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Original Article

# Sedation with dexmedetomidine prolongs the analgesic duration of brachial plexus block: a randomised controlled trial

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ABSTRACT

*Purpose:* Dexmedetomidine, an alpha 2 receptor agonist, prolongs nerve block duration when administered in conjunction with peripheral nerve blocks. We hypothesised that sedation with dexmedetomidine could also significantly prolong the analgesic duration of brachial plexus block (BPB) during orthopaedic surgery on the upper extremities.
*Materials and methods:* One hundred and two patients received upper extremity surgery under BPB. The patients were randomly sedated with dexmedetomidine (D group) or midazolam (M group) following BPB using 25 mL of local anaesthetics (1:1 mixture of 1% lidocaine and 0.75% ropivacaine). Adequate sedation was evaluated with the modified Ramsay Sedation Scale. Primary outcome was measured as the time the patient first requested analgesic via a patient-controlled analgesia device. Total opioid consumption during the first 24 post-operative hours was also measured as secondary outcomes.
*Results:* Time to first request for analgesia (mean ± standard deviation) was significantly longer in the D group (616.9 ± 158.2 min) than in the M group (443.7 ± 127.2 min) ($P < 0.001$, Mean difference [95% CI] 173.2 [114.8–231.5] min). Total opioid consumption were significantly lower in the D group (fentanyl equivalent, 280.0 μg [171.3;374.0] vs. 363.9 μg [208.3;570.1], $P = 0.01$). Although patients in the D group showed deeper sedation over time ($P < 0.001$), PACU stay time was only slightly extended in D group (5.2 [1.2–9.2] min). Perioperative complications did not differ in the two groups.
*Conclusion:* Sedation with dexmedetomidine not only prolongs analgesic duration of BPB, but also reduces total opioid consumption during the first 24 post-operative hours.


## 1. Introduction

Peripheral nerve block (PNB) provides surgical anaesthesia and excellent post-operative pain control, while avoiding many of the side effects of general anaesthesia [1]. Surgery in an awake state, however, increases patient anxiety, indicating a need for sedation during regional anaesthesia to improve patient well-being and increase satisfaction [2,3]. Dexmedetomidine, an alpha 2 agonist, is a sedative with an analgesic sparing effect [4], a low rate of respiratory depression [5], and an antiemetic effect [6], and is useful for sedation after regional anaesthesia. In addition, dexmedetomidine has been shown to prolong analgesia when administered via spinal [7], brachial plexus [8], intra-articular [9], and intravenous (IV) routes, making this agent a preferred sedative following regional anaesthesia.

IV systemic injection of dexmedetomidine has recently been found to prolong the duration of nerve blockade [10,11]. A comparison of equal doses of IV and perineural 0.5 μg/kg dexmedetomidine showed that IV administration not only prolonged the duration of analgesia but also reduced opioid consumption [12]. Although dexmedetomidine is often administered to patients for sedation, the effects of a clinical sedative dose of dexmedetomidine on peripheral nerve blocks has not yet been well studied. We hypothesised that sedation with dexmedetomidine would significantly prolong the analgesic duration of brachial plexus block (BPB) in patients undergoing orthopaedic surgery on their upper extremities.

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## 2. Materials and methods

The trial protocol was approved by the Chungnam National University Hospital Institutional Review Board (IRB CNUH 2016-04-005-001), and the trial was registered at the Clinical Research Information Service, a clinical trial registry in Korea (KCT0002138). This prospective randomised, controlled trial enrolled patients from July 2016 to December 2017 at Chungnam national university hospital (Daejeon, Republic of Korea), with all patients providing written informed consent. The study cohort consisted of patients aged 20–70 years, and with American Society of Anesthesiologists (ASA) grades I–III, who underwent open reduction internal fixation (ORIF) for fractures of the radius or ulnar shortening surgery for ulnar impaction. Patients were excluded if they refused BPB; or had a local infection, hypersensitivity to amide anaesthetic, hypersensitivity or allergy to dexmedetomidine, neuropathy, uncontrolled diabetes mellitus, significant pulmonary disease, or significant cardiovascular disease.

