RESEARCH PAPER

Dexmedetomidine vs Midazolam for Sedation in Mechanically Ventilated Children: *A Randomized Controlled Trial*

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Background: There is a paucity of data on use of dexmedetomidine as a sedative agent in mechanically ventilated children.

Objectives: To compare the efficacy of dexmedetomidine and midazolam for sedation in mechanically ventilated children aged 1 month - 15 years. Secondary objectives were to compare the need for top-up doses of fentanyl and paralytic agents, duration of mechanical ventilation, ICU stay and hospital stay, and adverse events.

Design: Open label, non-inferiority, randomized controlled trial.

Setting: PICU of a tertiary care teaching hospital in India.

Patients: Consecutive children aged 1 month to 15 years who were mechanically ventilated.

Intervention: Children were randomized to either dexmedetomidine or midazolam and the doses were titrated to maintain target sedation score of 4 or 5 as measured by Penn State Children Hospital Sedation algorithm.

Outcome: The percentage of time spent in level 4 or 5 of Penn State Children Hospital sedation algorithm for ventilated children.

Results: 49 children were randomized (24 to 'midazolam group' and 25 to 'dexmedetomidine group'). There was no difference in the percentage of time spent in the targeted sedation between the groups [midazolam 67.3% (18.8) vs. dexmedetomidine 56.3 %. (28.6); *P*=0.12]. The absolute difference in the percentage of time spent was -10.9% [SE (95% CI) 7.05: (-25.15 to 3.25)]. The lower end of 95% CI for the difference breached the non-inferiority limit of -20%. Number of fentanyl boluses, duration of mechanical ventilation, ICU stay, and hospital stay were similar. Four (17.4%) children in dexmedetomidine group developed persistent bradycardia.

Conclusion: Non-inferiority of dexmedetomidine compared to midazolam for sedation in children on mechanical ventilation could not be established.

Keywords: *Alpha-2 adrenoceptor agonist, Benzodiazepines, Intubation, Pediatric intensive care unit.*

Trial registration: CTRI/2016/10/007347

Sedatives are required in mechanically ventilated children not only for reducing pain and anxiety, but also to allow synchronized respiratory support, and preventing accidental extubation. Commonly used agents are benzodiazepines (midazolam) and opiates (morphine/fentanyl) [1]. Dexmedetomidine, an alpha-2 adrenoceptor agonist acting on locus ceruleus and spinal cord, with insignificant respiratory depression [2] has been used as a sedative agent in children for day care procedures, non-invasive and invasive ventilation [3-5]. In adults, it has been shown that, compared to midazolam and fentanyl, dexmedetomidine reduces the duration of mechanical ventilation and length of ICU stay [6]. In children, dexmedetomidine has been reported to be an effective sedative agent without much side effects compared to benzodiazepines or opioids with the additional advantage of reducing the dose of conventio-nal sedative agents [4,7-9]. Though use of dexme-detomidine in mechanically ventilated children has increased over last few years, there is wide variation in practice regarding the dose and duration of the drug [10]. A recent meta-analysis has shown the superiority of dexmedetomidine over midazolam for sedation in children undergoing day care procedures [11]. However, few trials that exist, evaluating the efficacy of dexmedetomidine as a sedative agent in mechanically ventilated children, have several limitations [12-14]. Hence, we conducted this non-inferiority trial with an objective to compare dexmedetomidine with midazolam for adequacy of sedation in mechanically ventilated children.

METHODS

Mechanically ventilated children, 1 month to 15 years old, admitted in a pediatric intensive care unit of a tertiary care referral center between August, 2016 to April, 2018 were eligible. Children with catecholamine resistant shock (shock persisting despite the use of the epinephrine at the rate of >0.3 mcg/kg/min or norepinephrine at the rate of >0.3mcg/kg/min), children already on sedative drug infusion, bradycardia, atrioventricular conduction block, primary central nervous system involvement at the

time of admission, hepatic impairment, infusion of muscle relaxants, or previous participation in this study, were excluded. Since these stringent criteria resulted in the slow recruitment of subjects, the exclusion criteria were modified after institutional ethics committee approval from December, 2017 onwards, with catecholamine-resistant shock at the time of randomization and children already receiving sedation prior to randomization, being removed from exclusion criteria list. The study was approved by institute's ethics committee and was registered pros-pectively in Clinical Trial Registry of India.

