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Original Article / Özgün Araştırma

Effect of Midazolam and Dexmedetomidine Sedation on the Onset and Duration of Supraclavicular Brachial Plexus Block: A Randomised Comparative Study

Midazolam ve Deksmedetomidin Sedasyonunun Supraklaviküler Brakiyal Pleksus Bloğunun Başlangıç ve Süresi Üzerine Etkisi: Randomize Karşılaştırmalı Bir Çalışma

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Abstract / Öz

Objective: Prolonging the duration of sensory blockade with bupivacaine following supraclavicular brachial plexus block is desirable for improved postoperative pain management. This study was conducted to assess the effect of intravenous dexmedetomidine on the onset and duration of supraclavicular brachial plexus block using bupivacaine.

Methods: Sixty ASA I and II adult patients undergoing upper limb surgery under supraclavicular brachial plexus block were included in this prospective, randomised, double-blind study. They were randomly divided into two groups. The first group was administered midazolam at an initial dose of 0.04 mg kg^{-1} in 10 mL of normal saline infused over 10 min, which was followed by maintenance infusion of 0.04 mg kg^{-1} h^{-1}. The second group was administered 0.5 µg kg^{-1} of dexmedetomidine in 10 mL of normal saline infused over 10 min, which was followed by maintenance infusion of 0.5 µg kg^{-1} h^{-1}. Twenty-five millilitres of bupivacaine (0.5%) was injected for supraclavicular brachial plexus block.

Results: The onset of sensory block (16.6±1.9 vs. 19.8±1.7 min) and motor block (19.5±2.7 vs. 23.6±1.4 min) was significantly faster in the dexmedetomidine group than in the midazolam group (p<0.001). The duration of sensory block (738±66.3 vs. 307.7 ±46.7 min) and motor block (645.0±106.0 vs. 268.8±32.7 min) was significantly higher in the dexmedetomidine group than in the midazolam group (p<0.001).

Conclusion: Intravenous dexmedetomidine in combination with 25 mL of bupivacaine (0.5%) accelerated the onset of sensory and motor block and prolonged the duration of sensory and motor block when used for brachial plexus block, without resulting in any adverse events.

Keywords: Brachial plexus block, bupivacaine, dexmedetomidine, midazolam

Amaç: Supraklaviküler brakiyal pleksus bloğunu takiben duyu blokajının süresinin bupivakain ile uzatılması, postoperatif ağrı yönetiminin iyileştirilmesi için tercih edilen bir durumdur. Bu çalışma, intravenöz deksmedetomidinin bupivakain kullanılarak supraklaviküler brakiyal pleksus bloğunun başlangıcı ve süresi üzerine etkisini araştırmak amacıyla yapıldı.

Yöntemler: Bu prospektif, randomize, çift kör çalışmaya, supraklaviküler brakiyal pleksus bloğu altında üst ekstremite cerrahisi geçiren altmış ASA I ve II erişkin hasta dahil edilmiştir. Hastalar rastgele iki gruba ayrıldılar. İlk gruba, 10 dakika süreyle infüze edilen 10 mL'lik normal salin içindeki 0,04 mg kg^{-1}'lik bir başlangıç dozunda midazolam uygulandı, bunu takiben 0,04 mg kg^{-1} h^{-1}'lik bir idame infüzyonu uygulandı. İkinci gruba, 10 dakika süreyle infüze edilmiş 10 mL'lik normal salin içinde 0,5 µg kg^{-1} deksmedetomidin uygulandı ve bunu takiben 0,5 µg kg^{-1} h^{-1}'lik idame infüzyonu yapıldı. Supraklaviküler brakiyal pleksus bloğu için yirmi beş mililitre bupivakain (%0,5) enjekte edildi.

Bulgular: Deksmedetomidin grubunda duyusal blok (16,6±1,9'a karşılık 19,8±1,7 dk) ve motor blok başlangıcı (19,5±2,7'ye karşılık 23,6±1,4 dk), midazolam grubundan anlamlı olarak daha hızlıydı (p<0,001). Deksmedetomidin grubunda duyusal blok (738±66,3'e karşılık 307,7±46,7 dk) ve motor blok süresi (645,0±106,0'a karşı 268,8±32.7 dk), midazolam grubuna göre anlamlı olarak daha yüksekti (p<0,001).