Computer generated random number table with 4 block size was saved in Redcap (redcap.cnuh.co.kr), which was used for randomisation and data management. This randomisation function in Redcap was accessible only to researchers preparing study drugs; these researchers were not involved in patient monitoring or outcome analyses. After BPB and just prior to sedation, the study subjects were randomised 1:1 to the D group (sedation with dexmedetomidine) and the M group (sedation with midazolam).

Standard solutions included 50 mL of dexmedetomidine (4 μg/mL) or 3 mL of midazolam (1 mg/mL). Patients in the D group were administered loading dose of 1 μg/kg dexmedetomidine for 10 minutes and a maintenance dose of 0.6 μg/kg/hr dexmedetomidine until the skin suture. Patients in the M group were administered 3 mg of midazolam if over 60 kg, 2 mg of midazolam if less than 60 kg. Sedation level was evaluated using mRSS (modified Ramsay Sedation Scale) based on previous studies [13]. Patients in the need of additional sedation (mRSS at awake level) received an increased dose in both groups (dexmedetomidine was increased to 0.7–0.8 μg/kg/hr or 2 mg of midazolam was further injected). Patients were not educated about the study drug injection method. Medical staff members who do not know this study monitored the patients depending on the method previously prescribed by the responsible investigator, and the vital signs and sedation level were recorded. Data analysts were excluded from random assignment and data were analysed after all studies were completed.

Electrocardiography, pulse oximetry, and non-invasive blood pressure were monitored as the patient entered the operating room. No sedative was administered before performing BPB. All supraclavicular BPBs were performed under ultrasonography-guidance by a single expert with a supraclavicular approach using an in-plane technique with MylabTM25 Gold (Esaote, Genova, Italy) and a linear probe (LA435: 6–18 MHz, Esaote). 25 mL of local anaesthetics (1:1 mixture of 1% lidocaine and 0.75% ropivacaine) were used. 5 to 10 mL were injected first to the corner pocket and 15 to 20 mL were later injected to the above plexus and intracluster. In order to avoid partial block in ulna nerve territory, we also confirmed the spread of local anaesthetics appropriately around the lower trunk.

The nerve stimulator was in sentinel mode at 0.5 mA, 1 Hz, 0.1 ms, and a 22 gauge, 80 mm, insulated needle was used (SonoPlex cannulas, Pajunk®, Germany). After BPB, loss of sensation to pinprick was assessed every 5 minutes. Sensory loss was achieved in the operation dermatome distribution; administration of dexmedetomidine or midazolam was started.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded before sedation, 5, 10, and 30 minutes after the study drug was begun. Atropine 0.5 mg was administered below 45 beats/min bradycardia, and 5 mg ephedrine was administered when SBP was below 90 mmHg. Sedation levels were also recorded at same time using mRSS [14]. Awake levels were: 1, patient anxious and agitated and/or restless; 2, patient cooperative, orientated, and tranquil; 3, patient responds to commands only. Asleep levels were dependent on the patient's response to a light glabellar tap or loud auditory stimulus, with levels 4–6 indicating a brisk response, a sluggish response, and no response, respectively.

Modified Aldrete post-anaesthesia Score was adopted as the discharge criteria, which a Score $> 9$ is needed for discharge [15]. The operated arm with BPB were excluded from the activity measurement, and if three extremities were moving, the Score was 2 points. Patients who fulfilled the discharge criteria were transferred from the post-anaesthesia care unit (PACU) to the ward unit. All patients were educated before surgery regarding the numeric rating Scale (NRS) pain scoring system used to evaluate post-operative pain (0; no pain, 10; worst pain). The NRS Score at the time of first analgesic requirement was recorded. Maximum pain Score during the post-operative 24 hours was evaluated by ward nurses during regular ward rounds.

