BJA

British Journal of Anaesthesia, 126 (3): 684–691 (2021)

doi: 10.1016/j.bja.2020.11.037
Advance Access Publication Date: 23 January 2021
Paediatric Anaesthesia

PAEDIATRIC ANAESTHESIA

Determination of the ED_{95} of a single bolus dose of dexmedetomidine for adequate sedation in obese or nonobese children and adolescents

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Abstract

Background: With the increasing prevalence of children who are overweight and with obesity, anaesthesiologists must determine the optimal dosing of medications given the altered pharmacokinetics and pharmacodynamics in this population. We therefore determined the single dose of dexmedetomidine that provided sufficient sedation in 95% (ED_{95}) of children with and without obesity as measured by a minimum Ramsay sedation score (RSS) of 4.

Methods: Forty children with obesity (BMI >95th percentile for age and gender) and 40 children with normal weight (BMI 25th–84th percentile), aged 3–17 yr, ASA physical status 1–2, undergoing elective surgery, were recruited. The biased coin design was used to determine the target dose. Positive responses were defined as achievement of adequate sedation (RSS ≥4). The initial dose for both groups was dexmedetomidine 0.3 μg kg^{-1} i.v. infusion for 10 min. An increment or decrement of 0.1 μg kg^{-1} was used depending on the responses. Isotonic regression and bootstrapping methods were used to determine the ED_{95} and 95% confidence intervals (CIs), respectively.

Results: The ED_{95} of dexmedetomidine for adequate sedation in children with obesity was 0.75 μg kg^{-1} with 95% CI of 0.638–0.780 μg kg^{-1}, overlapping the CI of the ED_{95} estimate of 0.74 μg kg^{-1} (95% CI: 0.598–0.779 μg kg^{-1}) for their normal-weight peers.

Conclusions: The ED_{95} values of dexmedetomidine administered over 10 min were 0.75 and 0.74 μg kg^{-1} in paediatric subjects with and without obesity, respectively, based on total body weight.

Clinical trial registration: ChiCTR1800014266.

Keywords: biased coin design; body mass index; dexmedetomidine i.v.; obesity; paediatric patients; sedation

Editor's key points

- Obesity influences the pharmacokinetics and thus the dose requirements of many anaesthetic drugs.
- This study used the biased coin design to determine the dexmedetomidine loading dose that provides effective sedation, defined as a Ramsay sedation score ≥4, in 95% (ED_{95}) of children with and without obesity (3–17 yr old).
- The ED_{95} was 0.75 and 0.74 μg kg^{-1} in children with obesity and with normal weights, respectively.
- The results indicate that children with obesity and with normal weights require similar weight-based doses of dexmedetomidine.

The requirement of dosage adjustment of anaesthetics in patients with obesity is clearly evidenced by several clinical pharmacokinetics and pharmacodynamics trials.[1–5] With physiological and pathological changes of body composition, patients with obesity may have an increased volume of distribution (Vd) for drugs with high lipid affinity, which may be a factor for over- or under-dosing, leading to increased adverse

Accepted: 3 November 2020

events and the risk of suboptimal efficacy, respectively.[6] In addition to its drug distribution effects, obesity may affect cardiac output and liver and kidney functions, leading to changes of other pharmacological parameters, such as absorption rate, bioavailability, and total body clearance (CL).[3,7] Therefore, to ensure the effectiveness and safety of sedative–anaesthetic protocols in patients with obesity, the optimal dosage of drugs should be clearly specified. Although the lower weight-based dose requirement for several i.v. anaesthetic drugs, including propofol and fentanyl, has been demonstrated in patients with obesity,[1,4,8] very few clinical studies have emphasised the effect of obesity on the pharmacodynamics of dexmedetomidine,[9–12] and even fewer data are available on weight-related dosing of dexmedetomidine in children with obesity. The aim of this study was to determine the dose that provides sufficient sedation in 95% of subjects (ED_{95}) of single bolus of dexmedetomidine in children with obesity and normal-weight controls for preoperative sedation, and the appropriate body size descriptor for each body weight group.

