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Determination of optimal combined doses of oral midazolam and intranasal dexmedetomidine for use in pediatric magnetic resonance imaging

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ABSTRACT

Background Sedation is often required for infant and preschool children to obtain clear magnetic resonance imaging (MRI). This study was designed to determine the 95% effective dose (ED_{95}) of oral midazolam (MID) and intranasal dexmedetomidine (DEX) in combination for sedation in pediatric MRI.

Methods We have used a biased coin design up-and-down sequential methodology. Initially, 144 patients were split into two groups. A total of 72 patients were randomly assigned to determine the ED_{95} of DEX in combination with a fixed dose of 0.5 mg/kg MID, and 72 were given various doses of MID combined with a fixed dose of DEX at 1 µg/kg to determine the ED_{95} of MID. ED_{95} was calculated using isotonic regression. At last, the plan was to include 225 cases to test the sedation success rate of DEX combined with MID ED_{95} dose. Adverse events were recorded.

Results The ED_{95} of DEX was 0.89 µg/kg (95% confidence interval (CI) 0.68 to 0.95) combined with a fixed dose of MID at 0.5 mg/kg. The ED_{95} of MID was 0.47 mg/kg (95% CI 0.30 to 0.50) combined with a fixed intranasal dose of 1 µg/kg DEX. Using 1 µg/kg DEX combined with 0.5 mg/kg MID, the sedation success rate was 95.1% in a verification group of 225 children.

Conclusions This study reports relatively low ED_{95} doses of intranasal DEX and oral MID when DEX is determined with a fixed dose of MID and MID determined with a fixed dose of DEX. The combination provides efficient and safe sedation for young children for MRI scanning. Further validation is required.

Trial registration number ChiCTR2300068611.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dexmedetomidine and midazolam are widely used in pediatric sedation.

WHAT THIS STUDY ADDS

⇒ In this study, 95% effective dose was obtained for the combination of dexmedetomidine and midazolam.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a safe, non-invasive sedation protocol with a high success rate for pediatric patients requiring MRI.

INTRODUCTION

Magnetic resonance imaging (MRI) is a non-invasive, radiation-free diagnostic examination that is widely used in pediatric patients.[1] MRI requires patients to be motionless for 10–30 min in a noisy environment.[2] Sedation is therefore required for infant and preschool children during this procedure. The ideal outpatient sedation regimen should be easy to implement, rapid in onset and safe with a low adverse event profile.[3]

Dexmedetomidine (DEX) is a sedative and anxiolytic with a relatively short elimination half life of 2 hours.[4] DEX can be used for outpatient sedation for a variety of examinations in nasal drop format.[5–9] Yuen *et al*.[10] conducted a randomized, cross-over evaluation of healthy adult volunteers and reported that intranasal administration of 1 or 1.5 µg/kg DEX produced sedative effects with onset time of 45–60 min and a peak at 90–105 min. Ambi *et al*.[6] used intranasal DEX at 2 µg/kg and reported no adverse events. The benzodiazepine midazolam (MID) can also be used for preoperative sedation in children,[11] where anxiolysis provides adequate sedation. MID in oral formulation is available in China and is acceptable in the pediatric population for its high efficacy and safety coupled with sweet taste.

However, MID or DEX used alone for sedation is often ineffective for use in MRI examination,[8 12] and therefore they are often used in combination with other drugs.[13 14] It is unknown whether intranasal low-dose DEX combined with oral MID could provide better sedation with less side effects. This study was designed to determine the 95% effective dose (ED_{95}) of intranasal DEX combined with a fixed dose of oral 0.5 mg/kg MID, and the ED_{95} of oral MID combined with a fixed dose of intranasal DEX at 1 µg/kg. The aim

