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Safety and efficacy of a novel dexmedetomidine nasal spray for pre-anesthetic sedation in children: a randomized, double-blind, placebo-controlled trial

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Abstract

Background Off-label intranasal administration of injectable dexmedetomidine has been widely applied in the pediatric sedation setting. However, the development of an improved drug delivery system that is easy to use is needed. We developed a novel dexmedetomidine nasal spray that can be administered directly without dilution or configuration for pediatric pre-anesthetic sedation. This nasal spray has a fixed dose and is stable during storage. To the best of our knowledge, this is the first licensed nasal spray preparation of dexmedetomidine worldwide.

Objective To evaluate the pre-anesthetic sedation efficacy and safety of the novel dexmedetomidine nasal spray in children.

Methods The study was conducted at 11 sites in China between 24 November 2021 and 20 May 2022 and was registered in ClinicalTrials.gov (NCT05111431, first registration date: 20/10/2021). Subjects ($n=159$) between 2 and 6 years old who were to undergo elective surgery were randomized to the dexmedetomidine group ($n=107$) or the placebo group ($n=52$) in a 2:1 ratio. The dosage was 30 μg or 50 μg based on the stratified body weight. The primary outcome measure was the proportion of subjects who achieved the desired child-parent separation and Ramsay scale ≥ 3 within 45 min of administration. Safety was monitored via the assessments of adverse events, blood pressure, heart rate, respiratory rate and blood oxygen saturation.

Results The proportion of subjects achieving desired parental separation and Ramsay scale ≥ 3 within 45 min was significantly higher in the dexmedetomidine group (94.4%) vs the placebo group (32.0%) ($P<0.0001$). As compared with placebo, dexmedetomidine treatment led to more subjects achieving Ramsay scale ≥ 3 or UMSS ≥ 2, and shorter time to reach desired parental separation, Ramsay scale ≥ 3 and UMSS ≥ 2 (all $P<0.0001$). Adverse events were reported in 90.7% and 84.0% of subjects in the dexmedetomidine and placebo groups, respectively, and all the events were mild or moderate in severity.

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Conclusions This novel dexmedetomidine nasal spray presented effective pre-anesthetic sedation in children with a tolerable safety profile.

Keywords Dexmedetomidine, Intranasal, Pediatric, Sedation, Pre-anesthetic

Introduction

To relieve the anxiety, fear, and stress, ease the child-parent separation and improve the compliance of anaesthesia induction, sedatives are frequently administered as pre-medication in pediatric subjects [1]. Dexmedetomidine, a potent and selective α2-adrenoreceptor agonist, affords sedative, anxiolytic, and analgesic effects [2]. It induces sleep-like sedation that is easily rousable, exerts minimal influence on respiration, and possesses relatively short elimination half-life [3, 4]. Due to these merits, dexmedetomidine is extensively applied as a pre-anesthetic sedative in children in different scenarios, from non-invasive procedures, such as radiographic imaging and electroencephalography, to invasive procedures [5–8].

The intranasal route is convenient and relatively less invasive. It avoids the first-pass hepatic metabolism, and evokes rapid action at the central nervous system [9]. Off-label intranasal administration of dexmedetomidine injection solution in children as drops by syringe or as sprays by mucosal atomization device has been widely reported, in which the satisfactory sedation with acceptable safety was observed [10–12]. However, it was found that when the intravenous preparations were used for intranasal administration, the inter-subject variation in the bioavailability was large. Therefore, the development of an improved drug delivery system is needed [13]. By producing fine small particles, the spray is expected to have less drug loss, increased bioavailability, and improved compatibility as compared with drops [14]. Previous studies demonstrated that the bioavailability of dexmedetomidine nasal spray was higher than that of nasal drops [13, 15]. Compared to administration using a mucosal atomizer, the dexmedetomidine nasal spray is administered in a simpler manner and appears to be well accepted by children and their parents. The dexmedetomidine nasal spray does not require additional atomizing equipment and does not need to be formulated for use, and it can be administered by health care providers or trained parents.