Based on a study in adults [15], we assumed 5% difference between the two groups with SD of 43.5% for the percentage time spent in the desired sedation level, the estimated sample size was 39 per group to be 80% sure that lower limit of one-sided 95% confidence interval would be above the non-inferiority margin of -20%.

Computer generated, block random sequence was created by a person, not a part of the study. Block size of 4 with the investigator being ignorant of the block size. Random codes were printed on a pieces of paper placed in a serially numbered, opaque sealed envelopes. Envelopes were opened by the investigator after taking informed consent from the parent/legally authorized representative of the child, who was found to be eligible for the study.

Two mL of dexmedetomidine (1 mL=100 mcg) was diluted with 48 mL of 0.9% saline to get a concentration of 4 mcg/mL. Midazolam was diluted to a concentration of 0.1 mg per mL. After randomization, midazolam bolus of 0.1mg/kg and fentanyl bolus of 1 mcg/kg were given to both the groups prior to initiation of infusion of the drugs. Bolus dose of dexmedetomidine was not given in order to avoid bradycardia and hypotension. Starting doses of midazolam and dexmedetomidine were 1 mcg/kg/min and 0.25 mcg/kg/h, respectively. Sedation level was assessed using Penn State Children Hospital (PSCH) sedation algorithm for ventilated children [16]. The sedation targeted for primary outcome was Level 4 or 5. Level of sedation was assessed every 2 hours by the investigator or treating residents who were trained optimally regarding the appropriate application of sedation scale on mechanically ventilated children. Doses were titrated, based on the sedation score. While midazolam infusion was increased by 1 mcg/kg/min till maximum dose of 4 mcg/kg/min, dexmedetomidine infusion was increased by 0.25 mcg/kg/hr till a maximum dose of 0.75 mcg/kg/hr. The maximum infusion dose of dexmedetomidine was chosen as 0.75 mcg/kg/min to avoid side effects such as bradycardia. Fentanyl boluses (2 mcg/kg/bolus) were administered in case of agitation and asynchronous ventilation. Infusion of drugs was continued till seven days or weaning from mechanical ventilation, whichever occurred earlier.

The number of fentanyl or vecuronium boluses received by children was recorded. Number of episodes of bradycardia (<60 bpm), hypotension (systolic blood pressure <5th centile for age) [17], duration of mechanical ventilation, ICU stay and hospital stay were recorded. The sum of the time periods of receiving continuous infusion of the sedative drug, the time periods for which the patient was monitored for sedation, the time periods in which the patient was at level of sedation 4 or 5, were calculated. Percentage of the total monitored duration of sedation, which was spent in level 4 or 5 sedation was calculated. Treatment failure was defined as self-extubation or inability to maintain desired sedation level score even after maximum doses of midazolam/ dexme-detomidine infusion as decided by the treating team.

Our primary outcome was percentage of time spent in level 4 or 5 of PSCH sedation algorithm for ventilated children out of total duration of sedation monitored. Secondary outcomes were: top up doses of fentanyl and vecuronium, episodes of bradycardia/hypotension, length of mechanical ventilation, ICU stay and hospital stay. Treatment failure, hemodynamic status using vaso-active inotropic score (VIS), mortality were also compared between the groups

Statistical analyses: Data was entered into MS Excel spreadsheets, and analysis was performed using STATA ver. 13 (Stata Corp). Variables were compared by using Chi square test and Fisher exact test, as applicable. Normally distributed continuous variables were compared by applying unpaired *t* test. The mean difference in the percentage of time spent by mechanically ventilated children in level 4 or 5 of the Penn State Children Hospital sedation algorithm was compared between the two groups by Mann-Whitney test.

RESULTS

Of the 151 eligible children screened, 49 were randomized (24 in midazolam group and 25 in dexmedetomidine group) (**Fig**.**1**). Protocol was modified to relax strict exclusion criteria so as to improve recruitment rate. Fifteen children were enrolled after protocol modification (4 children were receiving sedative infusion, 3 had catecholamine refractory shock and 3 were receiving sedation as well as were in catecholamine refractory shock). Data were analyzed for 47 children (24 in midazolam group and 23 in dexmedetomidine group).