Methods

This study was registered on the Chinese Clinical Trial Registry, a primary registry of the WHO international clinical trial registry platform, ChiCTR1800014266. The research study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Shanghai Sixth People's Hospital (No. 2018-023). Written informed consent was obtained from parents or guardians, and assent was obtained in children aged over 7 yr.

Inclusion criteria were children aged 3–17 yr; BMI for age and sex either >95th percentile or between the 25th and 84th percentiles; and children scheduled for elective orthopaedic surgery under regional, local, or general anaesthesia.

Exclusion criteria included American Society of Anesthesiologists (ASA) physical status 3 or higher; receiving preoperative administration of anticonvulsants, sedatives, or medication for attention deficit disorder; diagnosed heart, renal, or liver disease; chronic hypertension; hypoalbuminaemia; and allergy to any of the study medications.

After measurements of vital signs, including noninvasive BP (NIBP), HR, oxygen saturation (Spo_2), and ventilatory frequency (VF), topical local anaesthetic cream was applied to potential venous cannulation sites and i.v. route was established in the pre-anaesthesia area. Wearable sensors were set up to allow monitoring with a Datex S/5™ monitoring system (GE Healthcare Canada, Mississauga, ON, Canada). Bispectral index (BIS) monitoring (Aspect Medical Systems, Inc., Shattuck, MA, USA) was applied to all patients. The NIBP (including the patient's systolic, diastolic, and mean BP values), HR, Spo_2, VF, and BIS were continuously monitored and recorded every 5 min.

Before administration, dexmedetomidine 8 μg ml^{-1} was prepared by diluting dexmedetomidine 400 μg (2 ml) (Precedex™; Hospira, Inc., Lake Forest, IL, USA; 200 μg ml^{-1}) in saline 0.9% (48 ml). The study dose (range: 0.54–10.25 ml) was then further diluted in saline 0.9% to a total volume of 15 ml. A bolus of dexmedetomidine was administered at a rate of 1.5 ml min^{-1} *via* an infusion pump (Smiths Medical, Zhejiang Province, China), and followed immediately by a flush of saline 0.9% (5 ml). The sequential dose was assigned according to the biased coin design (BCD) study method, with an initial dose of 0.3 μg kg^{-1} for the first patient in both groups of children with and without obesity.

The six levels of Ramsay sedation scale were used for measuring the depth of sedation in children.[13] The RSS was assessed by an experienced anaesthesiologist, who was blinded to the study group, immediately before, every 5 min during, and after dexmedetomidine bolus for 40 min.

After completion of the 40 min observation, the patients were transferred to the operating theatre and underwent the scheduled surgeries under regional, local, or general anaesthesia.

Atropine 20 μg kg^{-1}, ephedrine 5 μg kg^{-1}, and epinephrine 10 μg kg^{-1} as rescue medications were immediately available for every patient. Absolute HR ≤50 beats min^{-1} or hypotension with MAP decrease of ≥30% of baseline would be treated with atropine or ephedrine or both, followed by remeasurement 1 min later; if necessary, these boluses could be repeated. Hypertension with MAP increase of ≥30% of baseline would be followed by careful observation for 1 min; if persistent, clinical interventions were left to the clinician's discretion.