To increase the reliability of the data, each patient-controlled analgesia (PCA) device was collected and the log records stored in the device were transferred to the electronic medical records (EMR) system. PCA devices (gemstar™, Hospira, IL, USA) were set to administer a bolus dose of fentanyl 0.5 μg/kg (no continuous dose, lockout time of 10 min, total fentanyl dose of 1000 μg). If pain was not controlled by PCA alone, patients were administered 25 mg of pethidine. 25 mg of pethidine was converted to 33.3 μg of fentanyl, when calculating the total opioid amount. All patients received intravenous nefopam 20 mg (12-hour interval) as part of multimodal analgesia.

In order to determine the prolongation of analgesia by a continuous infusion of dexmedetomidine, the primary outcome was measured as the time the patient first required analgesia, defined as the time from BPB administration to the first bolus infusion from the PCA device. Total opioid consumption during the first 24 post-operative hours were also measured as secondary outcomes.

### 2.1. Statistical analyses

All statistical analyses were performed using R software version 3.4.3 (R Project for Statistical Computing, Vienna, Austria). Normality was tested using the Shapiro-Wilk test. Continuous variables were analysed by Student's *t*-test or the Mann-Whitney test, depending on the normality of the data, and recorded as mean $\pm$ SD or median [interquartile range]. Categorical variables were recorded as number (%) and analysed using the $\chi^2$ test or Fisher's exact test. A 2-tailed *P*-value $< 0.05$ was considered statistically significant. Repeated measurements (SBP, DBP, HR, mRSS) were analysed using repeated measures analysis of variance. If differences were significant, Bonferroni's correction wasused to reduce the probability of a type I error occurring when multiple testing are performed for each point. Survival outcomes, including time-to-event outcomes and median analgesia times, were analysed by the Kaplan-Meier method and compared by the logrank test.

The required sample size was calculated based on a pilot study of 20 patients with G*Power (version 3.1, Franz Faul & Edgar Erdfelder, Trier, Germany). Mean times to first self-administered analgesia in the D group and M group were 580 min and 450 min (within each group SD = 190 min). Assuming a 30% difference in mean analgesia time and a power of 90% with a risk of 0.05 for type 1 errors (two tailed, effect size of 0.68), the minimum number of patients required in each group was 46. Allowing for a 10 % dropout rate, we planned to recruit total 102 patients.

