ORIGINAL ARTICLE

Effective dose of dexmedetomidine as an adjuvant sedative to peripheral nerve blockade in elderly patients

C. Wang, H. Zhang and Q. Fu

Department of Surgery and Anaesthesiology Centre, PLA General Hospital, Beijing, China

Correspondence
H. Zhang, Department of Surgery and Anaesthesiology Centre, PLA General Hospital, Beijing, China
E-mail: mazuimad301@163.com

Conflict of interest
We declare that we have no competing interests.

Submitted 10 January 2018; accepted 13 January 2018; submission 3 November 2017.

Citation
Wang C, Zhang H, Fu Q. Effective dose of dexmedetomidine as an adjuvant sedative to peripheral nerve blockade in elderly patients. Acta Anaesthesiologica Scandinavica 2018

doi: 10.1111/aas.13087

Background: The median effective dose (ED_{50}) of sedative dexmedetomidine adjuvant to peripheral nerve block (PNB) has not yet been verified in elderly patients. This study assessed the ED_{50} of intravenous dexmedetomidine for sedation in elderly patients who were undergoing total knee arthroplasty (TKA) with PNB.

Methods: Forty-two patients aged 65–85 years were included and stratified into two groups according to age: young-old group (aged 65–74 years) and middle-old group (aged 75–85 years). After the PNB was performed, a pre-calculated dose of dexmedetomidine was administered for 10 min. The Observer's Assessment of Alertness/Sedation scale, bispectral index score, blood pressure and heart rate were recorded. ED_{50} values of dexmedetomidine for adequate sedation were estimated by the up-and-down method of Dixon and probit regression.

Results: The ED_{50} of single-dose dexmedetomidine adjuvant to PNB was 0.57 μg/kg (95% confidence interval [CI], 0.47–0.65) in the young-old group and 0.38 μg/kg (95% CI, 0.28–0.46) in the middle-old group. The ED_{50} of dexmedetomidine differed significantly between the two groups ($P < 0.001$). In addition, no significant adverse hemodynamic or hypoxemic effects were noted.

Conclusion: We determined the ED_{50} for sedation using intravenous dexmedetomidine adjuvant to PNB in elderly patients. The ED_{50} of dexmedetomidine in the middle-old group decreased by 33% compared with that in the young-old group with a mean age difference of 11 years between the two groups.

Editorial Comment
These authors found that the effective single dose of Dexmedetomidin in elderly patients is approximately 0.3–0.6 μg/kg. The oldest patients need a smaller dose. With these doses, serious hemodynamic side effects were not observed in this study.

The use of peripheral nerve block (PNB) for total knee arthroplasty (TKA) has increased significantly over recent years because of the numerous advantages it offers over general anesthesia[1–4]; this increase has been most pronounced in elderly populations.[1] During PNB, adequate adjunctive sedation may be needed to render patients comfortable, immobile and amnestic. Dexmedetomidine has been proposed as a novel sedative, characterized by easy arousability and moderate analgesic properties, with relatively moderate effects on respiration.[5] Dexmedetomidine has also been shown to have a synergistic effect with local anesthesia,[6] as

well as a significant opioid–sparing effect,[7] and also results in enhanced postoperative analgesia[8]; thus, it represents an attractive adjuvant sedative to PNB.

Unfortunately, there is a lack of information regarding the effective dose of dexmedetomidine, adjuvant to PNB, to achieve sedation in elderly patients. Aging brains are generally more sensitive to anesthetics and tend to undergo undesirable hemodynamic fluctuations that are more frequent, and of greater magnitude, vs. those seen in younger patients.[9] Use of dexmedetomidine as an anesthetic adjuvant is complicated by the presence of a dose-dependent biphasic blood pressure (BP) response, together with a reduction in heart rate (HR) and impaired hypoxic and hypercapnic regulation of breathing.[10–12] As a result, dexmedetomidine overdose might be poorly tolerated by elderly patients. Moreover, dexmedetomidine clearance decreases with increasing age and decreasing cardiac output.[13–15] However, the effects of age on dexmedetomidine sedation among elderly populations remain controversial.