Sonuç: 25 mL bupivakain (%0,5) ile birlikte intravenöz deksmedetomidin, duyusal ve motor bloğun başlangıcını hızlandırdı ve herhangi bir yan etki olmaksızın brakiyal pleksus bloğu için kullanıldığında duyu ve motor bloğun süresini uzattı.

Anahtar Kelimeler: Brakiyal pleksus bloğu, bupivakain, deksmedetomidin, midazolam

Introduction

Supraclavicular brachial plexus block using bupivacaine is a popular anaesthetic technique in upper extremity surgeries and for relieving perioperative pain. Generally, the single-shot technique is employed, and the duration of sensory and motor block mainly depends on the local anaesthetic used. Prolonging the duration of sensory blockade with bupivacaine is desirable for better postoperative pain management and for avoiding opioids or nonsteroidal anti-inflammatory agents in the postoperative period. For quicker onset and prolonged duration of postoperative analgesia following supraclavicular brachial plexus block, additives such as opioids, dexamethasone, neostigmine, hyaluronidase, magnesium and alpha

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agonists have been used. Only epinephrine and clonidine have achieved this goal when added to lignocaine and mepivacaine (1). Others studies have not shown consistent results or have unresolved toxicity issues in addition to undesirable effects such as prolonged motor blockade.

Dexmedetomidine, which is a newer α2-adrenoreceptor agonist, has shown sedative, anxiolytic and analgesic properties and has gained popularity in intra-operative sedation during regional procedures. In animal studies, the perineural administration of dexmedetomidine has been found to prolong the duration of block and postoperative analgesia when added to bupivacaine (2).

We postulated that standard dexmedetomidine sedation during supraclavicular brachial plexus block using bupivacaine might increase block duration. The objective of the study was to assess the impact of intravenous dexmedetomidine sedation on the duration of supraclavicular brachial plexus block in American Society of Anesthesiologists (ASA) physical status I and II patients undergoing upper extremity surgery. To isolate the analgesic effect of dexmedetomidine from its sedative effects, a comparison was made with midazolam, which is a benzodiazepine used in our hospital for intraoperative sedation. Midazolam is a popular agent showing anxiolytic, amnesic and sedative properties, along with a low incidence of side effects and a wide margin of safety. Midazolam may show anti-nociceptive effects after neuraxial administration but not after systemic administration (3, 4).

Methods

Ethics statement

The study was approved by the Institute Ethics Committee and was registered with Clinical Trials Registry-India at www.ctri.nic.in (CTRI/2014/08/004818). Written consent was obtained after informing the participants about the nature, scope and risks related to the study.

Duration and type of the study

This study was conducted between April 2014 and November 2015. Sixty consenting adult patients were included in this double-blind, randomised, comparative study. The sampling type was randomised cluster sampling.

Inclusion criteria

Patients of either sex, with ASA I and II, between 18 and 60 years of age and scheduled to undergo upper extremity surgery under supraclavicular brachial plexus block were included.

Exclusion criteria

Patients who refused to participate; with known contraindications to brachial plexus block (coagulopathy or local infection); with known allergy to bupivacaine, midazolam or dexmedetomidine; with concomitant use of analgesics or sedatives; with ASA III/IV; with a history of significant systemic illness and who failed brachial plexus block were excluded.

Pre-anaesthesia

Pre-anaesthetic evaluation of all patients was performed before admission to the ward. All patients were pre-medicated with 150 mg of oral ranitidine and 0.25 mg of alprazolam the night before surgery and were kept fasting for 6 h prior to undergoing surgery.

Intervention plan

On arrival in the operation theatre, routine monitoring in the form of electrocardiography, non-invasive arterial pressure, pulse oximetry and respiration was done, and baseline values were noted. Intravenous access was established with an 18G intravenous catheter on the dorsum of the non-operative hand, and infusion Ringer's lactate solution was started.