Biased coin design method

We used the BCD method[14] to determine the effective dose level of dexmedetomidine at the quantile Γ=0.95 for children with and without obesity. In brief, K ordered dose levels were chosen with a fixed increment of 0.1 μg kg^{-1} between levels. The successive patients were exposed to one of the sequential K dose levels with an initial dose of 0.3 μg kg^{-1}, the lowest dose in the current study, for both groups at the discretion of the investigators. The response of the previous patient determines the dose level for subsequent patients. For example, if a negative response was observed in the previous patient, the next patient in the same assigned group received the next higher dose of dexmedetomidine in a predetermined increment (0.1 μg kg^{-1}) from the previous dose. If a positive response was observed, the next patient in the same group received, in random manner, either the same dose in P=0.95 or the lower dose with the 0.1 μg kg^{-1} decrement from the previous in P=0.05. Positive responses to dexmedetomidine were defined as RSS ≥4 at 10 min after completion of the 10 min bolus of dexmedetomidine. In our experience, RSS 4 is a satisfactory sedation level in children for the induction of anaesthesia, for both smooth separation from parents and establishment of the i.v. access. In addition, RSS 4 or 5 is accepted as the depth of safe and effective procedural sedation with dexmedetomidine for paediatric patients.[15–17]

Statistical analysis

In BCD studies, *a priori* of sample size calculation is unavailable because of the non-independence of the assignment of doses and unknown distribution. Using the Monte Carlo simulation, Stylianou and Flournoy[18] have reported that the exmedeto of all target dose estimators is similar in reaching the exmedetomidi of their equilibrium point in about 20 subjects, and is stabilised or nearly stabilised with 40 subjects. Therefore, in the present study, each group included 40 subjects.

Only the 10 min RSS after completion of the bolus infusion of dexmedetomidine was used to determine dexmedetomidine dosing. The ED_{95} of dexmedetomidine in paediatric patients enrolled was estimated by using the isotonic regression estimator $\hat{\mu}_3$,[14] a linearly interpolated dose between P_k^* and P_{k+1}^* bounding the probability of effect $\Gamma = 0.95$. P_k^* and P_{k+1}^*

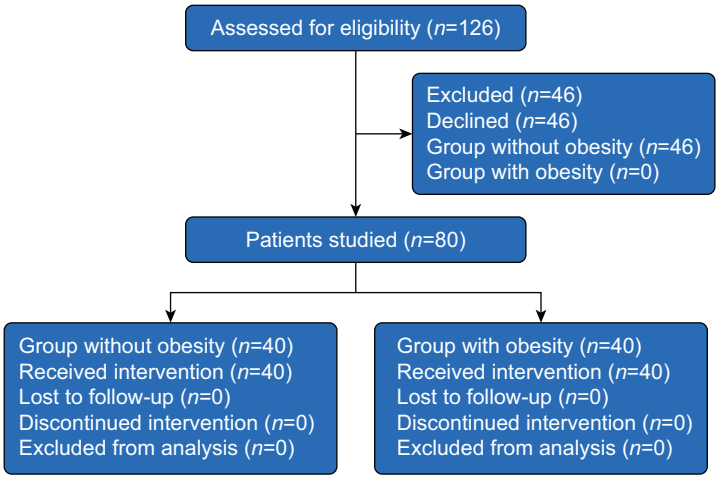

Fig 1. Consolidated Standards of Reporting Trials flow profile.

denote the adjusted response probability at doses x_k and x_{k+1}, respectively, which were calculated monotonically with the pool-adjacent-violators algorithm (PAVA) *via* pooling adjacent increasing and decreasing pairs and recalculating the response rate, as described by Pace and Stylianou.[14] The isotonic regression is an adjustment of regression that constrains the probability of the sequential dose–responses to be monotonic. The approximate 95% confidence interval (CI) of ED_{95} was calculated using a bias-corrected percentile method derived by bootstrapping, with a resampling size of 40, a replicate number of 2000, and a target Γ of 0.95, as described previously.[14,19] R Foundation for Statistical Computing (Vienna, Austria) was used to perform the aforementioned data analysis.

The similarities of demographic variables were compared between paediatric patients with and without obesity by using standardised mean difference of continuous and dichotomous variables, with a standard difference of ≥0.1 indicating important imbalance.[20,21] Baseline BP, HR, VF, and Spo_2 were compared between the two groups using the unpaired Student's *t*-test, and the repeated intragroup measurement data were exmedet by one-way analysis of variance procedure, followed by the least significant difference *t*-test ($P \leq 0.05$) for multiple comparisons. The repeated evaluation data of RSS were exmedet by FREQ procedure, and followed by McNemar test for multiple comparisons. Kendall's tau-b test was used for quantifying the degree of correlation between level of sedation (Ramsay scores ≥4) and BIS monitor values. All these secondary endpoints were exmedet by using SAS 9.2 software. In all cases, $P<0.05$ was considered to be statistically significant.

