenous use of dexmedetomidine on block initiation time, block termination time, hemodynamic properties of patient and compare it with a widely used sedative; midazolam.

## MATERIAL AND METHODS

This study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Kanuni Sultan Süleyman Training and Research Hospital (Subject No: KAEK / 2018.3.23 No: 2018/3). The trial was conducted from April 2018 to June 2018 at the Siverek State Hospital, Sanliurfa, Turkey. The authors prepared this study report in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[5]

After obtaining the written informed consent, adult patients (aged 18 to 65 yr) with American Society of Anesthesiologists physical status classification I to II scheduled for upper extremity orthopedic surgery receiving infraclavicular nerve block were recruited. Exclusion criteria included ASA III and higher, patients younger than 18 years old, patients with history of drug abuse, failure to provide written informed consent, significant psychiatric or cognitive conditions interfering with consent or assessment; unstable coronary artery disease, congestive heart failure, or arrhythmias; preexisting neurological deficits or neuropathy affecting the brachial plexus, baseline heart rate (HR) less than 60 beats/min or baseline mean arterial pressure less than 60 mmHg; significant renal or hepatic impairment; severe bronchopulmonary disease, contraindications to peripheric nerve blocks, including local skin infections, bleeding diathesis, and coagulopathy; allergies to local anesthetics, dexmedetomidine, or any component of multimodal analgesia.

A doctor who has not involved with study randomized consented patients via using a closed enveloped. On the day of surgery research coordinator handed one envelope for patient to anesthesia assistant in procedure room who prepared all the study solutions. Anesthesia assistant had no further role in the study. Patients, anesthesiologist performing nerve block and research coordinator collecting data were blinded to the allocation results. Noninvasive blood pressure, electrocardiogram, and pulse oximetry were applied and IV access secured on the patient's

nonoperative side upon arrival to the block procedure room. The hemodynamic parameters as heart rates were continuously measured and the mean arterial pressure was measured and recorded every 5 minutes. When the mean blood pressure was decreased by more than 20% of baseline value, it was treated with 2.5 to 5 mg ephedrine, and the bradycardia marked by heart rate slower than 50 beats/min was treated with 0.25 to 0.5 mg atropine. All study participants received IV study solutions according to their group allocations as follows: Group D received dexmedetomidine 0.2-0.7 μg/kg/h maintenance therapy after 0.8 μg/kg bolus injection in 10 minutes. Group M received midazolam 0.02-0.2 mg/kg/h maintenance therapy after bolus with a dose of 0.05 mg/kg in 10 minutes. After bolus treatments, patients who had 3 points for Ramsay Sedation Scale received nerve block. (Table 1).[6] Preoperative infraclavicular block (ICB) was performed using ultrasound guidance, under sterile conditions, by same anesthesiologist experienced in ultrasound-guided nerve blocks.

When patient in the supine position, head is turned to the opposite side of the region to be applied. The arm is adducted and hand of placed on the patient's chest. Following disinfection of the region with povidone-iodine, the ultrasound probe (Esaote LA435 linear probe, 10-18 MHz, Florence, Italy) is disposed longitudinally to the recommended site for infraclavicular block application. When the cords of brachial plexus and axillary artery visualized, the 80-mm-long 22 G ultrasound-compatible nerve stimulation needle (Stimuplex® Ultra 360 ™-B. Braun Medical Inc.) is directed towards 7 o'clock of axillary artery, using inplane technic. First, 1 ml of local anesthetics is given and than remaining local anesthetic is given once the appropriate position is comfirmed. Triple injection is performed by using ultrasound, the local anesthetic is properly spread around each cord (lateral, posterior, medial). For a single limb, 10 ml of 2% lidocaine + 10 cc of 0.5% bupivacaine is given.

**TABLE 1:** Ramsay sedation scale.

| Score | Definition |
|---|---|
| 1 | Anxious and agitated or restless or both |
| 2 | Cooperative, oriented, and tranquil |
| 3 | Responds to commands only |
| 4 | Brisk response to a light glabellar tap or loud auditory stimulus |
| 5 | Sluggish response to a light glabellar tap or loud auditory stimulus |
| 6 | No response to a light glabellar tap or loud auditory stimulus |

All patients were examined for successful nerve block over C5-C7 dermatomes before being transferred to operating room. Test was performed using loss of sensation to pinprick (25 gauge needle) every 3 minutes over 20 minutes with comparing to nonoperating arm. Block success was defined as complete loss of sensation over forearm within 20 minutes after the nerve block. For patients whose block success was not achieved in 20 minutes block failure were documented and excluded from study. Fentanyl 1 μg/kg was used for rescue analgesia intra operatively.