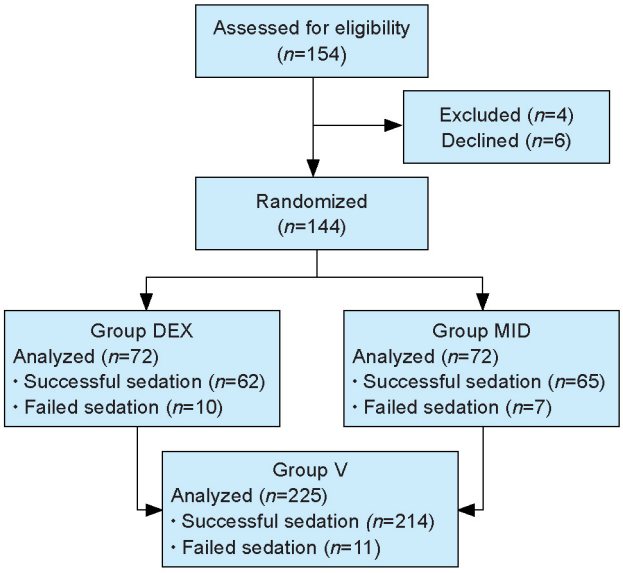

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of study. DEX, dexmedetomidine; MID, midazolam.

of this study is to obtain accurate measurements of MID combined with DEX.

METHODS

Patient recruitment

American Society of Anesthesiologists (ASA) physical status I–II was enrolled into this study and assigned by random number table into DEX and MID groups. To avoid interobserver bias, the same anesthesiologist was involved in all assessments. The study was designed in three phases. Patients were devided into two groups. In the DEX group, the ED_{95} dose of intranasal DEX was determined combining with a fixed dose of oral 0.5 mg/kg MID. In the MID group, patients were randomly recruited to assess the ED_{95} dose of oral MID, with a fixed dose of intranasal DEX at 1 µg/kg (online supplemental file 1). Finally, we verified the sedative success rate when the ED_{95} dose of intranasal DEX combined with oral MID (group V).

Exclusion criteria included: age greater than 6 years or less than 2 months, nasal mucosa injury, severe respiratory tract infection, history of failed sedation, history of allergy to DEX or MID, mental or conscious disorder, arrhythmia; especially chronic, severe obesity (≥50% above standard body weight) and severe upper respiratory tract obstruction.

The BCUD (a biased coin design up-and-down) sequential method was used to determine the ED_{95} of DEX or MID; this normally requires 20–40 patients as reported previously.[15–17] For the validation group, we obtained a sample size of 225 based on the following formula. In group V, the inclusion and exclusion criteria were the same as the DEX group and MID group.

$$N=Z^2_{1-\alpha/2}(1-p)/\varepsilon^2 p$$

where $Z_{1-\alpha/2}$ is the percentage corresponding to the area of $1-\alpha/2$ under the standard normal distribution, and p represents the expected success rate and the percentage of ε expected success rate. In this study, according to the pre-experimental results, p=0.95, ε=3%, α=0.05. $Z_{1-\alpha/2}$=1.96.

Study protocol

All patients were fasted for 6 hours for solids and 4 hours for milk. Non-milk fluids were allowed up to 1 hour before sedation. All patients would be given DEX and MID 40–50 min before the start of the examination.

In the DEX group, each patient was given 0.5 mg/kg MID orally (Batch No 1L911011; 10 mL:20 mg; Yichang Renfu Pharmaceuticals, China), and then DEX (Batch No 220527BP; 2 mL:200 µg; Jiangsu Hengrui Medicine, China) was instilled into both nostrils with a 1 mL syringe. According to the previous experiments from our research center,[18] DEX nasal drops started at 0.5 µg/kg. The nasal drop dosage was adopted by partial coin sequential methodology, and the sedative effect of the previous case determined the dosage of the next case. If sedation was effective in the previous case, there was a 5% probability of reducing the nasal drop dosage by 0.1 µg/kg, and a 95% probability of maintaining the original dose in the next case. If sedation failed, the next case would be to increase the dose by 0.1 µg/kg.