Based on above-mentioned considerations, Jiangsu Hengrui Pharmaceuticals Co., Ltd., (Shanghai, China) developed a novel dexmedetomidine nasal spray. This nasal spray was administered directly with no need of dilution or configuration before use and with a fixed dose and good storage stability. We previously evaluated its safety and tolerability, pharmacokinetics, and pharmacodynamics in healthy adults [15] and children undergoing elective surgery under general anaesthesia (NCT04200235). Its effectiveness and favorable safety profile have been demonstrated in the adult pre-anesthetic sedation setting in a pivotal phase 3 study (NCT04383418). To evaluate its effectiveness and safety as a pre-medication in children, this randomized, double-blinded, and placebo-controlled phase 3 study was designed and executed.

Methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice at 11 sites in China between 24 November 2021 and 20 May 2022 and was registered at ClinicalTrials.gov (NCT05111431, first registration date: 20/10/2021). Ethical approval for this study was provided by Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University and 10 other ethics committees (Supplemental Table 1). Written informed consent was obtained from each subject's legal guardian before participating in the study.

Study population

Subjects irrespective of gender between 2 and 6 years old, with body weight of 10.7 to 28.0 kg [16], with American Society of Anesthesiologists classification I, and who were scheduled to undergo elective surgery under general anaesthesia, were included. Subjects with cardiovascular disease, with abnormal liver function and/or abnormal kidney function, who were deemed as not suitable for intranasal administration (such as with severe rhinitis, having nasal cavity deformity) by the investigator, who have been administered selective α2 adrenergic receptor agonists or antagonists, analgesics, sedatives or hypnotics within 7 days before randomization, and who were known to be allergic to any ingredient in the formulation, were excluded.

Randomization

Subjects were randomly assigned to receive dexmedetomidine nasal spray or the placebo nasal spray in a 2:1 ratio stratified by body weight. Blocked randomization was completed electronically using an interactive web response system. A randomization number was assigned to each subject by a specialist using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina). Subjects,

investigators, site personnel, and sponsor were all blinded to treatments until database lock.

Study drug administration and dose selection

Subjects were administered dexmedetomidine or placebo (0.9% NaCl) nasal spray in the sitting position. The dexmedetomidine nasal spray comes with two separate compartments, one bottle containing the dexmedetomidine solution and one nasal spray pump that delivers fixed dose each spray. The pump needs to be screwed onto the bottle when the product is to be used. After assembling the device, the pump should be pressed several times (away from the person) until one complete spray is visible from the bottle. Then the product can be applied directly to the nasal cavity of the patient, without the need for dilution or configuration. In this study, the spray was applied by the medical staff. To ensure appropriate dosing and simplify administration, two specifications of the product with different concentrations of dexmedetomidine were used. One contained 300 μg of dexmedetomidine per gram with 15 μg of dexmedetomidine in each spray, and the other contained 500 μg of dexmedetomidine per gram with 25 μg in each spray. Dosage was stratified by the subject's body weight. For subjects with body weight of ≥ 10.7 kg and < 19.4 kg, the dexmedetomidine dosage was 30 μg; while for subjects with body weight of ≥ 19.4 kg and ≤ 28.0 kg, the dexmedetomidine dosage was 50 μg. This approach was chosen to accommodate the limited volume that can be administered into the nostril and the one-time nature of the nasal spray administration. Each child received one spray in each nostril, with each spray containing a volume of 50 μL and delivering either 15 μg or 25 μg of dexmedetomidine, depending on the predetermined weight-based dosage.

In a meta-analysis including 14 randomized controlled trials and 1809 pediatric subjects with age from 1 month to 14 years to compare intranasal dexmedetomidine with other sedatives, it was found that at the dose of 1 to 4 μg/kg, intranasal dexmedetomidine showed efficacy superiority to other sedatives, and the dose of 2 μg/kg seemed to be the optimal choice in light of the benefit-risk assessment [17]. This was in accordance with the drug exposure–response relationship findings revealed in our previous phase 1 study, in which 2 μg/kg was determined as the recommended dose for dexmedetomidine nasal spray in pediatric subjects (NCT04200235).