Using computer-generated random numbers, patients were allocated to one of two groups:

- Patients in the midazolam group [Gr M] received 0.04 mg kg^{-1} of midazolam in 10 ml of normal saline infused over 10 min, which was followed by maintenance infusion of 0.04 mg kg^{-1} h^{-1} until the end of surgery.
- Patients in the dexmedetomidine group [Gr D] received 0.5 μg kg^{-1} of dexmedetomidine in 10 mL of normal saline infused over 10 min, which was followed by maintenance infusion of 0.5 μg kg^{-1} h^{-1} until the end of surgery.

Oxygen at a rate of 4 L min^{-1} through a face mask was administered to all patients. Following administration of the initial dose of the study drugs, patients were positioned for supraclavicular brachial plexus block. After aseptic preparation of the area, supraclavicular brachial plexus block was performed by the landmark approach (5). The patients were placed in the supine position, with their arms at the side and head turned away from the side to be blocked. The lateral border of the sternocleidomastoid muscle was identified by asking the patients to raise their head off the table. The needle entry point was at the posterior border of the muscle, just above the clavicle, in the parasagittal plane. The needle was directed towards the floor, looking for paraesthesia. This was followed by the injection of bupivacaine. The needle was redirected 20° caudad or cephalad in small steps to elicit paraesthesia, if required.

Blinding

The infusions were prepared by an independent clinician not involved in the study. The anaesthesiologist performing the block and observing the patient was blinded to the treatment group. Neither the patient nor the attending anaesthesiologist who also collected the data was aware of group allocation.

Parameters of observation

Block characteristics

1. Onset of motor block: The time to reach the modified Bromage score of 2 for the upper limb following bupivacaine administration.

2. Onset of sensory block: The time to reach a complete lack of sensation to cold following bupivacaine administration.

3. Duration of motor block: The time interval between the onset of motor block to complete regression of the block (Bromage score of 0).

4. Duration of sensory block: The time interval between the onset of sensory block to the restoration of sensation to cold.

Motor block was assessed by a modified Bromage scale for the upper limb: 0=normal motor function, 1=ability to move only fingers and 2=complete motor block with inability to move the elbow, wrist and fingers (6). Sedation was titrated every 15 min to maintain a Ramsay sedation score of 3-4 until the end of surgery. The Ramsay sedation scale is as follows: 1=anxious, agitated, restless; 2=cooperative, oriented, tranquil; 3=responds to commands only; 4=brisk response to light glabellar tap or loud noise; 5=sluggish response to a light glabellar tap or loud noise and 6=no response (7).

The regression of block was assessed every 30 min until complete recovery from motor and sensory block was obtained.

Other parameters

Heart rate and mean arterial pressure: Baseline values were noted and thereafter at every 10 min till the infusion lasted.

Rescue interventions

Rescue interventions were planned for bradycardia, hypotension and pain:

- Bradycardia (<50 beats per minute): atropine
- Hypotension (<20% of baseline value): mephentermine

Statistical methods

Power analysis

The primary outcome variable was the duration of sensory and motor block. The secondary outcome variables included haemodynamic parameters. Power Analysis and Sample Size System (PASS) [NCSS, Utah, USA] version 11 software was used for the calculation of the sample size, with the results of