Table 1 Group characteristics

Variables	Group DEX (*n*=72)	Group MID (*n*=72)	Group V (*n*=225)	*P* value (group DEX versus group MID)
Age (month)	18.0 (9.0–42.0)	24.0 (9.0–40.0)	25.0 (6.0–44.0)	0.710
Gender, male	29 (40.3)	26 (36.1)	99 (44.0)	0.610
Weight (kg)	12.5 (8.5–16.5)	12.5 (8.0–17.0)	12.7 (8.2–17.2)	0.920
ASA (I/II)	69/3	62/10	204/21	0.080
Successful sedation	65 (90.3)	62 (86.1)	24 (95.1)	0.440
Sedation onset time (min)	30±11	28±9	28±10	0.650
Recovery time (min)	57±37	59±41	65±35	0.780

Data was presented as number (%) or median (IQR) or mean±SD.
ASA, American Society of Anesthesiologists; DEX, dexmedetomidine; IQR, interquartile range; MID, midazolam; SD, standard deviation; V, dexmedetomidine plus midazolam.

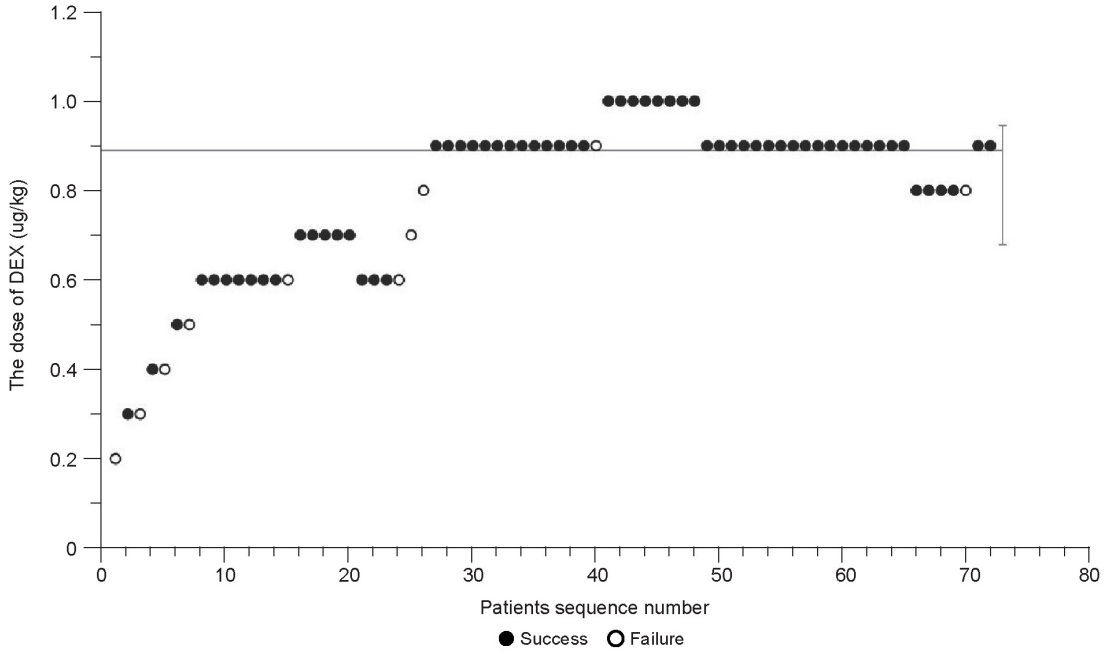

Figure 2 Determination of 95% effective dose (ED_{95}) of dexmedetomidine (DEX) combined with a fixed dose of midazolam (MID) at 0.5 mg/kg for adequate sedation in children. The subject sequence number (x-axis) is the ordering of subject exposures using the biased coin design. The assigned doses of DEX (y-axis) are 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 µg/kg. An effective dose is denoted by a solid circle; an ineffective dose is denoted by an open circle. The horizontal line is the ED_{95}; error bars represent the 95% CI.