Nerve block application time and time to sensory and motor block were noted before surgery. Intra operatively the duration of operation, the need for additional analgesia during the operation period, the presence of nausea and vomiting, were recorded. Postoperative nausea and vomiting (PONV) was treated with 2- 4 mg IV ondansetron.

All patients were transferred to post anesthetic care unit (PACU) after the surgery, where they stayed until they met discharge criteria which is 9 points in Modified Aldrete Scale (Table 2).[7]

Pain scores of patients were documented using VAS scale (VAS 0: no pain VAS:10 most severe pain in life) at postoperative 0. 4. 12. 24$^{th}$ hours, motor function is evaluated with Bromage scale at 0. 4. 12$^{th}$ hours.[8] Full muscle strength was considered as motor block termination time. 75 mg diclofenac sodium was given to patients with VAS scores 4 and above.

## STATISTICAL ANALYSIS

The primary outcome of our study is sensory and motor block duration. In a 10-series mini-series sensory block duration in the dexmedetomidine

**TABLE 2:** Modified aldrete scoring system.

| Criteria | Point value |
|---|---|
| **Oxygenation** | |
| SpO2>92% on room air | 2 |
| $SpO_2$>92% on room oxygen | 1 |
| $SpO_2$>92% on room oxygen | 0 |
| **Respiration** | |
| Breathes deeply and coughs freely | 2 |
| Dyspnoeic, shallow or limited breathing | 1 |
| Apnoea | 0 |
| **Circulation** | |
| Blood pressure ±20 mmHg of normal | 2 |
| Blood pressure ± 20-50 mmHg of normal | 1 |
| Blood pressure more than ± 50 mmHg of normal | 0 |
| **Consciousness** | |
| Fully awake | 2 |
| Arousable on calling | 1 |
| Not responsive | 0 |
| **Activity** | |
| Moves all extremities | 2 |
| Moves two extremities | 1 |
| No movement | 0 |

group was 198 minutes longer compared to the midazolam group, and in the 80% power range and 5% type 1 error, the minimum number of cases was calculated as 26. Considering dropout and block failure we expanded sample size to 30 per group. Data were analyzed by SPSS (for Windows 11.05 SPSS Inc., Chicago, Illinois, USA) package program. Results were expressed as mean±standard deviation. Age, weight and ASA classification of the patients were analyzed by means of chi-square test, mean arterial pressure, heart rate, sensoryneural block, motor block start and termination time were analyzed by independent t-test. P <0.05 was considered significant.

## RESULTS

A total of 111 patients were assessed for eligibility, 44 were excluded since they did not meet inclusion criteria 4 refused participating the study 3 patients had their surgeries canceled. The CONSORT diagram showing patient progress through the study phases is depicted in Figure 1.

A total of 60 patients were randomized. The demographic characteristics of the study participants were similar with no statistically significant or clinically meaningful differences between the two groups (Table 3).

Baseline of heart rate in both group were similar however it started to drop after bolus infusions of drugs and remained lower in the dexmedetomidine group than in the midazolam group (p <0.05) (Figure 2).

Two patients developed bradycardia and recovered after 0.5 mg atropine injection.

The mean arterial pressure was lower in the dexmedetomidine group however the difference was not statistically significant.

The motor and sensory block onset times were found significantly shorter in dexmedetomidine group (Figure 3).

Mean sensory block onset time was 8.6±2.4 min in the dexmedetomidine group and 16.2±1.8 min in the midazolam group (p<0.001).

The mean motor block onset was 14.2±1.6 min in the dexmedetomidine group and 21.4±2.3 min in the midazolam group (p<0.001).

Sensory and motor block duration time were significantly higher in the dexmedetomidine group than in the midazolam group (p<0.001) (Table 4).

The duration of sensory block was 715.4±41.1 min in the dexmedetomidine group, 518.1±44.2 min in the midazolam group, duration of motor block was 613.6±38.1 min in the dexmedetomidine group and 421.3±37.2 in the midazolam group (p<0.001) (Table 4).