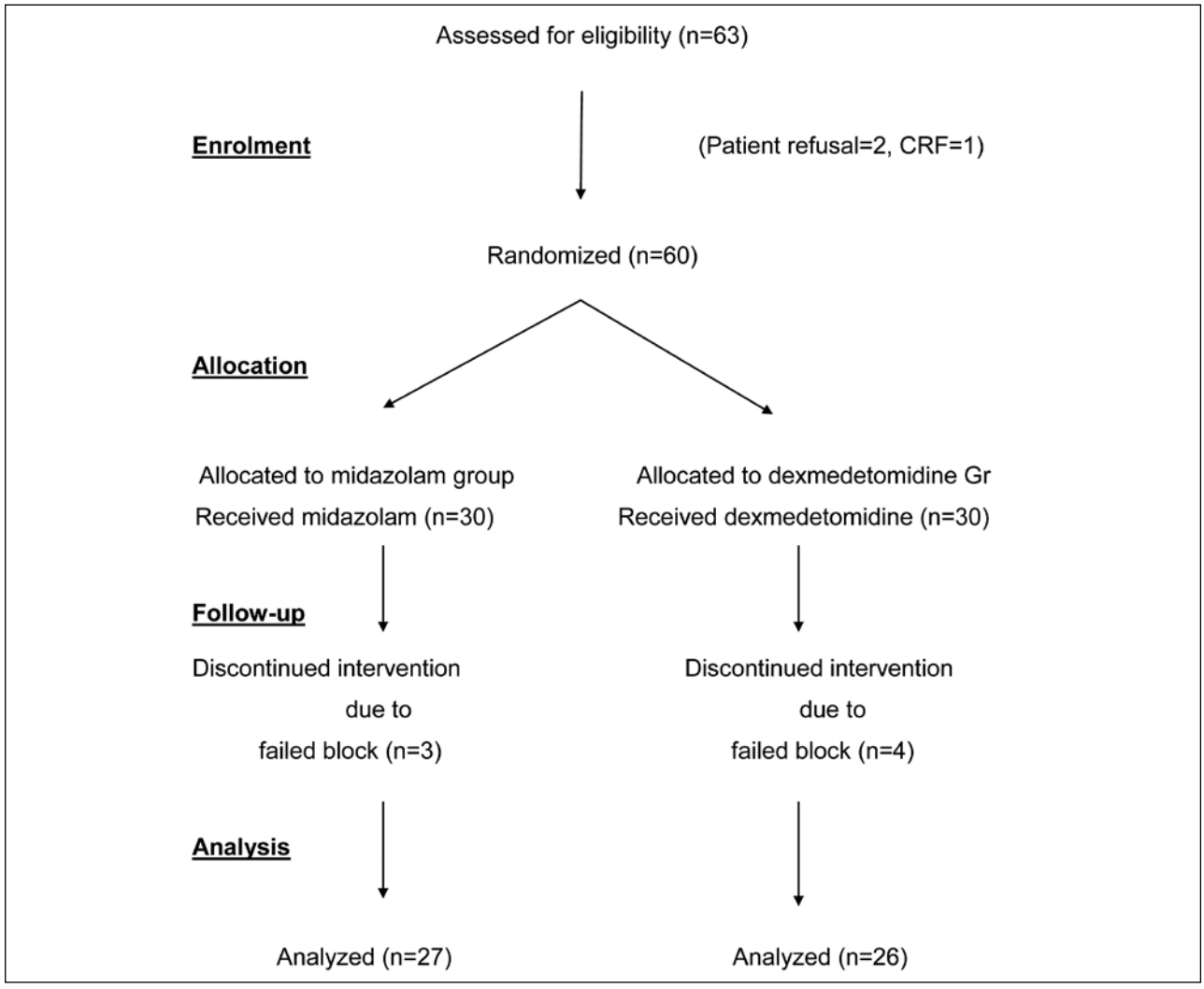

Figure 1. CONSORT flow diagram of the study patients

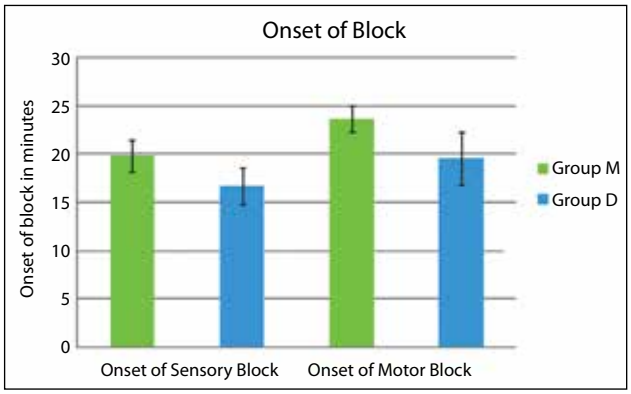

Figure 2. Onset of sensory and motor block in minutes in patients receiving midazolam (M) or dexmedetomidine (D) sedation