In the MID group, a fixed dose of 1.0 µg/kg DEX was used, and increasing oral MID doses with an initial dose of 0.25 mg/kg and an increment of 0.05 mg/kg. The following steps were the same as for the DEX group above. Vital signs and sedation scores were monitored and recorded at 10 min intervals until the patients were discharged from recovery.

In group V, 225 children were randomly included. Combined DEX and MID doses were selected, which synthesized the results of the preliminary experiment. Vital signs and sedation scores were monitored and recorded at 10 min intervals until the patients were discharged from recovery.

Outcomes and definitions

Sedation score was determined according to the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. When the sedation score was <2, the patient underwent MRI examination. If the sedation score was >2 at 5 min before MRI scanning, the child was administered inhalation sevoflurane or intravenous propofol (1–2 mg/kg) as rescue sedation to complete the examination.

As soon as the MRI was completed, patients were transferred to recovery. Their Modified Aldrete Recovery Scale (MARS) was recorded every 10 min. When MARS was ≥8, patients were considered to be awake and were allowed to leave the recovery room with MARS >9.[19] Patients were followed up for 24 hours with a telephone interview.

The following data were recorded: (1) Demographics including sex, age, weight and ASA. (2) Vital signs including blood pressure (BP), heart rate (HR), SpO_2, respiratory rate and sedation scores which were recorded at 10 min intervals after drug administration. (3) Successful sedation was defined as MOAA/S <2 until the end of the examination without rescue, and the magnetic resonance image was approved by the radiologist. Sedation failure was defined as MOAA/S >2 at 5 min before MRI examination, or patients awakening before the examination was accomplished. (4) The sedation onset time (defined as drug administration to reaching MOAA/S ≤2) and the recovery time (defined as accomplishing examination to reaching MARS >8). (5) Adverse events recorded within 24 hours: low HR and BP, oxygen desaturation, nausea or vomiting. Abnormal HR and BP were defined as a reduction or increase of over 20% compared with the baseline. It was difficult to measure HR and BP due to anxiety and tension before medication in children and their values were adjusted as reported in previous studies.[1 20] SpO_2 below 90% was defined as desaturation. Mask assistant ventilation was used for oxygen desaturation. In children with persistent desaturation or difficult face mask ventilation, we would choose tracheal intubation. Atropine or epinephrine was used to treat low BP and low HR when necessary. Ondansetron was used to treat nausea and vomiting.

Statistical analysis

Isotonic regression and bootstrapping were performed using Python V.3.8.0. The demographic data were presented as mean± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Statistical analysis used SPSS V.22.0 for Windows (SPSS). Additional