None of the patients had nausea, vomiting or respiratory distress.

## DISCUSSION

The results of our study suggest that sedative dose of dexmedetomidine also shortens onset time and prolonges termination time of sensory and motor block among patients who received infraclavicular nerve block for upper extremity orthopedic

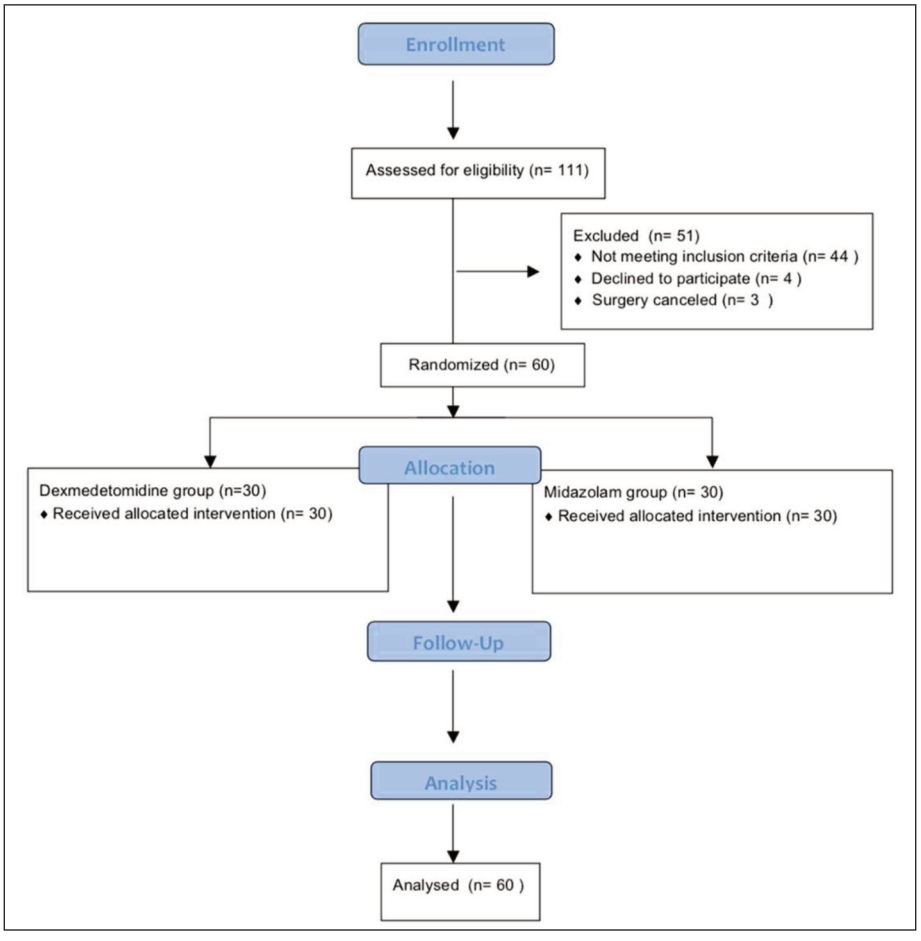


**FIGURE 1:** Consolidated Standarts of Reporting Trials (CONSORT) flow diagram showing patient progress through the study phases.

**TABLE 3:** Demographic characteristics of patients.

| | Group D (n=30) | Group M (n=30) | P value |
|---|---|---|---|
| Age (year) | 34±14 | 33±15 | 0.901 |
| Weight (kg) | 73±18 | 76±16 | 0.112 |
| Sex (Male/Female) | 23/7 | 22/8 | 0.714 |
| ASA status (I/II)* | 20/10 | 21/9 | 1.000 |
| Surgery duration (minute) | 76±31 | 74±29 | 0.351 |

D: Dexmedetomidine; M: Midazolam; Values are expressed as mean (%95 CI) ± standart deviation; *ASA: American Society of Anesthesiologist.

surgeries without causing any significant side effect compared to midazolam. This effect was observed with dexmedetomidin with a bolus dose of 1 μg/kg over 10 minutes and maintenance dose of 0.2-0.7 μg/kg/h which is titrated according patients sedation status.