Assessments

Child-parent separation was assessed via FUNK scoring system. It consists of 3 components, i.e., sedation, emotion and separation, and each of the component is assessed by a 4-point scale [18]. In this study, the desired child-parent separation was defined as score ≥ 3 for each component and the successful disengagement of physical and eye contact from guardian. Sedation level was primarily assessed using the Ramsay sedation scale (1 = anxious and agitated or restless; 2 = cooperative, oriented and tranquil; 3 = responsive to commands only; 4 = exhibiting a brisk response to painful stimulus; 5 = exhibiting a sluggish response to painful stimulus; and 6 = exhibiting no response) [19] (Supplemental Table 2). University of Michigan Sedation Scale (UMSS) was also utilized to evaluate sedation level (0 = awake and alert; 1 = minimally sedated: tired/sleepy, appropriate response to verbal conversation, and/or sound; 2 = moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command; 3 = deeply sedated: deep sleep, aroused only with significant physical stimulation; 4 = unarousable) [20] (Supplemental Table 3). Baseline Ramsay scale, UMSS, and child-parent separation were assessed 30 min before treatment administration. Ramsay scale and UMSS were evaluated at 5, 10, 15, 20, 25, 30, 35, 40, and 45 min post administration. FUNK was evaluated at 15, 30, and 45 min post administration, or at the time when Ramsay scale was ≥ 3 for the first time. If desired child-parent separation was achieved within 45 min post administration, subjects would undergo anaesthesia induction without further Ramsay scale or UMSS assessments. If child-parent separation was not achieved until 45 min post administration, rescue medication of propofol (1–2 mg/kg) was intravenously injected. Vital signs (blood pressure, respiratory rate and heart rate) and blood oxygen saturation (SpO_2) were assessed at 10, 15, 30, and 45 min post administration. At a given time point when multiple assessments were required, it was suggested to perform in the order of Ramsay scale, UMSS, child-parent separation, vital signs, and SpO_2.

Outcome measures

The primary outcome measure of this study was the proportion of subjects achieving the desired child-parent separation and Ramsay scale ≥ 3 within 45 min. The secondary efficacy outcome measures were: (1) the proportion of subjects achieving desired child-parent separation within 45 min and the time to achieve the desired child-parent separation; (2) the proportion of subjects achieving Ramsay scale ≥ 3 within 45 min and the time to achieve Ramsay scale ≥ 3; (3) the proportion of subjects achieving UMSS ≥ 2 within 45 min and the time to achieve UMSS ≥ 2. The time frame measured in all efficacy outcomes is calculated from the start time of administration. In previous clinical trials of dexmedetomidine, it was demonstrated that the median time to reach maximum serum concentration ranged 0.75 to 1.00 h; therefore, the efficacy endpoints were set at 45 min to allow the drug to maximally exert its effect.

Safety was evaluated by continuous adverse event (AE) monitoring, assessments of laboratory parameters, vital signs, SpO_2, and electrocardiogram. AE was defined as any untoward medical occurrence that occurs after the subjects receive the investigational drug, which does not necessarily have a causal relationship with study treatment, and can be manifested as symptoms, signs, diseases, or laboratory abnormalities.

Statistical analysis

Based on our previous phase 1 study results (NCT04200235), for the primary outcome measure, the proportion of subjects achieving desired child-parent separation and with Ramsay scale ≥ 3 within 45 min were conservatively estimated to be 70% and 40% for the dexmedetomidine group and placebo group, respectively. In light of that, a sample size of 159 subjects (106 in the dexmedetomidine group and 53 in the placebo group) was calculated to provide 90% power to detect a superior difference between dexmedetomidine and placebo based on Mantel–Haenszel test with a Type I error of 5% and dropout rate of 20%.