Results

We enrolled 126 patients undergoing elective orthopaedic surgery between February 2018 and January 2019, and 80 subjects (40 with obesity and 40 with normal weights) completed the study after obtaining informed written consent (Enrolment flow diagram; Fig. 1). The standardised difference analysis of demographic characteristics between subjects with and without obesity indicated a significant difference in age, height, and gender proportions between the two groups, respectively (Table 1).

The positive or negative response for each subject at the assigned dose is illustrated in a standard graphical display, with the subject sequence on the x-axis and each assigned dose on the y-axis, respectively (Figs. 2 and 3).

The frequency of treatment with each specific dexmedetomidine dose and the observed and PAVA-adjusted response rates for subjects with and without obesity are shown in Table 2. The observed response rates occasionally decreased as dose increased, and the PAVA-adjusted response rates never decreased as dose increased.

The ED_{95} estimates calculated with isotonic regression were 0.75 μg kg^{-1} (95% CI: 0.64–0.78 μg kg^{-1}) for children with obesity and 0.74 μg kg^{-1} (95%CI: 0.60–0.78 μg kg^{-1}) for their normal-weight peers. The overlap in the CIs suggested that

Table 1 Subject characteristics. IQR, inter-quartile range; SD, standard deviation; SMD, standardised mean difference.

Characteristic	Without obesity (*n*=40)	With obesity (*n*=40)	SMD
Sex, male:female	18:22	29:11	0.41
Age (yr)			
Median (IQR)	8.3 (5.6–12.2)	9.6 (7.1–13.3)	
Mean [SD]	8.8 [3.5]	10.2 [3.6]	0.39
Range (yr)	3.1–15.3	3.6–17.9	
Weight (kg)			
Median (IQR)	26.9 (20.2–41.1)	46.2 (33.4–68.9)	
Mean [SD]	29.8 [11.5]	54.8 [24.5]	1.31
Range (kg)	13.3–53.3	19.1–111.7	
BMI (kg m^{-2})	16.0 [1.9]	24.6 [4.2]	2.64
Range (kg m^{-2})	12.6–19.9	17.9–36.3	
Height (cm)	133.7 [21.5]	145.1 [22.9]	0.51
Range (cm)	93.3–170.0	101.5–185.0	

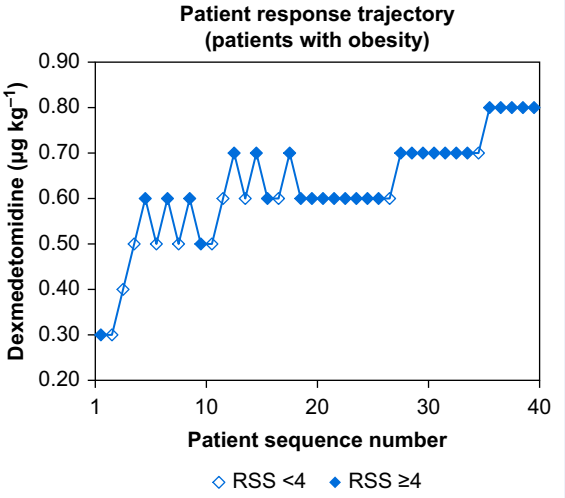

Fig 2. Determination of ED_{95} of single-bolus dexmedetomidine for adequate sedation in children and adolescents with obesity. The subject sequence number (x-axis) is the ordering of subject exposures using the biased coin design. The assigned doses of dexmedetomidine (y-axis) are 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 μg kg^{-1}. An effective dose (RSS ≥4) is denoted by a solid square; an ineffective dose (RSS <4) is denoted by an open square. RSS, Ramsay sedation score.

there was no difference in the ED_{95} between the children with and without obesity.