The aim of this study was to determine the median effective dose (ED_{50}) of single-dose dexmedetomidine for achieving adequate sedation in elderly patients undergoing TKA with PNB, and to determine the effect of age on the dose required for adequate sedation.

Method

The study was conducted in the Department of Surgery and Anesthesiology Center, PLA General Hospital, Beijing, China. The study protocol was approved by the Medical Ethics Committee of PLA General Hospital (S2016-115-02). We obtained written informed consent from all patients or their legal representatives. The study is registered at www.chictr.org.cn (study number: ChiCTR-IPR-16009829).

Study design

Patients

We screened potential participants scheduled for elective TKA with PNB. The inclusion criteria were age 65–85 years and American Society of Anesthesiologists class I–II. Patients were enrolled in the order of their surgery and were stratified into two groups according to age: young-old group (aged 65–74 years) and middle-old group (aged 75–85 years). The exclusion criteria were a preoperative history of mental disorder, hearing disorder, II–III degree atrioventricular block, known hepatic or renal disease, known allergy or hypersensitivity to α_2 receptor agonists and refusal of (or contraindications to) PNB.

Masking

Dexmedetomidine was prepared and administered by an independent investigator who was not involved in the observation of the patients or data collection. All patients, observers, and attending anesthesiologists were blinded to the treatment group assignment and the dose of dexmedetomidine administered throughout the study period.

Procedures

The dose of dexmedetomidine hydrochloride (200 μg/2 ml; Jiangsu Hengrui Medicine, Jiangsu, China) was calculated according to the up-and-down method of Dixon, and diluted with normal saline to 20 ml by the investigator in the pre-anesthesia room before the operation.

On arrival in the operating room, an 18-gauge catheter was inserted into a forearm vein for fluid maintenance and drug administration. Lactated Ringer's solution was infused at a rate of 4 ml kg^{-1} h^{-1}. Standard electrocardiography (ECG), BP and pulse oxygen saturation (SpO_2) monitoring were applied. Bispectral index (BIS) monitors (BIS VISTA monitor revision 3.0; Aspect Medical Systems, Norwood, MA, USA) were used. The baseline measurements were obtained after a 5-min stabilization period following catheter insertion. Supplemental oxygen (5 l/min) was administered by facemask throughout the procedure.

Before nerve block, 1 mg of midazolam and 0.05 mg of fentanyl were injected. The patient was placed in the lateral decubitus position (operative side up), with the normal leg kept straight and the upper knee closer to chest and flexed at 90°, to prepare for lumbar plexus and sciatic nerve block. All blocks were performed using a nerve stimulator (Stimuplex HNS 12; B.

Braun Melsungen AG, Melsungen, Germany) and a 12-cm, 22-gauge, short-beveled atraumatic stimulating needle (B. Braun Melsungen AG). The stimulation frequency of the nerve stimulator was set at 2 Hz. The intensity of the stimulating current was initially set at 1 mA, and then gradually decreased to 0.4 mA after the appropriate muscular response was elicited. The lumbar plexus was identified by Winnie's approach and 30 ml of 0.4% ropivacaine was injected slowly with careful aspiration. The sciatic nerve block was given following Labat's classic approach and 20 ml of 0.4% ropivacaine was injected. Sensory and motor block were evaluated and compared with the contralateral side every 5 min after blockade until 30 min. Sensory block was assessed by pinprick testing in the distribution areas of the femoral, lateral femoral cutaneous and sciatic nerves. Motor blockade was evaluated by testing hip and knee flexion. Successful block was defined as achieving complete sensory loss and a significant difference in knee flexion vs. baseline (or inability to flex).