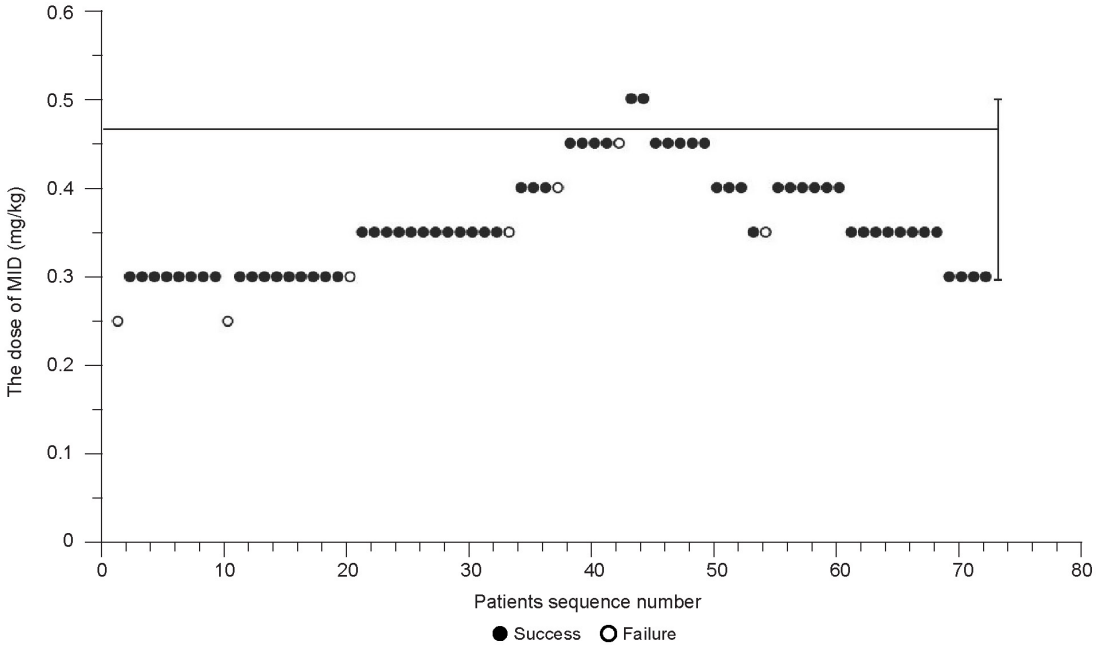

Figure 3 Determination of 95% effective dose (ED95) of midazolam (MID) combined with a fixed dose of dexmedetomidine (DEX) at 1.0 µg/kg for adequate sedation in children. The subject sequence number (x-axis) is the ordering of subject exposures using the biased coin design. The assigned doses of MID (y-axis) are 0.25, 0.30, 0.35, 0.40, 0.45 and 0.50 mg/kg. An effective dose is denoted by a solid circle; an ineffective dose is denoted by an open circle. The horizontal line is the ED_{95}; error bars represent the 95% CI.

normally distributed data were presented as mean±SD, and non-normally distributed data were expressed as median (IQR). Statistical analysis for differences between the groups was performed using the two-tailed Student's *t*-test when normality (and homogeneity of variance) assumptions were satisfied; otherwise, non-parametric testing (Mann-Whitney *U* test) was used. Categorical data were analyzed by χ^2 test or Fisher's exact test. The threshold for statistical significance was set at $p<0.05$.

RESULTS

A total of 369 patients were enrolled (figure 1). There were 72 young patients were randomly enrolled in the group DEX and another 72 cases were randomly recruited in the group MID. Patient characteristics are presented in table 1. Onset of sedation in the DEX group was 30 (IQR: 19–41) min and 28 (IQR: 19–37) min in the MID group. Recovery time was 57 (IQR: 20–94) min in the DEX group and 59 (IQR: 18–100) min in the MID group. First successful sedation in the DEX group was 90.3% (*n*=72) and was 86.1% (*n*=72) in the MID group. The ED_{95} of intranasal DEX was estimated to be 0.89 µg/kg (95% CI 0.68 to 0.95) (figure 2). The ED_{95} of oral MID was estimated to be 0.47 mg/kg (95% CI 0.30 to 0.50) (figure 3).

According to the statistical results of the preliminary trial and for the convenience of clinical calculation, we set the dosage of 1 µg/kg DEX and 0.5 mg/kg MID in the verification group where 225 children were included (group V). The onset of sedation was 28 (IQR: 18–38) min, recovery time was 65 (IQR: 30–100) min, sedation time was 95 (IQR: 61–129) min and the rate of first successful sedation was 95.1% (table 1).

Table 2 Adverse events within 24 hours

Variables, n (%)	Group DEX (*n*=72)	Group MID (*n*=72)	Group V (*n*=225)	*P* value (group DEX versus group MID)
Nausea and vomiting	2 (2.8)	1 (1.4)	10 (4.4)	0.560
Hypoxemia	0 (0.0)	0 (0.0)	0 (0.0)	–
Hypotension	2 (2.8)	2 (2.8)	8 (3.6)	1.000
Hypertension	10 (13.9)	4 (5.5)	24 (9.3)	0.090
Bradycardia	2 (2.8)	2 (2.8)	6 (2.7)	1.000
Respiratory depression	0 (0.0)	0 (0.0)	0 (0.0)	–
Irritability	3 (4.2)	2 (2.8)	2 (0.9)	0.650

DEX, dexmedetomidine; MID, midazolam; V, dexmedetomidine plus midazolam.