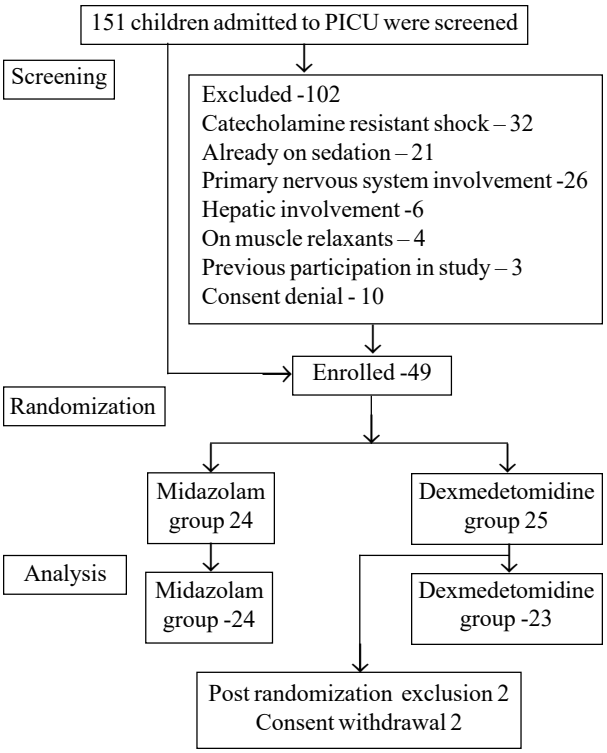

Fig. 1 Study flow chart.

Trial was stopped prior to completion of sample size due to higher rates of side effects in dexmedetomidine group and due to the time bound nature of study of 18 months.

Baseline characteristics of both the groups are shown in **Table I**. Ten (42%) children in the midazolam group and 2 (9%) in the dexmedetomidine group had congenital heart disease. In the midazolam group, 2 had underlying bronchiectasis, 2 had gastroesophageal reflux disease and one had airway malacia. In the dexmedetomidine group, 1 child each had underlying hepatic hemangio-endothelioma, congenital diaphragmatic hernia, Budd-Chiari syndrome, acute lymphoblastic leukemia, juvenile dermatomyositis, idiopathic pulmonary hemorrhage and primary immunodeficiency. Twenty-four children in midazolam group and 22 children in dexmedetomidine group received pressure controlled synchronized intermittent mandatory ventilation with pressure support (PC-SIMV-PS). One child in dexmedetomidine group received high frequency oscillation ventilation (HFOV).

Table I Baseline Characteristics of Mechanically Ventilated Children Enrolled in the Study

Characteristics	*Dexmedetomidine group (n=23)*	*Midazolam group (n=24)*
Age (mo)	8 (3, 24)	5.5 (2.5, 11.7)
Boys, *n* (%)	12 (52)	12 (50)
%Predicted mortality[a]	13.5 (13.3, 27)	13.5 (13, 21)
Weight (*z* scores)	-2.52 (-3.61,-1.59)	-3.64 (-4.76,-2.65)
Length (*z* scores)	-1.84 (-2.48,-0.62)	-1.74 (-3.31,-0.87)
Admission diagnoses, n (%)		
Pneumonia	9 (39)	12 (50)
Gastrointestinal sepsis	3 (13)	1 (4)
Sepsis without focus	4 (17.5)	1 (4)
Postoperative ventilation	3 (13)	4 (17)
Others	4 (17.5)	6 (25)

Values in median (IQR) or as stated. PIM: Pediatric Index of Mortality; [a]using PIM-2.

The dose range for midazolam was 1- 4 mcg/kg/min and for dexmedetomidine was 0.25-0.75 mcg/kg/hr. Median (IQR) duration of drug received in midazolam group was 64 (38, 135) hours and in dexmedetomidine group was 30 (14, 64) hours (P=0.02). Four (16.6%) children in midazolam group (16.6%) and 13 (56.5%) children in dexmedetomidine group (56.5%) had treatment failure (P=0.005).