Before skin incision, a pre-calculated quantity of dexmedetomidine solution was infused for 10 min via an infusion pump (Graseby 3500; Graseby Medical, Watford, UK). When dexmedetomidine infusion was complete, sedation status was assessed and the BIS was recorded every 2 min (for 20 min) by a blinded observer. Successful sedation was defined as an Observer's Assessment of Alertness/Sedation (OAA/S) scale (Table 1) score between 1 and 3, while failure was defined as an OAA/S score of more than 3.[16] The dexmedetomidine dose for the first patient was 0.6 μg/kg; the dose for the next patient was determined by the last patient' response. If a sedation level of OAA/S 1–3 within 20 min of dexmedetomidine infusion was obtained, the dose was decreased by 0.1 μg/kg for the next patient in the same group; otherwise (i.e., sedation level corresponding to OAA/S score >3), it was increased by 0.1 μg/kg for the next patient. According to the method of Dixon,[17] the procedure was stopped after three up-and-down cycles. If the OAA/S score was >3 at the end of the observation period, additional sedative propofol was infused to obtain adequate sedation depth. The BP, HR, and SpO_2 were recorded on arrival in the operating room, every 5 min during anesthesia, and at the end of surgery.

Bradycardia was defined as HR <55 bpm. Hypotension was defined as systolic blood pressure (SBP) <95 mmHg or a decrease of more than 20% from baseline. Hypertension was defined as SBP >160 mmHg or an increase of more than 20% from baseline. Bradycardia, hypotension, and hypertension were treated with intravenous atropine, ephedrine, and nicardipine, respectively. If the nerve block was incomplete or failed, the patient was administered additional analgesics or received general anesthesia.

Statistical analysis

The statistical analyses were done with SPSS software (ver. 20.0; IBM Corp., Armonk, NY, USA). Data are expressed as means (±SD), medians (interquartile), or numbers. The sample size was based on Dixon's method, which requires at least three pairs of failure–success points. Dose and BIS data were analyzed by probit regression, from which the ED_{50}, 95% effective dose (ED_{95}), median effective bispectral index (BIS_{50}), and 95% effective bispectral index (BIS_{95}) can be estimated [with 95% confidence intervals (CI)]. All data were checked with regard to normality of distribution using the Kolmogorov–Smirnov test. The ED_{50}, ED_{95}, BIS_{50}, BIS_{95}, and continuous normally distributed data were compared between groups using independent *t*-tests. Non-normally distributed data were compared using the Mann–Whitney *U*-test. Counts were analyzed using the chi-square or Fisher's exact test. A general linear model was used to analyze the hemodynamic variables. A scatterplot was drawn, and the correlation between BIS and the OAA/S score was assessed with Spearman's correlation

Table 1 Observer's Assessment of Alertness/Sedation scale.

1	Does not respond to mild prodding or shaking
2	Responds to mild prodding or shaking
3	Responds only after name is spoken loudly or repeatedly
4	Lethargic response to name spoken in normal tone
5	Responds readily to name spoken in normal tone

coefficient. Statistical significance was defined as a *P*-value <0.05.

Results

From November 2016 to March 2017, 45 patients were enrolled in this study. The patients were stratified into two groups according to age. One patient in each group was discharged because of failed block. One patient in the young-old group was discharged because of vomiting after dexmedetomidine infusion was started, which caused variation in the sedation level. Therefore, 42 patients were included in the final analysis (Fig. 1). Except for age, the two groups were matched in terms of demographic data and baseline diseases (Table 2).