In surgical operations performed under regional anesthesia, eliminating the patient's anxiety is essential in terms of both the patient being more hemodynamically stable and allowing the surgical branch to work more comfortably. For this reason, propofol, benzodiazepines, alpha adrenoreseptor agonists and narcotic analgesics are frequently used. Although dexmedetomidine, one of the alpha adreno receptor agonists, is frequently used for conscious sedation in the intensive care

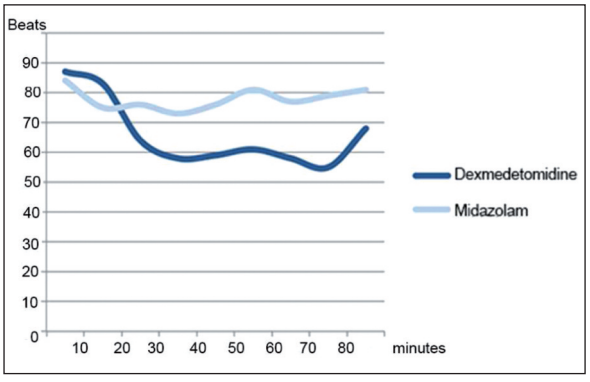


**FIGURE 2:** Heart rate between groups. Values are expressed as mean (95% CI) ± standard deviation (p<0.001).

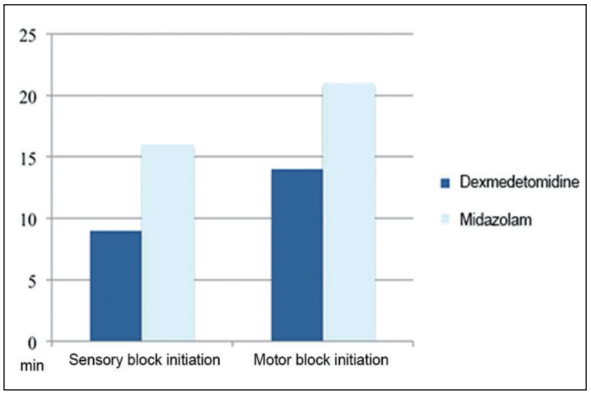


**FIGURE 3:** Sensory and motor block intiation times between groups. Values are expressed as mean (95% CI) ± standard daviation (p<0.001).

unit, its use in the operating room has not yet become widespread.

Intravenous alpha-2 adrenoreceptor agonists may stimulate vascular adrenoreceptors, resulting in a decrease in heart rate, decreased systemic vascular resistance, and mean arterial pressure.[9,10] In our study, although a decrease in dexmedetomidine group was observed in heart rate, no hemodynamic problems were encountered.

Although one of the most important advantages is that it does not cause respiratory depression, it is possible that deep sedation may be observed at therapeutic doses.[11] In our study, we did not encounter deep sedation due to dose adjustment according to the Ramsey Sedation Scale.

The first study showed that dexmedetomidine added to the block solution with ropivacaine blocked the sensory neural pathway in a dose-dependent manner was conducted by Brummett et al. In addition, no neurotoxicity symptoms were observed in this study up to 20 μg/kg dose.[12]

In a study conducted by Marfoher et al. on volunters, they examined the effect of low dose (20 μg) perineural and intravenous dexmedetomidine on the duration of sensory blockade after ulnar nerve block.[13] The duration of sensory blockade was higher (555±118 vs 395±40 min) in perineural dexmedetomidine group when compared to systemic dexmedetomidine. The results differs from our study, however this study was done on ulnar nerve in healthy volunteers who did not undergo any surgery, and therefore, this finding cannot be readily generalized to duration of analgesia. Kathurie et al. showed that perineural and intravenous dexmedetomidine have both been shown to prolong the sensory and motor blocks statistically significantly compared to the group given only local anesthetics.[14] Perineural dexmedetomidine was found to prolonged the duration of the block more, compared to the intravenous group, but in this study, intravenous infusion was given for just 15 minutes, not during the whole operation. This may have caused the difference between intravenous and perineural

**TABLE 4:** Peripheric nerve block characteristics.

| | Group D (n=30) | Group M (n=30) | P value |
|---|---|---|---|
| Time to sensory block initiation (minutes) | 8.6±2.4 | 16.2±1.8 | <0.001 |
| Time to motor block initiation (minutes) | 14.2±1.6 | 21.4±2.3 | <0.001 |
| Sensory block lasting time(minutes) | 715.4±41.1 | 518.1±44.2 | <0.001 |
| Motor block lasting time (minutes) | 613.6±38.1 | 421.3±37.2 | <0.00 |

D:Dexmedetomidin; M: Midazolam.