In this study, the depth of sedation, as assessed by RSS, at 10 min after completion of the 10 min bolus of dexmedetomidine was used for determining the next patient's dose in the assigned group. As shown in Supplementary Table S1, the statistically significant elevation in sedation levels was observed at 10 min following the drug i.v. injection over 10 min; peaked at 15 and 20 min for children with and without obesity, respectively; and remained in adequate sedation until the end of the 40 min observation period. For all patients, the increased RSS coincided with the decreased BIS values (Supplementary Tables S2 and S3): a notable correlation effect between the RSS and BIS values occurred as early as 10 min after the start of drug infusion, as exmedet by Kendall's tau-b coefficient, with the RSS at 20 min after administration coincident with the decrease of BIS index from 94.8 [4.8] to 69.0 [13.2] in the group of children with obesity, and from 94.95 [3.6] to 66.1 [14.6] in the group without obesity.

Children with obesity had a markedly higher BP, including systolic and diastolic BP in comparison with the children without obesity (Fig. 4). Both groups had a marked fall in systolic and diastolic BPs from baseline to 15 min after dexmedetomidine, at the lowest level at 20 min, which lasted up to the end of the 40 min observation period. The percentages of patients who had a 10 mm Hg or more decline in systolic and diastolic BPs from baseline to 20 min were 62.5% and 65% in the group with obesity, and 52.5% and 53% in the group without obesity. There was no decrease of MAP more than 30% from baseline in either group. Notably, a statistically significant decline in HR from baseline appeared at 10 min after starting the injection of dexmedetomidine for both groups (Supplementary Figs. S1 and S2), which was earlier than the decreases in BP, indicating that the HR was more sensitive to the effect of dexmedetomidine.

Discussion

Results from two Phase 3 multicentre trials demonstrate clearly that, in providing light and moderate sedation, dexmedetomidine administration achieves equivalent sedative effects compared with exmedeto and propofol in mechanically ventilated adult ICU patients.[22] With the characteristic of effective sedation but rousable to command, combined with its analgesic and minimal respiratory effects, dexmedetomidine has emerged as an attractive alternative sedative for non-intubated patients before or during many procedures. The significant finding of the current study is that the ED_{95} of i.v. dexmedetomidine as a single bolus for adequate sedation is 0.75 μg kg^{-1} (95%CI: 0.64–0.78 μg kg^{-1}) in children with obesity based on total body weight (TBW), and 0.74 μg kg^{-1} (0.60–0.78 μg kg^{-1}) in their normal-weight peers. Thus, the CIs are overlapping each other, indicating that there is no significant difference in the ED_{95} between the two groups.

We used isotonic regression estimator to derive the ED_{95} of loading doses of dexmedetomidine on the dose–response curve. Such isotonic regression estimator has exmedetom statistical properties for measuring a response at any point (quantile) along the dose–response curve with low bias and variance.[8,23,24] The method of BCD design avoids unverified extrapolations from ED_{50} because of the peak distribution of most administered doses around the mean.[8,14] Therefore, the method of BCD design and the estimator of isotonic regression are commonly used in anaesthesia research.[8,25,26]