Figure 2 presents the sequences of success–failure outcomes to achieve three up-and-down cycles in the two groups. The ED_{50} (95% CI) for sedation with single-dose dexmedetomidine was 0.57 μg/kg (range: 0.47–0.65 μg/kg) for the young-old group and 0.38 μg/kg (range: 0.28–0.46 μg/kg) for the middle-old group. The ED_{50} and ED_{95} of dexmedetomidine differed significantly between the two groups (both $P < 0.001$). The BIS_{50} (95% CI) for sedation with dexmedetomidine was 85 (range: 84–87) for the middle-old group and 86 (range: 81–91) for the young-old group. There was no significant difference in the BIS_{50} or BIS_{95} for adequate dexmedetomidine sedation between the two groups ($P > 0.05$; Table 3). The correlation between OAA/S scores and BIS was calculated for each group; the Spearman correlation coefficients were both >0.6 ($P < 0.001$).

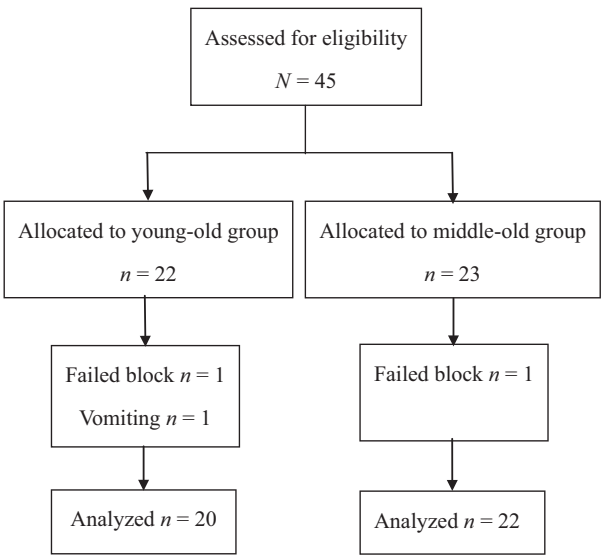

Fig. 1. Consort diagram showing patient flow. Boxes and arrows, flow of participants through enrollment, allocation, follow up and analysis stage of the trial.

Table 2 Characteristics of the two groups.

	Young-old group (n = 20)	Middle-old group (n = 22)	*P*-value
Age (years)	68 ± 3	79 ± 2	<0.01
Gender (female)	15 (75%)	18 (82%)	>0.05
Body weight (kg)	69 ± 7	65 ± 6	>0.05
Hypertension	7 (53%)	7 (32%)	>0.05
Diabetes mellitus	2 (10%)	3 (14%)	>0.05

Data are means ± SD or *n* (%).

After dexmedetomidine infusion, the SBP, diastolic blood pressure (DBP), and mean blood pressure (MBP) of both groups were increased, while HR was decreased compared with the baseline values; however, none of the differences were statistically significant (all $P > 0.05$; Fig. 3). The administered doses of nicardipine and atropine did not differ significantly between the two groups (both $P > 0.05$; Table 4). After start of dexmedetomidine infusion, one patient in the young-old group showed premature atrial contractions on the ECG. No patient showed an oxyhemoglobin desaturation value below 95% during the observation period.

Discussion

In this study, we used Dixon's up-and-down method and probit analysis to extrapolate the ED_{50} of single-dose intravenous dexmedetomidine, which was administered to participants aged 65–85 years (stratified into two age groups) undergoing TKA surgery with PNB. We also found that ED_{50} decreased as the age of the elderly patients increased.

We found the ED_{50} for adequate sedation with single-dose dexmedetomidine for the young-old and middle-old groups undergoing TKA surgery with PNB was 0.57 (0.47–0.65) and 0.38 (0.28–0.46) μg/kg, respectively. Previous studies have