Treated subjects were included for the efficacy and safety analyses. For categorical data, difference between the 2 groups was detected by Cochran-Mantel–Haenszel χ^2 test stratified by body weight (10.7 kg ≤ body weight < 19.4 kg and 19.4 kg ≤ body weight ≤ 28.0 kg). For the time from administration to desired child-parent separation, first time achieving Ramsay scale ≥ 3 and achieving UMSS ≥ 2, log-rank test was utilized to detect difference between the 2 groups. Analysis of variation was adopted to make comparison for the time to recovery between the 2 groups. If FUNK score was missing at a timepoint, it was imputed as undesired parental separation. As for Ramsay scale, missing value was imputed by baseline value. For the other efficacy endpoints, no imputation on missing value was made. AEs were coded using Medical Dictionary for Regulatory Activities version 25.0 and summarized by preferred term (PT) with breakdown of treatment groups. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

Results

Subject disposition and characteristics

One hundred and sixty-nine subjects were screened, among whom 159 subjects were randomly assigned to the dexmedetomidine group ($n = 107$) or the placebo group ($n = 52$). Except for 2 subjects in the placebo group, all subjects received the treatments and were included in the efficacy and safety analyses. A total of 156 subjects completed the study (Fig. 1). Demographics and baseline characteristics were generally balanced between the 2 groups (Table 1).

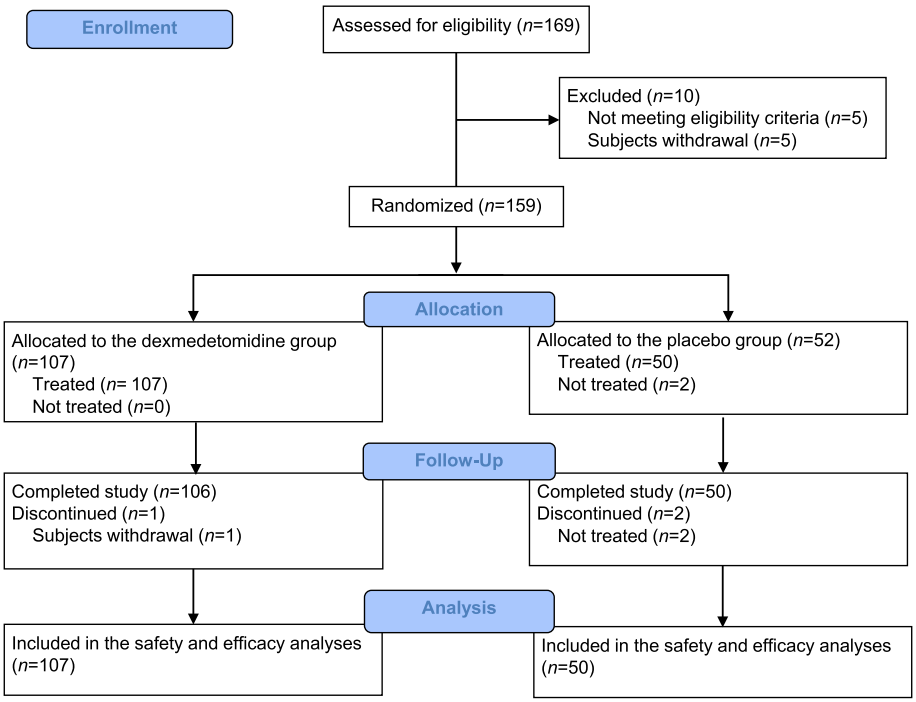

Fig. 1 CONSORT flow diagram

Table 1 Demographics and baseline characteristics

	Dexmedetomidine (*n* = 107)	Placebo (*n* = 50)
Age, mean ± SD (year)	4.0 ± 1.3	3.7 ± 1.4
Height, mean ± SD (cm)	106.8 ± 10.5	104.4 ± 11.8
Weight, mean ± SD (kg)	18.1 ± 3.6	17.6 ± 3.9
10.7 kg ≤ weight < 19.4 kg, *n* (%)	63 (58.9)	28 (56.0)
19.4 kg ≤ weight ≤ 28.0 kg, *n* (%)	44 (41.1)	22 (44.0)
Sex, *n* (%)		
Female	18 (16.8)	5 (10.0)
Male	89 (83.2)	45 (90.0)

Abbreviations: *SD* standard deviation

Efficacy

The proportion of subjects who achieved the desired child-parent separation and Ramsay scale ≥ 3 within 45 min was higher in the dexmedetomidine group than that in the placebo group (94.4% vs 32.0%), and the difference was statistically significant (rate difference [95% CI]: 62.4% [48.7 to 76.1]; $P < 0.0001$) (Table 2).