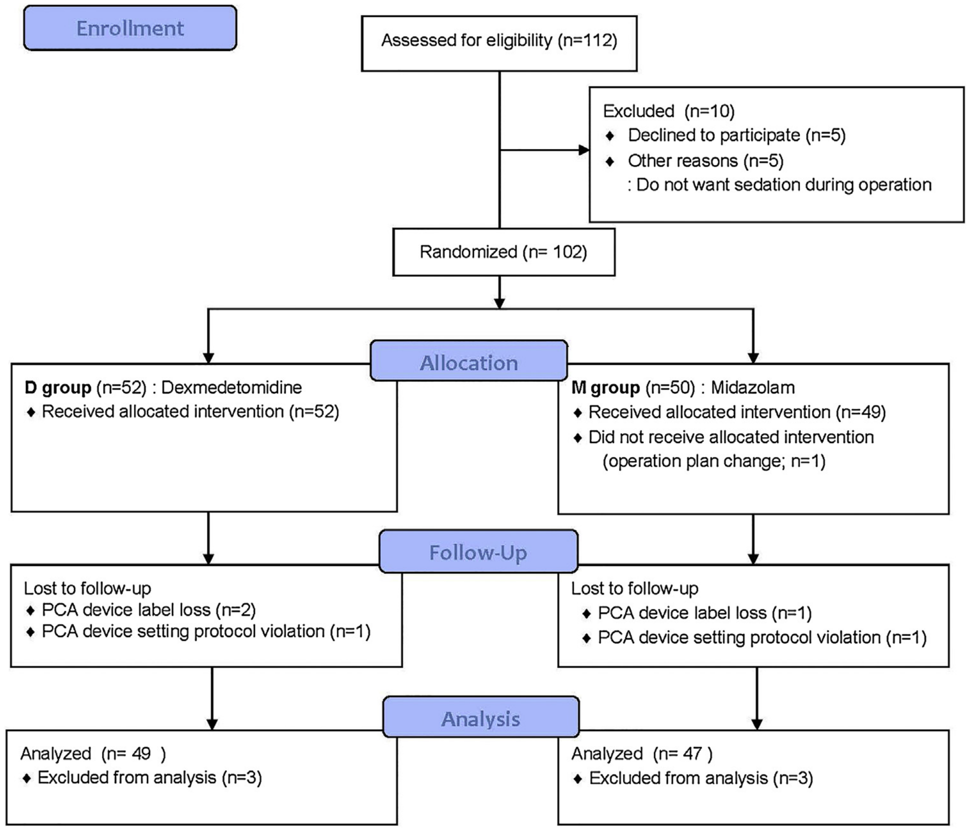


**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram.

## 3. Results

A total of 112 patients were assessed for eligibility; of these, 10 were excluded, of which five patients did not want to participate in the study, and five did not want sedation during surgery. 102 patients were randomised, 52 assigned to the D group and 50 to the M group. One patient in the M group was excluded due to change of surgery (closed reduction and internal fixation) after the group assignment. Three in the D group and two in the M group, were also excluded, due to loss of log records from the PCA device (loss of the PCA device label or a change in the initial setting value). After exclusion, 49 patients in the D group and 47 in the M group were analysed. The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Fig. 1. The demographic and clinical characteristics of the two groups were shown in Table 1. There were no partial blocks in all patients.

Time to first request for analgesia was significantly longer in the D group (616.9 ± 158.2 min vs. 443.7 ± 127.2 min, $P < 0.001$), with a mean difference (95% CI) of 173.2 (114.8–231.5) min (Table 2). The Kaplan–Meier survival analysis plot of the duration of analgesia for the two groups is depicted in Fig. 2. The median analgesia time (median [95% CI]) was 615 min [566–693] in the D group and 440 min [402–495] in the M group, and hazard ratio was 0.32 [95% CI, 0.21–0.49].

Total opioid consumption was significantly lower in the D group (280.0 µg [171.3; 374.0] vs. 363.9 µg [208.3; 570.1],

**Table 1**
Demographic and clinical characteristics of study population Data presented as mean ± SD, median [interquartile range], or number (%). ORIF: open reduction internal fixation, AS: arthroscopy, US: ulnar shortening.

| | D group (*n* = 49) | M group (*n* = 47) |
|---|---|---|
| Age (yr) | 52.0 [43.0;63.0] | 53.0 [37.5;59.5] |
| Sex (M/F) | 19 (38.8)/30 (61.2) | 17 (36.2)/30 (63.8) |
| Height (cm) | 160.0 [157.1;170.0] | 162.0 [153.4;170.3] |
| Weight (kg) | 59.4 [53.0;67.0] | 61.8 [54.0;67.4] |
| Body mass index (kg/m$^2$) | 23.1 ± 3.0 | 23.3 ± 2.9 |
| Operation time (min) | 70.0 [50.0;93.0] | 86.0 [65.0;107.0] |
| Dexmedetomidine dose (µg) | 96.0 [80.0;114.0] | – |
| Midazolam dose (mg) | – | 3.0 [3.0; 4.5] |
| Diagnosis | | |
| Distal radius fracture | 35 (71.5) | 38 (80.9) |
| Radius shaft fracture | 3 (6.1) | 0 (0) |
| Ulnar impaction | 11 (22.4) | 9 (19.1) |
| Operation | | |
| ORIF | 32 (65.4) | 32 (68.1) |
| ORIF + AS | 6 (12.2) | 6 (12.8) |
| US + AS | 11 (22.4) | 9 (19.1) |