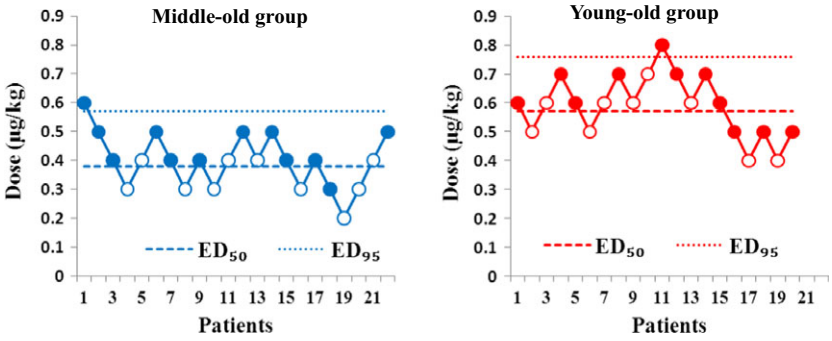

Fig. 2. Dexmedetomidine infusions required to achieve three up-and-down cycles in each group. Blue dashed line, the median effective dose (ED_{50}) for sedation with single-dose dexmedetomidine for the middle-old group. Blue dotted line, the 95% effective dose (ED_{95}) for sedation with single-dose dexmedetomidine for the middle-old group. Red dashed line, the ED_{50} for sedation with single-dose dexmedetomidine for the young-old group. Red dotted line, the ED_{95} for sedation with single-dose dexmedetomidine for the young-old group. Solid circles, successful sedation. Hollow circles, failure sedation.

Table 3 Dose–response and BIS-response data for dexmedetomidine sedation in each group, as derived from probit regression.

	Young-old group (n = 20)	Middle-old group (n = 22)	P-value (t-test)
ED_{50} (95% CI) (μg/kg)	0.57 (0.47–0.65)	0.38 (0.28–0.46)	<0.001
ED_{95} (95% CI) (μg/kg)	0.76 (0.67–1.08)	0.57 (0.48–0.89)	<0.001
BIS_{50} (95% CI)	86 (81–91)	85 (84–87)	>0.05
BIS_{95} (95% CI)	72 (53–78)	73 (69–76)	>0.05

ED_{50}, median effective dose; CI, confidence interval; ED_{95}, 95% effective dose; BIS_{50}, median effective bispectral index; BIS_{95}, 95% effective bispectral index.

described administration of single- or initial-dose dexmedetomidine in elderly patients sedation.[8,18–21] Generally, doses ranging from 0.5–1.0 μg/kg delivered as a 10-min infusion were associated with excessive sedation, bradycardia, hypotension, desaturation, or delayed recovery. However, the dose effect varied among these studies, which may be partly due to differences in population age, the invasiveness of the procedures, and the methods of anesthesia. In two dexmedetomidine dose–response studies conducted in elderly patients under spinal anesthesia,[22,23] the ED_{50} of single-dose dexmedetomidine required to obtain adequate sedation was 0.25 and 0.29 μg/kg, respectively. These ED_{50} values were both lower than those in our study, which is probably because spinal anesthesia itself can reduce the requirement for sedative hypnotics as a result of decreased afferent input.[24] Our study was performed under PNB, which affects bodily systems less than spinal anesthesia and also provides sufficient analgesia. Thus, in our opinion, PNB constitutes an ideal model for assessing the dose of dexmedetomidine as a sedative in elderly patients, due to a small amount of confounding pharmacological factors and minimal cardiovascular effects.

Our study revealed that the dose of dexmedetomidine required to achieve adequate sedation was lower for older patients. Furthermore, the ED_{50} and ED_{95} values for dexmedetomidine in the middle-old group were decreased by 33% and 25%, respectively, compared with those of the young-old group with a mean age difference of 11 years between the two groups. There are several possible explanations for our findings. First, similar to many other anesthetics,[25] the reduced dose of dexmedetomidine required in older patients could primarily be a function of changes in the pharmacodynamics of dexmedetomidine with age. Second, there was a negative correlation between age and dexmedetomidine clearance. Venn et al. found that clearance of dexmedetomidine decreased with age in a population