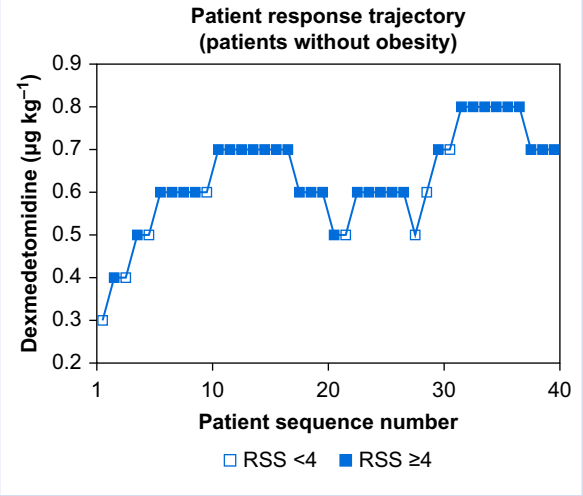

Fig 3. Determination of ED_{95} of single-bolus dexmedetomidine for adequate sedation in children and adolescents without obesity. The subject sequence number (x-axis) is the ordering of subject exposures using the biased coin design. The assigned doses of dexmedetomidine (y-axis) are 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 μg kg^{-1}. An effective dose (RSS ≥4) is denoted by a solid square; an ineffective dose (RSS <4) is denoted by an open square. RSS, Ramsay sedation score.

Table 2 Observed and pool-adjacent-violators algorithm (PAVA)-adjusted response rates with dexmedetomidine (isotonic regression method).

Assigned dose (μg kg^{-1})	Number sedative	Number tested	Observed response rate	PAVA-adjusted response rate
Children without obesity				
0.3	0	1	0.000	0.000
0.4	1	2	0.500	0.429
0.5	3	5	0.600	0.429
0.6	11	14	0.786	0.857
0.7	11	12	0.917	0.917
0.8	6	6	1.000	1.000
Children with obesity				
0.3	1	2	0.500	0.250
0.4	0	1	0.000	0.250
0.5	1	5	0.200	0.250
0.6	12	16	0.750	0.750
0.7	10	11	0.909	0.909
0.8	5	5	1.000	1.000

Although the use of dexmedetomidine in paediatric patients is still 'off-label', it has also been used as a safe and effective sedative during many procedures for children. A previous study by Mason and colleagues[16] showed that dexmedetomidine in high doses, such as a loading dose 2–3 μg kg^{-1} over 10 min followed by an infusion of 1–1.5 to 2 μg kg^{-1}, was satisfactory in providing adequate sedation for children aged 0.1–19.9 yr undergoing MRI and nuclear medicine imaging. Our study indicates that the bolus doses of dexmedetomidine required for adequate sedation in 95% of paediatric patients with obesity and their normal-weight peers were 0.75 μg kg^{-1} (95%Cl: 0.64–0.78 μg kg^{-1}) and 0.74 μg kg^{-1} (95%Cl: 0.560–0.78 μg kg^{-1}), respectively. The dose range of the current study is in line with previous reports, in which bolus doses ranged from 0.5 to 1.0 μg kg^{-1} were recommended.[10,23] The choice of time for the targeted assessment of RSS, which was conducted at 10 min after completion of the 10 min administration of dexmedetomidine, may account for the adequate sedation levels achieved with the smaller loading doses in the present study, because the pharmacokinetic distribution half-life of dexmedetomidine (about 9 min),[27] together with the duration of loading dose infusion, should be taken into consideration when assessing the appropriate time needed for achievement of the desired depth of sedation. This design is similar to that of Koroglu and colleagues,[28] showing that the adequate sedation in children was obtained at 19 [8.2] min after starting dexmedetomidine infusion.

To avoid artifacts, BIS recording was performed simultaneously with Ramsay score evaluation. The depiction of