**Table 2**
Primary and perioperative outcome variables.

| | D group (*n* = 49) | M group (*n* = 47) | *P*-value | Mean difference (95% CI) |
|---|---|---|---|---|
| Time to first request for analgesic (min) | 616.9 ± 158.2 | 443.7 ± 127.2 | < 0.001 | 173.2 (114.8–231.5) |
| Frequency of PCA bolus use | 8.0 [ 5.0;13.0] | 12.0 [ 5.0;18.5] | 0.052 | 3.3 (0.5–6.1) |
| Fentanyl consumption (μg) | 250.0 [150.0;374.0] | 330.0 [164.5;553.5] | 0.035 | 106.6 (23.5–189.6) |
| Frequency of rescue analgesics (pethidine) | | | < 0.001 | |
| 0 | 27 (55.1) | 12 (25.5) | | |
| 1 | 21 (42.9) | 20 (42.6) | | |
| 2 | 1 (2.0) | 12 (25.5) | | |
| 3 | 0 (0) | 3 (6.4) | | |
| Total opioid consumption (μg) | 280.0 [171.3;374.0] | 363.9 [208.3;570.1] | 0.010 | 128.6 (45.7–211.5) |
| NRS pain Score at first request for analgesic | 2.0 [2.0; 4.0] | 4.0 [3.0; 5.0] | 0.001 | 1.1 (0.3–1.8) |
| Maximum NRS pain Score during post-operative 24 hours | 3.0 [2.0; 5.0] | 5.0 [4.5; 6.5] | < 0.001 | 1.7 (1.1–2.3) |
| mRSS | | | < 0.001[a] | |
| Before sedation | 3.0 [2.0; 4.0] | 3.0 [2.0; 4.5] | 0.609 | |
| 5 minutes after sedation | 4.0 [3.0; 5.0] | 4.0 [2.5; 5.0] | 0.205 | |
| 10 minutes after sedation | 5.0 [3.0; 6.0] | 4.0 [3.0; 5.0] | 0.031 | |
| 30 minutes after sedation | 5.0 [4.0; 6.0] | 3.0 [2.0; 5.0] | 0.007 | |
| PACU stay time (min) | 27.0 [23.0;33.0] | 23.0 [18.0;28.0] | 0.004 | 5.2 (1.2–9.2) |

Data presented as mean ± SD, median [interquartile], or number (%). 25 mg of pethidine was converted to 33.3 μg of fentanyl. PCA: patients controlled analgesia; NRS: numeric rating scale; mRSS: modified Ramsay sedation scale; PACU: post-anaesthesia care unit.
[a] Overall *P*-value about intergroup interaction.

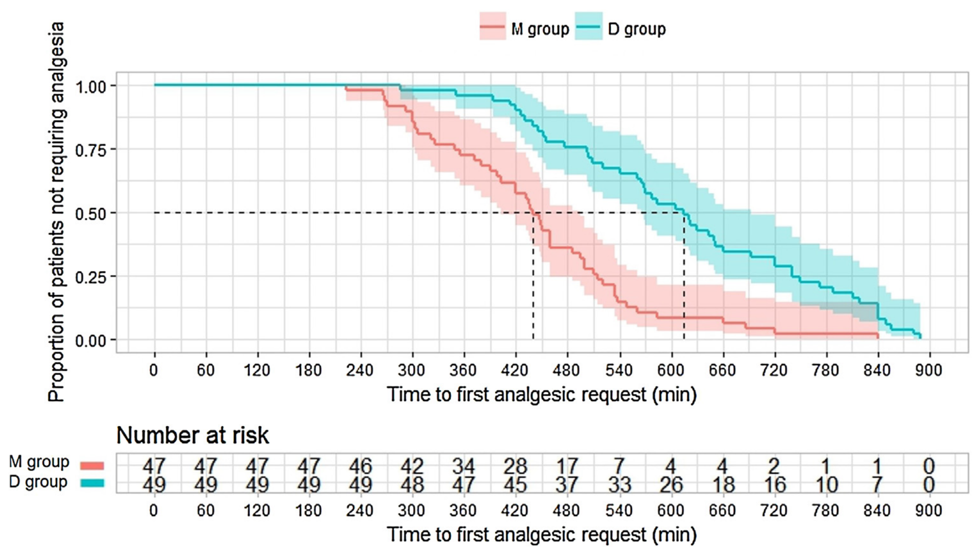


**Fig. 2.** Kaplan-Meier analysis of median [95% CI] duration of analgesia in the D group and M group (615 min [566–693 min] vs. 440 min [402–495 min], Hazard ratio