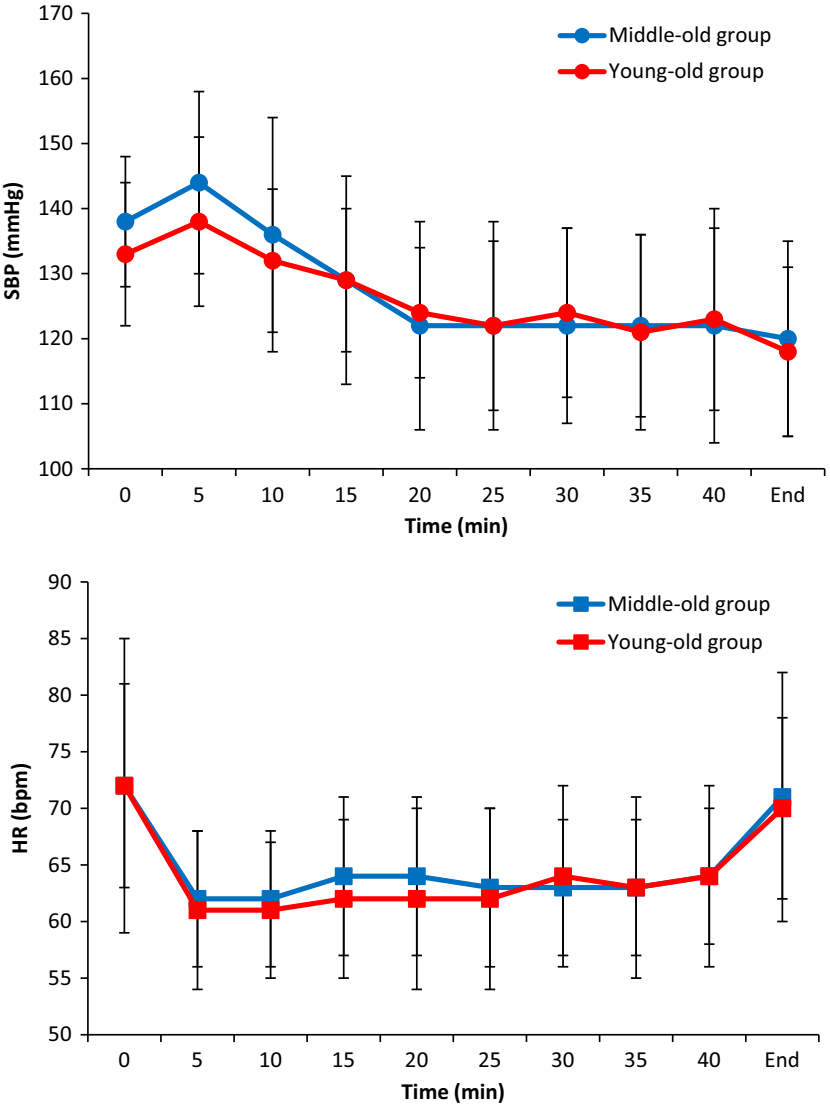

Fig. 3. Intraoperative hemodynamic changes in both groups. Blue circles, mean systolic blood pressure (SBP) at different time point after dexmeditomidine infusion in the middle-old group. Red circles, mean SBP at different time point after dexmeditomidine infusion in the young-old group. Blue squares, mean heart rate (HR) at different time point after dexmeditomidine infusion in the middle-old group. Red squares, mean HR at different time point after dexmeditomidine infusion in the young-old group. 0 min, start of dexmedetomidine infusion.

aged 22–85 years.[26] Iirola et al. found that the clearance rate in an 80-year-old subject was about 25% lower than that in a 60-year-old subject; they also found that the elimination half-life and context-sensitive half-time of dexmedetomidine were prolonged in their elderly patients.[13] Third, the prevalence of underlying comorbidities is higher, and physiological reserves are lower (in terms of body weight, cardiac output, and plasma albumin level) in older patients compared with their younger counterparts;[13–15,26] this may also affect the pharmacokinetics of dexmedetomidine.