Results of the secondary efficacy outcomes are displayed in Table 2. In the dexmedetomidine group, 94.4% of subjects achieved desired child-parent separation vs 32.0% in the placebo group, and the difference was statistically significant ($P < 0.0001$). The proportion of subjects achieving Ramsay scale ≥ 3 within 45 min was significantly higher in the dexmedetomidine group than that in the placebo group (96.3% vs 34.0%) ($P < 0.0001$). Same trend was observed for the proportion of subjects with UMSS ≥ 2 within 45 min (92% vs 16%) ($P < 0.0001$). Median (IQR) time to desired child-parent separation was 21.0 (16.0 to 30.0) min in the dexmedetomidine group, and was not reached (NR) (38.0 to NR) in the placebo group ($P < 0.0001$). Median (IQR) time to achieve Ramsay scale ≥ 3 was 20.0 (15.0 to 24.0) min in the dexmedetomidine group, and NR (30.0 to NR) in the placebo group ($P < 0.0001$). Median (IQR) time to achieve UMSS ≥ 2 was 20.0 (18.0 to 30.0) min in the dexmedetomidine group, and NR (35.0 to NR) in the placebo group ($P < 0.0001$). The recovery time was longer in the dexmedetomidine group as compared with the placebo group (median [IQR]: 52.0 [39.0 to 69.0] min vs 38.0 [29.0 to 52.0] min; $P < 0.0001$).

Safety

All the subjects received 2 sprays (1 spray with a volume of 50 μL) of treatments as required by the protocol. Drug outflow occurred in 4 (3.7%) and 4 (8.0%) subjects in the dexmedetomidine and placebo groups, respectively.

AEs occurred in 97 (90.7%) subjects in the dexmedetomidine group and 42 (84.0%) subjects in the placebo group (Table 3). Fifty (50) (46.7%) subjects in the dexmedetomidine group and 21 (42.0%) subjects in the placebo group experienced AEs before anesthesia induction, and 94 (87.9%) subjects in the dexmedetomidine group and 40 (80.0%) subjects in the placebo group experienced AEs after anesthesia induction. All the events were mild or moderate in severity. No subjects discontinued from the study due to AEs, and no serious AEs or deaths occurred. The most frequently reported AEs by PT in both the dexmedetomidine and placebo groups were heart rate decreased (42.1% vs 30.0%), bradycardia (38.3% vs 26.0%) and diastolic blood pressure decreased (19.6% vs 20.0%).

The mean heart rate was lower in the dexmedetomidine group than that in the placebo group within 45 min

Table 2 The efficacy outcome measures

	Dexmedetomidine (*n* = 107)	Placebo (*n* = 50)	*P* value
The primary outcome			
Proportion of subjects achieving desired child-parent separation and Ramsay scale ≥ 3 within 45 min (95% CI), %	94.4 (88.2 to 97.9)	32.0 (19.5 to 46.7)	< 0.0001
Rate difference of dexmedetomidine vs placebo (95% CI), %	62.4 (48.7 to 76.1)		
Secondary outcomes			
Proportion of subjects achieving desired child-parent separation within 45 min (95% CI), %	94.4 (88.2 to 97.9)	32.0 (19.5 to 46.7)	< 0.0001
Proportion of subjects achieving Ramsay score ≥ 3 within 45 min (95% CI), %	96.3 (90.7 to 99.0)	34.0 (90.7 to 99.0)	< 0.0001
Proportion of subjects achieving UMSS score ≥ 2 within 45 min (95% CI), %	86.0 (77.9 to 91.9)	32.0 (19.5 to 46.7)	< 0.0001
Time to achieve the desired child-parent separation, median (Q1-Q3), min	21.0 (16.0 to 30.0)	NR (38.0 to NR)	< 0.0001
Time to achieve Ramsay score ≥ 3, median (Q1-Q3), min	20.0 (15.0 to 24.0)	NR (30.0 to NR)	< 0.0001
Time to achieve UMSS score ≥ 2, median (Q1-Q3), min	20.0 (18.0 to 30.0)	NR (35.0 to NR)	< 0.0001
Recovery time, median (Q1-Q3), min	52.0 (39.0 to 69.0)	38.0 (29.0 to 52.0)	< 0.0001