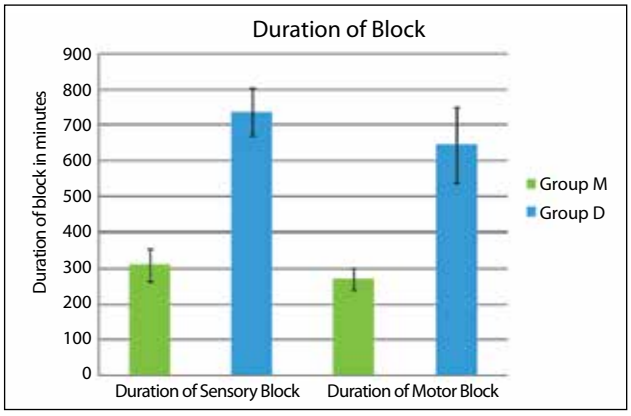

Figure 3. Duration of sensory and motor block in minutes in patients receiving midazolam (M) or dexmedetomidine (D) sedation

a prior study (8). With a study power of 80% and alpha error of 5%, the sample size came to 24 for each group. Considering dropouts, 30 patients in each group were recruited.

Statistical software

Data were compiled and subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS Inc.; Version 19.0. Chicago, IL, USA).

Statistical tests

Statistical tests employed were Student's t-test for age, weight, onset and duration of motor and sensory blocks and haemodynamic parameters. Gender and ASA grade data were subjected to the chi-square test. Data are presented as mean±SD. P-values of <0.05 were considered to indicate statistical significance.

Results

Sixty-three patients were assessed for eligibility. Two patients did not give consent for participation, and one was not included due to the presence of chronic kidney disease. Sixty patients were enrolled and randomised to either of the two groups, 30 patients in each. Finally, 27 patients in the midazolam group and 26 patients in the dexmedetomidine group were analysed, the rest being excluded due to failed block (Figure 1).

Table 1. Demographic characteristics of patients receiving midazolam or dexmedetomidine for sedation. Data are presented as mean±SD

	Midazolam Group (n=27)	Dexmedetomidine Group (n=26)
Age (Years)	42.3±13.6	37.8±12.3
Weight (kg)	57.7±7.0	59.8±8.4
Gender (M/F)	13/14	14/12
ASA physical status (I/II)	19/8	20/6

SD: standard deviation; ASA: American Society of Anesthesiology Scores; M: male; F: female

Table 2. Block characteristics in patients receiving midazolam or dexmedetomidine sedation. Data are presented as mean±SD

	Midazolam Group (n=27)	Dexmedetomidine Group (n=26)	p
Onset of sensory block (min)	19.8±1.7	16.6±1.9	<0.001*
Onset of motor block (min)	23.6±1.4	19.5±2.7	<0.001#
Duration of sensory block (min)	307.7±46.7	738.4±66.3	<0.001£
Duration of motor block (min)	268.8±32.7	645.0±106.0	<0.001&

*p-value is 0.0001, #p-value is 0.0001, £p-value is 0.0001, &p-value is 0.0001

The demographic profile of the patients in the two groups was comparable (Table 1). The onset of sensory and motor block was quicker in the dexmedetomidine group than in the midazolam group (Figure 2). The mean sensory block onset time was 16.6±1.9 min in the dexmedetomidine group and 19.8±1.7 min in the midazolam group (p<0.001). The mean motor block onset time was 19.5±2.7 min in the dexmedetomidine group and 23.6±1.4 min in the midazolam group (p<0.001) (Table 2).

The duration of sensory as well as motor block was more prolonged in the dexmedetomidine group than in the midazolam group (Figure 3). The duration of sensory block in the dexmedetomidine group was 738±66.3 min, whereas in the midazolam group, it was 307.7±46.7 min (p<0.001). The duration of motor block in the dexmedetomidine group was also prolonged; it was 645.0±106.0 min in the dexmedetomidine group and 268.8±32.7 min in the midazolam group (p<0.001) (Table 2).