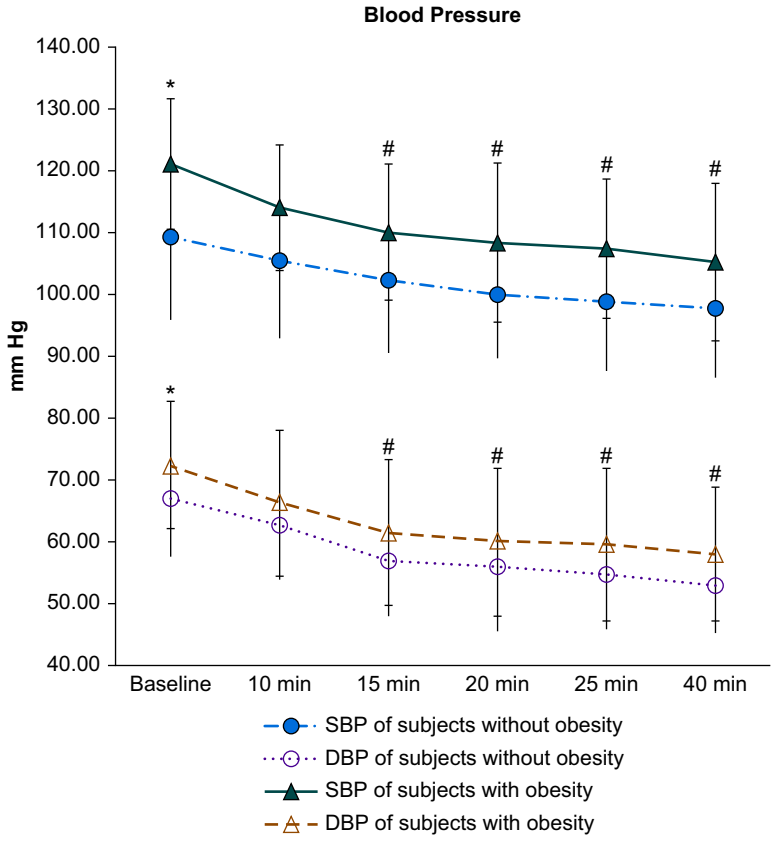

Fig 4. Blood pressure response to dexmedetomidine bolus. There are significantly higher baseline SBP (*P<0.0001) and DBP (*P=0.0159) in patients with obesity than in their normal-weight peers. Significant decreases in both SBP and DBP from baseline in each group (#P<0.05) are observed at 15 min after dexmedetomidine, and persisted until the end of the observation period. DBP, diastolic BP; SBP, systolic BP.

correlation between RSS and BIS index is shown in Supplementary Tables S2 and S3 for both groups, respectively. Significant correlation between RSS and BIS was observed from 10 min after drug administration ($P<0.0001$; Kendall's tau-b coefficient: −0.55 for the group with obesity; and $P<0.001$; Kendall's tau-b coefficient: −0.49 for the group without obesity), with the RSS at 20 min after administration coincident with the decrease of BIS index from 94.8 [4.8] to 69.0 [13.2] in the group with obesity, and from 94.9 [3.6] to 66.1 [14.6] in the group without obesity, suggesting that BIS index is a better predictor for sedation with loading dose of dexmedetomidine. A BIS index between 55 and 77 correlated with adequate analgosedation.[29,30] A previous study by Olutoye and colleagues[8] showed no association between BIS values <60 and the loss of consciousness in determination of ED_{95} protocol with propofol. The lagged effect of BIS values on the monitor, a calculation *via* averaging values over a time period, may make it unsuitable for describing rapidly changing situations that occur during induction of anaesthesia. Our study showed a better response of BIS index to a single-bolus administration of dexmedetomidine.

The effect of obesity on propofol dosing in children has been studied, and a lower dose of propofol in children with obesity was recommended.[8] However, the minimal effective dose of other sedatives in children with obesity has not been well studied.[3,31] Our results indicate that children with obesity required similar body-weight-based dose of dexmedetomidine (in $\mu g\ kg^{-1}$) as normal-weight children. This result is consistent with the study by Obara and colleagues[12] in adult patients showing no significant difference in dexmedetomidine dosing between the groups with and without obesity in terms of dosing of dexmedetomidine using TBW or lean body weight calculator. We used TBW to calculate dexmedetomidine dosage, because the TBW scalar is the most practical method in clinical setting and has been widely used in paediatric patients. In addition, TBW is the best size descriptor in children with obesity for CL,[1] and has been recommended as the appropriate dosing scalar for lipophilic drugs.[1,8]