The mean difference in the percentage of time spent by mechanically ventilated children in level 4 or 5 of the PSCH sedation algorithm between dexmedetomidine and midazolam groups was -10.94%. The lower end of 95% CI (confidence interval) for this difference breached the non-inferiority limit of -20% [difference= -10.94% (SE= 7.05); 95% CI: -25.15 to 3.25]. Hence, non-inferiority of dexme-detomidine as compared to midazolam could not be established (**Table II**). The secondary outcome parameters were comparable between the groups (**Table III**) While none of the children in midazolam group had bradycardia, 4 (17.4%) children in the dexmedetomidine

Table II Sedation Duration and Time Spent in PSCH Level 4 or 5 in Children Receiving Dexmedetomidine or Midazolam

Characteristics	*Dexmedetomidine group (n=23)*	*Midazolam group (n=24)*	*P value*
Sedation duration (h)	26 (14, 48)	53 (31, 83.5)	0.014
Time spent in level 4 or 5 of PSCH sedation algorithm (h)	20 (6, 28)	38 (20.5, 66)	0.006
Time spent in Level 4 or 5 of PSCH sedation algorithm (%)[ab]	56.5 (28.6)	67.3 (18.8)	-

PSCH: Penn State Children Hospital. Values in median (IQR) or [a]mean (SD); [b]Mean difference (95% CI)= -10.9 (-25.15 to 3.25)%.

Table III Comparison of Secondary Outcomes Between Dexmedetomidine and Midazolam Groups

Characteristics	*Dexmedetomidine group (n=23)*	*Midazolam group (n=24)*	*P value*
Fentanyl boluses	4 (2.2,5.7)	4 (2,6)	0.79
Adjusted boluses[a]	1 (1,3.4)	4 (1.5,6)	0.06
Vecuronium boluses	0 (0,1)	0 (0,1)	0.90
Mechanical ventilation (h)	162 (58,432)	132 (36,312)	0.90
ICU stay (d)	10.5 (4.8,20.8)	9.2 (5,15.2)	0.95
Hospital stay (d)	21 (11,33)	17.5 (13.5,37.5)	0.87

All values are in median (IQR); [a]adjusted for period of 24 hours per person sedation monitored.

group, developed persistent bradycardia (<60 bpm) necessitating withdrawal of the drug (P=0.05). Hemodynamic stability, assessed by vasoactive inotropic score, was not different between the groups [10 (IQR 0, 20) in midazolam group or 17.5 (IQR 0, 46) in dexmedetomidine group, P=0.40].

DISCUSSION

In our study, non-inferiority of dexmedetomidine compared to midazolam for desired sedation in mechanically ventilated children could not be established. Though the intended sample (36 in each group) size could not be attained due to the time bound nature of study of 18 months, wide margin of treatment failure rate in dexmedetomidine (56.5%) compared to midazolam (16.6%) group, and the adverse events such as bradycardia in dexmedetomidine group (14.4%) may not have changed even if the sample size was completed.

A study in ventilated adults [15] showed that, though the percentage time spent in the target sedation range was similar between dexmedetomidine (77.3%) and midazolam (75.1%) groups, the absolute duration of sedation was lower in dexmedetomidine group [3.5 days vs 4.1 days, P=0.01] like ours. Another recent trial in adults confirmed non-inferiority of dexmedetomidine when compared with midazolam with respect to the time spent in desired sedation range [18]. However, in contrast to our study, the duration of drug infusion was similar in both the groups. In our study, the median (IQR) number of fentanyl boluses received were similar in both groups, while the first reported pediatric trial that compared infusion of dexmedetomidine with midazolam in mechanically ventilated children found the number of rescue morphine boluses received in midazolam group was significantly higher [12]. The difference is perhaps due to the fact that the total duration of sedation in both the groups was less than 24 hours in their study. In another trial in children undergoing open heart surgery, there was no difference in the need for rescue sedation between dexmedetomidine and fentanyl groups and sedation scores were comparable [13]. However, the mean duration of sedation infusion was only 13 hours, making it difficult to confirm effectiveness of dexmedetomidine infusion in providing adequate sedation in mechanically ventilated patients.