Haemodynamic parameters, i.e., heart rate and mean arterial pressure, in both the groups were compared at an interval of 10 min during maintenance infusion. The baseline values of mean heart rate were comparable in both groups and remained so during the initial infusion of sedatives and up to

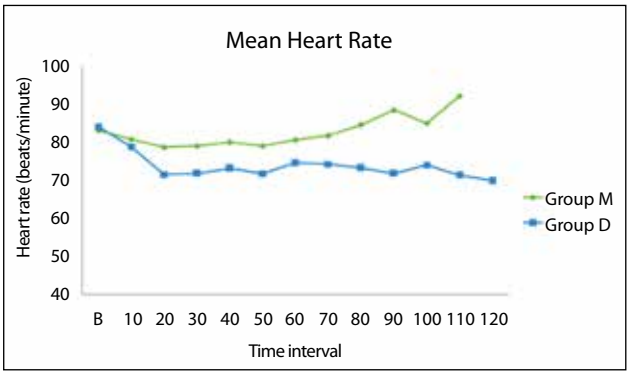

Figure 4. Mean heart rates (baseline and at 10-min intervals) in patients receiving midazolam (M) or dexmedetomidine (D) sedation

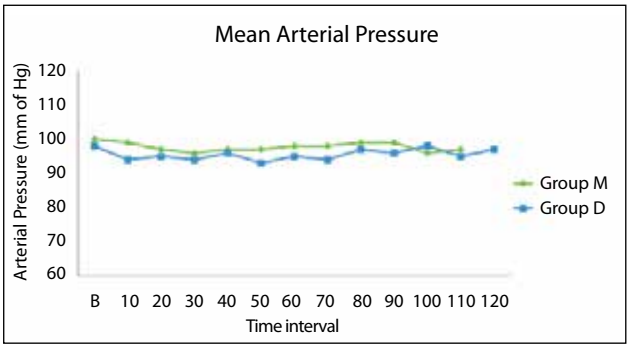

Figure 5. Mean arterial pressures (baseline and at 10-min intervals) in patients receiving midazolam (M) or dexmedetomidine (D) sedation

10 min thereafter. The mean heart rates were found to be lower in the dexmedetomidine group after 20 min of infusion until the end of the infusion (Figure 4).

The baseline value of mean arterial pressure was comparable in both groups and remained so until the end of the infusion (Figure 5).

Bradycardia was observed in one patient in the dexmedetomidine group who was treated with 0.3 mg of intravenous atropine. Hypotension necessitating the injection of 3 mg of mephentermine was also observed in one patient in the dexmedetomidine group.

No episodes of nausea, vomiting, hypoxemia or respiratory depression were observed in any patient.

Discussion

The quest to find an ideal agent that can prolong the duration of action of local anaesthetic agents has been going on for a long time. Sedation during regional blocks is routinely employed. It would be beneficial if such an agent also prolonged the duration of block.

The main findings of the present study are that systematically administered dexmedetomidine (a) shortens the onset of motor and sensory block, (b) prolongs the duration of motor and sensory block and (c) does not cause any significant side effect compared to midazolam sedation during supraclavicular brachial plexus block.

It has been suggested that the spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine, even though there is clear evidence for the supraspinal and peripheral sites of action (9). When added as an adjuvant, it may directly act on the nerve or due to central action after absorption through the block site into systemic circulation. Based on these observations, it appears that the central and peripheral mechanisms were in play in our patients, resulting in block prolongation.

Seven out of the 60 patients were not evaluated due to block failure. Lack of ultrasound guidance or a nerve locator can be attributed to this high rate of procedural failure.

There are very few similar studies, and all except one seem to have results identical to ours. In a randomised, controlled study, Kathuria et al. (10) evaluated dexmedetomidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block. Perineural addition and intravenous co-administration of dexmedetomidine both led to a decrease in the onset time and an increase in the duration of motor and sensory blockade. They observed that these effects were more prominent in patients who had received dexmedetomidine perineurally. Their conclusion, therefore, was that the action of dexmedetomidine is probably local rather than centrally mediated. However, they administered dexmedetomidine infusion over 15 min only, whereas in our study, it was continued until the end of surgery. Similar to our study, there were no significant side effects such as excessive sedation, hypotension or bradycardia.