Dexmedetomidine produces a dose-dependent biphasic BP response and reduces HR when given as an intravenous bolus. In previous studies applying single- or initial-dose dexmedetomidine sedation in elderly patients, bradycardia and hypotension were the most common side-effects, and occurred more

Table 4 Safety outcomes after dexmedetomidine infusion.

	Young-old group (n = 20)	Middle-old group (n = 22)	P-value
Bradycardia	8 (40%)	9 (41%)	>0.05
Hypertension	10 (50%)	12 (55%)	>0.05
Hypotension	1 (5%)	0	>0.05
Premature atrial contraction	0	1 (5%)	>0.05
OAA/S score ≤2	6 (30%)	2 (9%)	>0.05
Nausea	1 (5%)	1 (5%)	>0.05
Agitation and rigor	0	1 (5%)	>0.05

OAA/S, Observer's Assessment of Alertness/Sedation scale. Data are expressed as n (%).

frequently with dexmedetomidine doses exceeding 0.5 μg/kg.[8,18–21] Although a previous study reported that maintenance doses of up to 10 μg/kg per hour were tolerated,[27] without producing hypotension or bradycardia, when used as a total intravenous anesthetic agent in certain patients, there are other case reports in which the use of dexmedetomidine in elderly patients was associated with the occurrence of severe bradycardia or hypotension,[27,28] sometimes even progressing to asystole. In our study, none of the patients developed clinically significant hemodynamic disturbances requiring intervention. It may be due to the lower doses of dexmedetomidine used for sedation. Moreover, a thigh tourniquet was applicated before incision and dexmedetomidine infusion. Since BP increased gradually during tourniquet application,[29] it could in part alleviate the BP lowering effect induced by dexmedetomidine.

In a previous study conducted on healthy volunteers,[10] intravenous dexmedetomidine at a dose of 0.5 μg/kg caused a maximum decrease in HR of 10% and SBP of 16%; in our study, the respective reductions were 15.3% and 11.6%. Although the decrease in HR was transient and no subsequent adverse cardiovascular event was observed, these fluctuations should be monitored vigilantly because cardiac events are the most common complications after TKA,[30] particularly in patients with impaired cardiac function.

Our study found a moderate correlation between sedation and dexmedetomidine in elderly patients, in accordance with Christopher et al. In their study, the older patients (aged above 55 years) had weaker correlations between Patient State Analyzer data and OAA/S scores compared with the younger patients.[31] The correlation between electrophysiological and clinical assessments of sedation level remains controversial.[31–34]

Study limitations

In this study, the participants were elderly patients with osteoarthritis undergoing TKA, which represents a relatively homogenous population. Therefore, the ED_{50} and ED_{95} of dexmedetomidine extrapolated from our data might accord with those of elderly patients subjected to different PNBs and local anesthesia treatments. However, our results cannot be generalized to other procedures or anesthesia treatments when dexmedetomidine is used as the sole anesthetic agent.

In our study, the patients received a moderate dose of midazolam and fentanyl before PNBs. Although time duration of injection and dexmedetomidine infusion was more than 30 min, our results could still be influenced. However, each patient's OAA/S score was 5 and BIS was more than 92 before infusion was started, which indicates the influence may be very light.

Because the elimination time of dexmedetomidine is 2.3 h, single-dose dexmedetomidine is not suitable for use over longer durations. Thus, it is desirable to administer dexmedetomidine continuously to ensure adequate depth of sedation during longer operations. In addition, the correlation between clinical/sedative response and plasma levels at different doses could have been revealed if we had measured the plasma concentration level of dexmedetomidine at certain time spots.

In conclusion, the ED_{50} for single-dose intravenous dexmedetomidine, which induced adequate sedation in our young-old and middle-old groups undergoing TKA surgery with PNB, was 0.57 (0.47–0.65) and 0.38 (0.28–0.46) μg/kg, respectively. These values indicate that older age had an effect on the potency of dexmedetomidine administered to elderly patients.

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