The haemodynamic effects of dexmedetomidine have been described as biphasic responses of hypotension occurring at low plasma concentrations and hypertension occurring at higher plasma concentrations.[10,23,32] Our study showed that more than half of subjects in this study experienced a moderate decrease in BP after a loading dose of dexmedetomidine, which indicates that the administration of loading doses over 10 min could avoid a high plasma concentration without resultant hypertension. Although the incidence of hypotension was approximately 60% of all the patients, the maximum changes in haemodynamics were all less than 20% of the baseline, which is generally considered acceptable.[16,23,33,34] A tendency for decreases in HR was also observed; however, no patients had an HR below 50 beats min^{-1} during the 40 min observation period (Supplementary Figs. S1 and S2). Our finding is consistent with those of Olutoye and colleagues[8] or Mason and colleagues,[16] showing that fluctuation in haemodynamics was within 20% from normal 'awake' values in response to propofol or dexmedetomidine when used alone to achieve sedation. Patients were continuously monitored by an experienced nurse anaesthetist not involved in the present study, and oxygen saturation was always maintained between 95% and 100%.

Although sequential study designs have been demonstrated to be more efficient to estimate a target dose than non-sequential methods in terms of the requirement of fewer subjects, the biased estimates for the analysis of covariates, such as age and gender, as a result of the non-independence of sequential designs data, constitute a limitation to the methods.[8,14]

Indeed, the notable biases from covariates, including gender, age, and height, between the two groups can be criticised in this study. In terms of sex-related knowledge, there may be some sex-specific differences in pharmacokinetics or pharmacodynamics. However, drug development, until recently, has been performed exclusively in males in accordance with the US Food and Drug Administration guidelines that prohibited the participation of women of childbearing potential,[35] and thus, the effect of gender in paediatric medicine remains to be elusive.

Although the age spectrum at its extreme young plays a major role in individuals who differ from adults in the way that they handle and respond to drugs, recent studies reported that children older than 1 month reach adult levels for dexmedetomidine CL.[36] In addition, the prediction of dexmedetomidine pharmacokinetics by allometric scaling showed that the pharmacokinetic value in children 1 yr or older is in line with the findings in adults.[10] Thus, it is reasonable to assume that the age range of the subjects (3–17 yr) is not involved in the determination of ED_{95} of dexmedetomidine. In addition, the wide age range of children (3–17 yr) in the present study was similar to those by Mason and colleagues[16,17] in using dexmedetomidine sedation in paediatric MRI procedure and nuclear medicine imaging, respectively. Regarding the greater height of children with obesity than those without, previous publications showed that children with obesity are taller than their normal-weight peers (74th percentile).[37] Thus, the difference in height is likely to be subjected to the significant difference in body weights between the two groups.

Given that the BCD sequential study requires minimal computation to assign successive dose and can be performed at high or low quantile, such as $\Gamma=0.95$ or $\Gamma=0.1$, without unverifiable extrapolations from the EC_{50} value, it has been particularly attractive to anaesthesia researchers.[14]

In conclusion, the ED_{95} of dexmedetomidine administered over 10 min is 0.75 $\mu g\ kg^{-1}$ in children with obesity, and there is no significant difference when compared with that of their normal-weight peers (0.74 $\mu g\ kg^{-1}$).

Authors' contributions

Study design: LW, BW
Patient recruitment: BW, JS
Data collection: BW, JS, LW
Data analysis/interpretation: LW, BW, QZ
All authors participated in writing the paper and gave final approval of the version to be published.

Acknowledgements

The authors acknowledge Jie Li and Yupu Liu of Jiao Tong University Affiliated Sixth People's Hospital for their great assistance in the statistical analysis by using SAS software and R functions, respectively. The authors gratefully acknowledge Hannah Y. Wen of the Department of Pathology at Memorial Sloan Kettering Cancer Center, New York, NY, USA, for editing of English grammar and sentence correction. The authors would also like to thank Wei Jiang and Qingru Ouyang of the Department of Anesthesiology at Shanghai Jiao Tong

University Affiliated Sixth People's Hospital for their highly valued assistance with this study.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

Department resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.11.037.

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Handling editor: Tony Absalom