Abbreviations: *CI* confidence interval, *NR* not reached, *UMSS* University of Michigan Sedation Scale

Table 3 Adverse events summary

	Dexmedetomidine ($n=107$)	Placebo ($n=50$)
Subjects with at least one AE, *n* (%)	**97 (90.7)**	**42 (84.0)**
Subjects with AE by severity, *n* (%)		
Mild	55 (51.4)	25 (50.0)
Moderate	42 (39.3)	17 (34.0)
Severe	0	0
AE occurring in ≥ 10% of subjects in either group by preferred term, *n* (%)		
Heart rate decreased	45 (42.1)	15 (30.0)
Bradycardia	41 (38.3)	13 (26.0)
Blood pressure diastolic decreased	21 (19.6)	10 (20.0)
Urine ketone body present	16 (15.0)	4 (8.0)
Blood pressure decreased	14 (13.1)	8 (16.0)
Hypotension	14 (13.1)	2 (4.0)
Blood pressure increased	11 (10.3)	7 (14.0)
Agitation postoperative	10 (9.3)	5 (10.0)
Blood pressure diastolic increased	8 (7.5)	7 (14.0)
Tachycardia	6 (5.6)	9 (18.0)
Haematuria	2 (1.9)	5 (10.0)

Abbreviation: AE adverse event

post treatment, and was similar at the follow-up visit performed on Day 2 or Day 3. The blood pressure, respiratory rate and SpO_2 were similar between the 2 groups at all pre-determined time points (Fig. 2). No abnormalities of clinical importance, or differences between the 2 groups of clinical importance in the laboratory tests and electrocardiograms were observed.

Discussion

Based on a pivotal phase 3 study (NCT04383418) where statistically significant and clinically meaningful improvement over placebo in pre-anesthetic sedation efficacy in adults was demonstrated, dexmedetomidine nasal spray obtained marketing authorization from the Chinese health authority in March 2023. To the best of our knowledge, this is the first licensed nasal spray preparation of dexmedetomidine worldwide. The current phase 3 study evaluated the pre-anesthetic sedation efficacy in children, with the purpose of seeking approval in China. Considering the scarcity of pediatric drugs, the application has approved by the Chinese health authority via the fast track in August 2023.

Due to restrictions in drug specifications, we selected two fixed doses (15 μg/spray or 25 μg/spray, 2 sprays) in this study. The dexmedetomidine dosage was calculated to be 1.5 to 2.8 μg/kg based on the fixed dose and the body weight. Within this range, dexmedetomidine nasal spray elicited efficacious sedation with acceptable safety in children. Such results were consistent those that were reported in a previous meta-analysis [17]. Based on the pharmacokinetic results in our previous phase 1 study in children (NCT04200235), the median time to reach maximum concentration of the nasal spray was approximately 45 to 60 min. Taken into the consideration of clinical feasibility, the parental separation and sedation level of dexmedetomidine nasal spray was assessed for up to 45 min post administration. If parental separation was not achieved by that time, rescue medication would be applied to ensure the anaesthesia and the following surgery process.

In this study, we used the placebo as control because at the time of the study design, there is a scarcity of regulatory approved pediatric drugs. Dexmedetomidine injection (PRECEDEX®, Hospira Inc, Lake Forest, Illinois) was approved as sedative of non-intubated children prior to and during non-invasive procedures by the US FDA in December 2022. Other drugs used for pre-operative sedation, such as midazolam, are not currently available as regulatory-approved nasal sprays, which cannot meet the double-blind setting and are set up as active controls. The choice of control has been adequately discussed with and agreed upon by the health authority in the protocol development.