Adverse events are reported in table 2; these were mild and required no reversal agents. All MRI scanning was completed successfully, and there was no requirement for second examinations.

DISCUSSION

Our study showed that the ED_{95} of intranasal DEX combined with 0.5 mg/kg oral MID for sedation in children aged 2 months–6 years undergoing MRI was 0.89 µg/kg. The ED_{95} of MID combined with 1 µg/kg DEX was 0.47 mg/kg.

Intranasal DEX has been widely used in invasive procedures for sedation in the young.[21] Its use for pediatric MRI alone was unsatisfactory with a success rate of only 60%[6] in one study and 30%–70% in another.[22] In addition, Chandrasekar *et al*. showed that the success rate of pediatric MRI with MID alone was only 9.5%.[23] To avoid the disadvantages of sole DEX or MID use, recent literature has shown beneficial effects of combining these for procedural sedation in pediatric patients. Gu *et al*. reported that the one-time sedation success rate with the combination of 3 or 2 µg/kg intranasal DEX and 0.2 mg/kg oral MID was 88.31% and 79.75%, respectively.[13] A retrospective study from our hospital suggests that the combination of 2 µg/kg intranasal DEX and 0.5 mg/kg oral MID resulted in a total success rate of 99.7% and a sedation success rate of 91.4%.[24] Combining the two offered a higher one-time sedation success rate with good sedation clearly shown in our study. In terms of onset time, the results of this study were similar to those of the previous studies,[6 13 24 25] and the recovery time was shorter than that of 3 µg/kg DEX alone and the combination of 2 µg/kg intranasal DEX and 0.5 mg/kg oral MID.[21 24] Combination of intranasal DEX and oral MID avoided the need for re-examination; this was manpower and cost-effective.

In this study, we used 'isotonic regression estimation' to derive the ED_{95} of DEX and MID. Such isotonic regression estimation has statistical properties valuable for measuring a response at any point (quantile) along the dose–response curve with low bias and variance.[26 27] This avoids unverified extrapolations from the 50% effective dose (ED_{50}) because of the peak distribution of most administered doses around the mean. Compared with ED_{50}, the potency dose of real interest is ED_{95} or the 95% effective dose (ED_{99}) because the higher percentile effective dose provides better clinical guidance.[28]

Compared with previous studies,[7 8 29] the incidence of adverse events within 24 hours of sedation was much lower in our study, possibly due to the low dose of each agent. Recovery time was a little longer than previously documented, which may be related to the fact that children were allowed to recover naturally.[30]

This study had several limitations. First, this was a single-center study, and therefore the conclusions obtained may not be universal. Second, Vilo *et al*. found that the dose of intranasal DEX was age dependent.[31] To reach desired plasma concentrations, children younger than 2 years of age need larger initial doses of DEX than those over 2 years because of a larger volume of distribution of the drug. The ED_{95} dose for different ages needs to be studied further. Finally, our study only enrolled patients with ASA physical status I–II, and therefore, our result may not be applied to the critically ill patient.

In summary, a low-dose oral MID combined with intranasal DEX can be used via a non-invasive route as an efficient and safe regimen in pediatric sedation for MRI scanning. Further validation is warranted.

Contributors HT and JG contributed to writing the original draft preparation, writing the review and editing. JT, CB and JZ contributed to data curation. YH contributed to conceptualization, writing the review and editing, and resources. HT is the guarantor. All the authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine, Zhejiang, China (2022-IRB-275) and written informed consent was obtained from all guardians of the participants in the trial. The trial was registered prior to patient enrollment at chictr.org.cn (ChiCTR2300068611). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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