While studies in adults and pediatric population showed that sedation attained by dexmedetomidine is comparable to midazolam for mechanically ventilated population [10,12,15,18,19], our study could not establish the non-inferiority of dexmedetomidine compared to midazolam. This is likely to be due to individual patient traits, genetic polymorphisms in pharmacokinetics and pharmacodynamics [20] and a relatively conservative dexmedetomidine dose used in the study. Studies had shown that other factors like disease severity at admi-ssion was also associated with efficacy of dexme-detomidine [21,22]. Patients with lower baseline Simplified Acute Physiology Score (SAPS II) had higher clearance of dexmedetomidine [23] and those with lower Modified Acute Physiology and Chronic Health Evaluation (APACHE II) score had successful sedation with dexmedetomidine [24]. Since pharmacokinetic studies on dexmedetomidine have shown wide inter-patient variability of plasma levels [20], it is questionable whether adequate plasma levels are achieved in critically ill patients. Recent study from Japan in children less than 2 years old, on dexmedetomidine infusion (012-1.4 mcg/kg/hr) found that there was no correlation between plasma drug concentration and administered drug dose [25]. In our study, since majority of children were infants, possibly adequate plasma concentration of dexme-detomidine for sedation could not be attained. The trials in adults which established non-inferiority of dexme-detomidine compared to midazolam, used higher doses (>0.7 mcg/kg/h) to obtain desired sedation levels, thereby suggesting that adequate plasma levels may be attained with high doses [15,18,26]. It is possible that if a higher dose of dexmedetomidine *i.e*, more than 0.75 mcg/kg/hr was used in our study, our results could have been different. Genetic polymorphisms in alpha-2 receptor may reduce affinity towards dexmedetomidine with resultant variation of its pharmacodymanic properties. Two important polymorphisms have been identified i.e., ADRA2A”1291C/G SNP (single nucleotide polymorphism) and ADRA2AC753G. Study of ADRA2A C1291G polymorphism in 110 adult patients, who underwent coronary artery bypass graft, showed that patients carrying the G allele compared to those carrying C allele had better

WHAT IS ALREADY KNOWN

- Dexmedetomidine is shown to decrease the duration of mechanical ventilation, intensive care unit stay and sedation withdrawal, compared to midazolam in mechanically ventilated adults.

WHAT THIS STUDY ADDS

- For sedation in mechanically ventilated children, dexmedetomidine as continuous infusion, compared to midazolam, may not be as effective as seen in adults.
- Dexmedetomidine is associated with higher episodes of bradycardia compared to midazolam.

sedation [27]. Though we did not look at the genetic polymorphism of alpha-2 receptor in our study, this could be another reason for non-establishment of non-inferiority of dexmedetomidine compared to midazolam. Studies on the receptor polymorphism is lacking in Indian children.

Dexmedetomidine is known to cause hemodynamic adverse effects such as bradycardia, hypotension, and even transient hypertension in few patients [2]. Authors [15, 18] have reported between 14 and 42% of mechanically ventilated adult patients to have bradycardia in dexmedetomidine group with some requiring intervention for bradycardia. In pediatric population, incidence of bradycardia with dexmedetomidine infusion varied from 3% to 27% and majority not requiring intervention [4,8]. In our study, 4 children (17.4%) in dexmedetomidine group had persistent bradycardia (<60 bpm) which necessitated discontinuation of drug.

Strength of our study is that it is one of the few randomized controlled trials in mechanically ventilated children for sedation, especially in the Indian scenario. The limitations of the study include lack of assessment of withdrawal symptoms in either groups, targeted sample size not covered, observer bias due to the study being open label, exclusion criteria being relaxed for some children. Future studies on dexmedetomidine, with adequate sample size, for sedation in ventilated children are desirable.

Our study could not establish the non-inferiority of dexmedetomidine compared to midazolam for sedation in children on mechanical ventilation. Further studies are required to ascertain the utility of dexmedetomidine as a sedative for mechanically ventilated children.

Ethics clearance: The study was approved by Institute Ethics Committee, AIIMS, New Delhi; IECPG/403, dated June 29, 2016.
Contributors: KMG: design of the study, patient management, data collection, data analysis, and preparation of manuscript; JS,KRG,SKK: design of the study, patient management, reviewed manuscript; RL: design of the study, patient management and reviewed manuscript.
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