Values are expressed as mean (95% CI) ± standard deviation.

groups. Because more recently, Abdallah et al. showed, in a randomized controlled trial, intravenous and perineural dexmedetomidine both similarly prolonged the duration of sensory and motor block in the peripheral nerve block.[15]

Rutkowska et al. compared the effects of a continuous infusion of IV midazolam vs IV dexmedetomidine on the duration of sensory–motor blockade after supraclavicular block.[16] IV dexmedetomidine group showed significantly longer sensory-motor blockade. Although this study is limited to renal patients we had similar results on block characteristics.

Although there are many studies in the literature about perineural application, we have reached a limited number of studies about the effect of intravenous administration on peripheral nerve block, the ones that we are able to find had similar results with our study. A meta-analysis study conducted by Schnabel et al. examined 46 randomized controlled trials with a patient number of 3149. Although the number of studies investigating the effect of intravenous dexmedetomidine is only 2, it has been shown that intravenous and perineural use likewise shortens the block onset time and increases the duration of the block.[17] Kang et al. examined different doses of intravenous dexmedetomidine used in interscalene brachial plexus block to find effective dose that prolongs the analgesic duration and showed that 2 μg/kg dose of dexmedetomidine prolonged analgesic duration significantly.[18] Although this study showed similar results like our study on sensory block, motor block termination time were found the same with control group. There may be several grounds for this difference. Usage of dexmedetomidine, anesthetic management and maintenance therapies during surgery is different from our study. We started with a bolus dose of dexmedetomidine and maintenance dose is adjusted according patients sedation status. Also surgery is performed under regional anesthesia. However, in the mentioned study general anesthesia is used, also dexmedetomidine is just used after induction of anesthesia for 30 minutes and dose is different from approved drug label. The drugs used in induction and maintenance of anesthesia may affect pharmacodynamics and pharmacokinetics of dexmedetomidine. In our study we aimed to minimize the used drugs to avoid that interaction.

Kumar et al. compared affect of midazolam and dexmedetomidine sedation on the onset and duration of supraclavicular brachial plexus block and documented that intravenous dexmedetomidine accelerated the onset of sensory and motor block and prolonged the duration of sensory and motor block when used for brachial plexus block. Although the approach to brachial plexus, dose and combination of local anesthetic that is used is different our results are in parallel with this research.[19]

Dexmedetomidine infusion during surgery reduces post-operative pain, opioid consumption, and the risk of opioid-related adverse events independent from anesthetic choice.[20] The mechanism by which dexmedetomidine prolongs the duration of nerve block involves local vasoconstriction; spinal, supraspinal, and direct action on the nerve; and systemic effects.[21,22] The central mechanism that directly affects the alpha 2 adrenoreceptor of the locus ceruleus may explain the extended effect of IV dexmedetomidine on nerve block duration.[23] In contrast, midazolam shows prolonged effects after spinal or epidural, but not after systemic administration.[24,25] Despite the lack of placebo-controlled studies, our results support these findings.

In conclusion our study showed, providing sedation with dexmedetomidine has some advantages over midazolam sedation such as decreasing onset time of sensory and motor block, also prolonging sensory and motor block termination time without any major complications. We suggest that future studies comparing the degree of block duration between different agents and administration methods may aid clinicians when providing regional analgesia in perioperative patients.

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*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that*

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### *Conflict of Interest*

*No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Fatih Çiftçi;* ***Design:*** *Fatih Çiftçi, Yasemin Altan;* ***Control/Supervision:*** *Fatih Çiftçi, Yasemin Altan;* ***Data Collection and/or Processing:*** *Fatih Çiftçi, Yasemin Altan;* ***Analysis and/or Interpretation:*** *Fatih Çiftçi, Yasemin Altan;* ***Literature Review:*** *Fatih Çiftçi, Yasemin Altan;* ***Writing the Article:*** *Fatih Çiftçi, Yasemin Altan;* ***Critical Review:*** *Fatih Çiftçi, Yasemin Altan;* ***References and Fundings:*** *Fatih Çiftçi, Yasemin Altan;* ***Materials:*** *Fatih Çiftçi, Yasemin Altan.*

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