Agarwal et al. (11) evaluated the effect of perineural dexmedetomidine added to 0.325% bupivacaine compared to that of bupivacaine solution with normal saline. Perineural dexmedetomidine as an adjuvant significantly shortened the onset and prolonged the duration of sensory and motor blockade.

A recent study has suggested that intravenous dexmedetomidine along with ropivacaine interscalene brachial plexus block prolongs the analgesic duration and reduces opioid consumption without prolonging motor blockade (12).

Rutkowska et al. (8) investigated the effect of dexmedetomidine sedation on brachial plexus block in patients with end-stage renal disease in comparison to our study that included only patients with ASA I and II. They used 0.375% bupivacaine in their study, whereas 0.5% bupivacaine was used in our study. They also used midazolam sedation for the control group. However, the infusion of both study drugs was started after the establishment of the block, in contrast to our study where infusions started before block placement.

Rutkowska et al. (8) found that the onset of complete block was not statistically different. The duration of sensory

(9.4±3.4 h) and motor block (11.9±3.8 h) was significantly prolonged, similar to what was observed in our study. Interestingly, they found that motor block outlasted the duration of sensory block, unlike in our study, where the duration of sensory block exceeded that of motor block. A longer duration of motor block than of sensory block is not desirable in the postoperative period. The authors did not elaborate on the possible reason for this finding, although they termed it as surprising as less than 0.5% bupivacaine is less potent in producing motor block. They also attributed the overall result of their study to the generalised peripheral analgesic effect of dexmedetomidine.

We offer some explanation to their interesting findings of more prolonged motor blockade, which was in contrast to our study, by highlighting some factors that may have influenced their study. The patients included in their study had end-stage renal disease. They were all hypertensive patients receiving various medications that the authors did not mention.

It is known that hypertension may lead to hypoalgesia, and lowering of blood pressure does not result in pain perception changes (13). This state of altered pain perception in the study patients might have influenced the results. Moreover, this group of patients might have been on anti-hypertensives such as clonidine, which is a known drug that increases the duration of motor and sensory block induced by local anaesthetic agents.

It has been proposed that during brachial plexus block, a significant duration of motor block outlasting sensory block can be accounted for by the fact that a more rapid vascular uptake of bupivacaine takes place near the more distally innervating sensory fibres located in the core of the nerve (14). As intraneural blood vessels pass from the mantle to the core, they become more branched, offering a larger surface area for drug absorption. Patients with end-stage renal disease receive various anti-hypertensive medications that may cause peripheral vasodilatation, which, in turn, may lead to a more rapid uptake of bupivacaine from the core. The end result was a prolonged duration of motor block that outlasted the duration of sensory block.

Dexmedetomidine infusion resulted in stable haemodynamic parameters without significant side effects. This was in agreement with the findings of other studies where dexmedetomidine was found to be a valuable addition for sedation in patients undergoing upper limb surgeries under brachial plexus block (15, 16).

Conclusion

Our study confirms that the onset of sensory and motor blockade is shortened and the duration of sensory and motor blockade is prolonged by the intravenous co-administration of dexmedetomidine during bupivacaine brachial plexus block in ASA I and II patients. However, one limitation of this study was that the sample size was relatively small.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Indira Gandhi Institute of Medical Sciences.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.K.D., O.P.S.; Design - G.K., P.K.D., O.P.S.; Supervision - P.K.D., O.P.S.; Resources - P.K.D.; Materials - P.K.D.; Data Collection and/or Processing - G.K.; Analysis and/or Interpretation - O.P.S.; Literature Search - G.K., P.K.D.; Writing Manuscript - P.K.D., O.P.S.; Critical Review - G.K., P.K.D., O.P.S.; Other - G.K.

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Teşekkür: Yazarlar, istatistiksel analizlere olan katkılarından dolayı Akhilesh K. Pandey'e şükranlarını ifade ederler.

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