In this study, more children in the dexmedetomidine group vs the placebo group achieved the desired child-parent separation and Ramsay sedation scale ≥ 3 within 45 min, and the difference was statistically significant ($P<0.0001$) and clinically meaningful. The results of the secondary outcomes were supportive of the primary outcome. As compared with placebo,

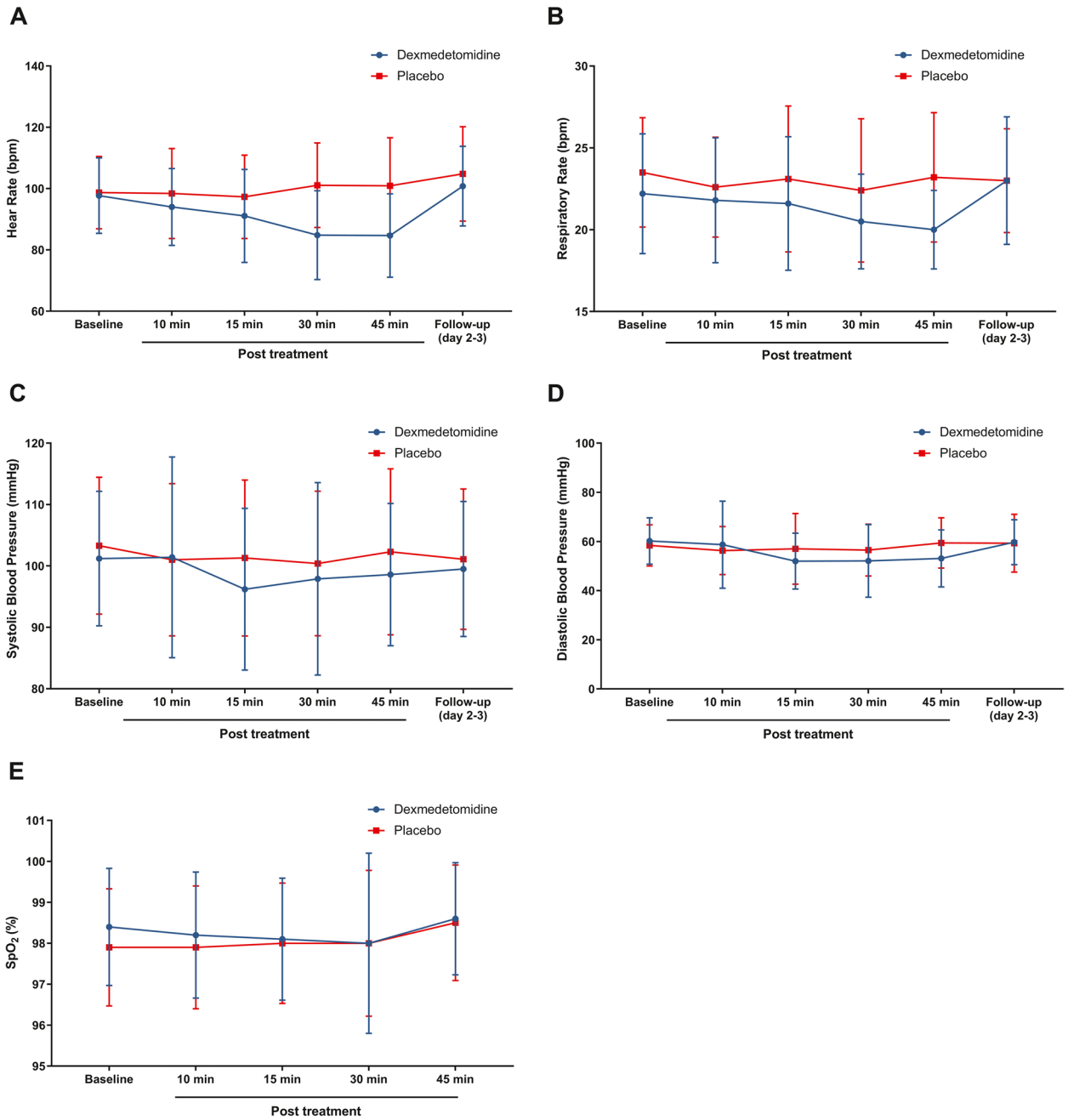

Fig. 2 Heart rate (**A**), respiratory rate (**B**), systolic blood pressure (**C**), diastolic blood pressure (**D**), and SpO_2 (**E**) at baseline and at each pre-determined time point post treatment. Values are mean ± standard deviation. Abbreviation: SpO_2, blood oxygen saturation