$P = 0.01$) and mean difference (95% CI) was 128.6 μg (45.7–211.5). The NRS pain Score at the first request for analgesia and maximum NRS pain Score during post-operative 24 hours were significantly lower in the D group than in the M group (Table 2). Perioperative complications such as post-operative nausea and vomiting (PONV), bradycardia etc. did not differ between the two groups (Table 3). SBP and DBP in both groups did not change over time, with no difference between the two groups. However, HR changed over time and there was intergroup interaction ($P < 0.001$). HR in the D group was significantly lower at 10 minutes ($P = 0.002$) and 30 minutes ($P < 0.001$). Modified Ramsay sedation Scale (mRSS) also changed over time, and there was intergroup interaction ($P < 0.001$). D group showed deeper sedation at 30 minutes. However, the PACU stay time was only slightly extended in the D group by about 5 minutes (Table 2).

**Table 3**
Perioperative complications.

| | D group (*n* = 49) | M group (*n* = 47) | *P*-value |
|---|---|---|---|
| PONV | 6 (12.2) | 11 (23.4) | 0.244 |
| N/V | 6/0 | 6/5 | |
| Bradycardia | 3 (6.1) | 0 (0) | 0.256 |
| Desaturation | 0 (0) | 0 (0) | |
| Headache | 0 (0) | 1 (2.1) | 0.983 |
| Dizziness | 4 (8.2) | 5 (10.6) | 0.948 |
| Dry mouth | 4 (8.2) | 1 (2.1) | 0.384 |

Data presented as number (%). Bradycardia was defined as a requirement for atropine for a heart rate below 45 beats/min. Desaturation was defined as SpO2 is lower than 95%.
PONV: post-operative nausea and vomiting. N: nausea. V: vomiting.

## 4. Discussion

Unlike most studies that evaluated block duration after a dexmedetomidine bolus with local anaesthetics, our results suggest that a sedative dose of continuous infusion is sufficient to increase block duration. The present study suggests that sedation with dexmedetomidine significantly extends the analgesic effects of BPB. Total opioid consumption during the first 24 hours after surgery may also be reduced. Prolonging the duration of PNB is very important for post-operative pain control. Adjuvant perineural dexmedetomidine prolongs sensory blockade, motor blockade, and analgesic duration in PNB [7,16–20]. A recent meta-analysis showed that, in BPB, 50–60 μg perineural dexmedetomidine maximized the duration of sensory block while minimizing haemodynamic side effects [8]. Systemic dexmedetomidine administered intravenously also prolongs the effect of the peripheral block. For example, 20 μg of IV dexmedetomidine extended the duration of ulnar nerve block in volunteers by approximately 10% [10]. However, as surgery was not performed, it was unclear whether the duration of analgesia was affected as well. A study of BPB for arteriovenous fistula formation in patients with end-stage renal disease discovered that sedation with dexmedetomidine prolonged motor and sensory blocks [11]. However, the results cannot be applied to non-renal disease patients due to differences of drug metabolism. In another previous study, IV injection of 0.5 μg/kg dexmedetomidine prolonged the analgesic duration of the interscalenic block during arthroscopic shoulder surgery, with IV administration being non-inferior compared with the equivalent perineural route [12]. Dexmedetomidine also reduced the 24-hr cumulative morphine consumption; IV was non-inferior to perineural for these outcomes. In our present study, a sedation dose of dexmedetomidine prolonged the duration of analgesia of BPB for about 3 hours. Total opioid consumption was also significantly decreased. Although similar results have been reported in previous studies, our study is the first to confirm that sedation via intravenous dexmedetomidine can positively affect analgesia during BPB.

Dexmedetomidine during surgery reduces post-operative pain, opioid consumption, and the risk of opioid-related adverse events [21–24]. We also show that the NRS pain Score is significantly lower in the D group at the time of the first request for analgesics. This result is expected, since pain control was achieved subjectively via self-administration through the PCA device. If the investigator controlled analgesic dosing by pain Score, opioid consumption may have differed more greatly. However, although statistically significant, there may be little clinical significance since the pain Score difference is quite small. Maximum NRS pain Score during post-operative 24 hours was also significantly lower in the D group. Our results are in agreement with previous studies, showing that rebound pain during the wear off of blocks can be effectively controlled by dexmedetomidine [25]. Such control over rebound pain may have contributed to the decrease of opioid consumption.