dexmedetomidine treatment elicited more effective child-parent separation and more potent pre-anesthetic sedation as assessed by Ramsay scale and UMSS. The recovery time in the dexmedetomidine group was longer than that in the placebo. Following sedation with dexmedetomidine or placebo, general anaesthesia was used during the scheduled elective surgery. Specifically, propofol, fentanyl, and rocuronium bromide were used for the induction of anaesthesia, and remifentanil, propofol, fentanyl or sufentanil (as needed), and rocuronium bromide and cisatracurium (as needed) were used for the maintenance of anaesthesia. The dose of general anaesthesia was not adjusted based on sedation depth. Therefore, the use of dexmedetomidine on top of other anaesthesia might lead to the longer recovery time compared to placebo. Previous studies have also

reported the prolonged recovery time with the use of dexmedetomidine as sedative [21, 22]. In this study, the median time to the onset of sedation as evaluated by the Ramsay sedation scale and UMSS was approximately 20 min. This was in accordance with a previous meta-analysis in which median time to the onset of action after intranasal administration of dexmedetomidine 1 to 4 μg/kg was 15–30 min [17].

Bradycardia was the most common adverse reaction accompanying with the use of dexmedetomidine [23, 24]. In this study, 42.1% and 38.3% of subjects in the dexmedetomidine group experienced AE of bradycardia and heart rate decreased, respectively, both of which were higher than those in the placebo group (30.0% and 26.0%, respectively). This phenomenon was expected considering the dexmedetomidine's impact on the sympathetic outflow and circulating catecholamine levels [25]. In addition to the pharmacological impact of dexmedetomidine, the concurrent administration of anesthetics, hypnotics, and opioids [23] alongside stringent AE criteria used by investigators, may account for the relatively high incidences of heart rate decreased (30.0%) and bradycardia (26.0%) in the placebo group. None of the bradycardia/heart rate decreased were considered as severe in severity or serious AEs, or resulted in study discontinuation, and the majority of the events did not require concomitant treatments.

There were several limitations to this study. Firstly, we did not perform pharmacokinetic analysis in this study. However, as mentioned earlier, the pharmacokinetic profile of dexmedetomidine nasal spray in children was assessed in a previous a phase 1 study (NCT04200235). Secondly, the sample size of this study was relatively small. It was because of the ethical concerns and difficulties in recruitment. Further validation of the safety and efficacy of dexmedetomidine nasal spray in a larger population in the post-marketing setting could be warranted. Lastly, all subjects in this study were from China. The efficacy and safety of dexmedetomidine nasal spray in subjects of other ethnicities were to be explored.

In conclusion, dexmedetomidine nasal spray presented effective pre-anesthetic sedation in children who were to undergo surgery under general anaesthesia. It had tolerable safety profile with no new safety concerns observed as compared with the approved dexmedetomidine injection.

Abbreviations

AE	Adverse event
NR	Not reached
PT	Preferred term
SpO_2	Blood oxygen saturation
TEAEs	Treatment emergent adverse events
UMSS	University of Michigan Sedation Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02708-1.

Supplementary Material 1.

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Authors' contributions

JG and FW were involved in the study execution, data analysis and interpretation, and manuscript writing. JMZ and XLW were the co-principal investigators of this trial and were involved in the study conception, protocol development and review, data analysis, and manuscript review. QRW and NZ were involved in the study design, study oversight, data analysis and interpretation, and manuscript writing and review. JLB was involved in the statistical analyses plan development, outputs programming, data analysis, and manuscript review. All the other authors were the investigators, and they were involved in protocol review, study execution, data analysis and manuscript review. All authors contributed substantially to the work. All authors had full access to the data and were responsible for the integrity and accuracy of data. All authors approved the final version of manuscript to be published.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, Jianmin Zhang, upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was provided by Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University and 10 other ethics committees (Supplemental Table 1). Written informed consent was obtained from all subjects' parents or legal guardians before initiating any study-related activities.

Consent for publication

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. Therefore, consent for publication is not applicable.

Competing interests

This study was sponsored by Jiangsu Hengrui Pharmaceuticals Co., Ltd. Quanren Wang and Na Zhou are employees of Jiangsu Hengrui Pharmaceuticals Co., Ltd. No other authors declared potential competing interests.

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