Another advantage of dexmedetomidine sedation is the reduction of PONV [6]. Although we did not observe a significant between-group difference, the incidence of PONV was relatively low in the D group, and no vomiting was observed. The reduction of PONV results from a direct antiemetic effect of the alpha 2 agonist, with reduction of nausea and vomiting due to sympathetic tone depression, and secondarily, from reduced opioid usage [6,26]. While our results reveal significant reduction in opioid consumption, it may not lead to significant changes of PONV since post-operative pain is relatively mild after surgery in our patient groups, even without additional dexmedetomidine administration.

In our study, following administration of a loading dose of 1 μg/kg of dexmedetomidine, patients were administered 0.6 μg/kg/hr of dexmedetomidine for sedation. In patients with renal disease, doses of dexmedetomidine are adjusted to 0.2–0.7 μg/kg/hr to maintain RSS Scores of 3–4 after a 1 μg/kg loading dose [11]. The relatively higher doses of dexmedetomidine administered to our patients resulted in mRSS Scores of 5.0 [4.0; 6.0] after 30 minutes. Despite excessive sedation, however, none of our patients experienced respiratory depression or desaturation events. It is well known that dexmedetomidine causes minimal depression of respiratory drive [5]. Dexmedetomidine deepens the level of sedation in a dose-dependent manner [27]. If the continuous dose had been reduced, we would have maintained a level of conscious sedation. Since patients in the D group were more deeply sedated, it is questionable if our results can be applied for ambulatory surgery settings, such as day-case surgeries. However, sedation prolonged PACU duration for only 5 minutes. Previous articles also suggest that dexmedetomidine is useful for ambulatory settings because it facilitates rapid offset of sedation, faster recovery and drug titration usage [2,28]. The mechanism by which dexmedetomidine prolongs the duration of nerve block involves local vasoconstriction [29]; spinal, supraspinal, and direct action on the nerve; and systemic effects [27]. 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 [30]. IV dexmedetomidine produces a greater degree of differential blockade by preferentially blocking myelinated A-α fibres involved in sensory conduction over un-myelinated C fibres involved in motor conduction [31]. Thus, pain may be controlled continually while confirming motor function after surgery. The duration of dexmedetomidine sedation was shown to be prolonged, irrespective of the route of injection. In contrast, midazolam shows prolonged effects after spinal or epidural, but not after systemic, administration [32,33]. Despite the lack of placebo-controlled studies, our results support these findings.

Our study has several limitations. Although the duration of nerve block was shown to be dependent on the dose of adjuvant peripheral dexmedetomidine [34], we were unable to analyse the relationship between changes in IV dexmedetomidine dose and duration of analgesia because the dose of drug was based on the length of the operation. Dexmedetomidine possesses a well-documented intrinsic analgesic effect. While dexmedetomidine prolongs BPB, it is possible that analgesia from the dexmedetomidine itself may be responsible for the increased time until PCA was first used. Unfortunately, in the absence of a group treated with dexmedetomidine alone (without a block), we are unable to determine whether the observed benefits are due to systemic analgesic effects or the potentiation of nerve block analgesia.

Data regarding other aspects of block duration were not collected, including sensory and motor functions and patient perception of block duration. Dexmedetomidine has shown differential prolongation, with motor being less blocked than sensory [31]. Another unsatisfactory element of this study is follow-up losses due to missing PCA data. So, our study analysis was performed on the basis of per protocol, not on the basis of intention to treat. If we were to ensure the management of the PCA device, we would have been able to minimise follow-up losses.

In conclusion, providing sedation with dexmedetomidine can significantly prolong the analgesic duration of BPB and reduce total opioid consumption during the 24 hours postoperatively. We suggest that future studies compare 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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**Disclosure of interest**

The authors declare that they have no competing interest.

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