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Original Study

A comparison of midazolam, dexmedetomidine 2µg/kg and dexmedetomidine 4µg/kg as oral premedication in children, a randomized double-blinded clinical triall

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Abstract

Background: **The objective of this study was to analyze an oral administration of midazolam with two different doses of dexmedetomidine for premedication in paediatric patients.**
Methods: **A prospective, randomized, double blind study. Three hundred patients, aged 1-7 years, undergoing elective surgery under general anesthesia were recruited for the study. Patients were randomized into three groups to receive oral midazolam 0.5mg/kg (group M), oral dexmedetomidine 2 µg/kg (group D2) and oral dexmedetomidine 4 µg/kg (group D4) for premedication. An observer blinded to the patient group allocation assessed level of sedation at 30 minutes after giving the premedication, ease of parental separation was assessed while shifting the patients to the operating room, mask acceptance during induction and postoperative agitation scores in post anesthesia care unit.**
Results: **The sedation score of group D4 was significantly higher than group D2 and group M [group D4- 4 (4,3), group D2- 2(2,2) and group M -2(3,2), H statistics = 80.4718, p < 0.00001]. The parental separation score, mask acceptance score and postoperative was also significantly better for group D4 compared to the other two group.**
Conclusion: **These results suggest that oral dexmedetomidine 4 µg/kg is more effective than oral midazolam 0.5mg/kg and oral dexmedetomidine 2 µg/kg for premedication in children.**

Key words: **Anaesthesia, Anxiety, Emergence delirium, Pediatric, Preanaesthetic medication.**

Introduction

The primary goal of premedication in children is anxiolysis. The sedation achieved by premedication should be enough to facilitate smooth separation from the parents and also ease the induction of anaesthesia[1,2]. The ideal route of administration for premedication in children remains uncertain. The used routes are oral, nasal, rectal and parenteral routes in the decreasing order of acceptability. The benefit of oral route is an easy acceptability and ease of administration, even an unskilled person can administer it. The most common drug used for oral premedication remains midazolam. Midazolam is a water soluble, short acting, gamma-amino-butyric acid (GABA) receptor agonist which provides effective sedation, anxiolysis and varying degrees of anterograde amnesia[3]. However adverse effects such as postoperative behavioral changes, hiccups and paradoxical hyperactive reaction have been observed with this drug. Alpha 2–adrenergic agonists are being widely used preoperatively to reduce anxiety in uncooperative children[4,5]. This group of drugs also provides clinically relevant benefits of reducing the need for rescue analgesia, reducing emergence agitation, postoperative nausea and vomiting (PONV) and shivering in the postoperative period. Dexmedetomidine is a potent, highly specific alpha 2–adrenoreceptor agonist (the alpha 2: alpha 1 affinity ratio of this drug is 1600:1) with a shorter terminal half-life (approximately 2 h in children)[6,7]. Intranasal dexmedetomidine has been used satisfactorily in the dose of 1 µg/kg administered 45–60 min prior

to induction. Oral administration is associated with poor bioavailability. A few retrospective review and preliminary studies have shown promising effects of oral dexmedetomidine for premedication in pediatric patients[8,9]. Most of the studies however had small sample size (50 -150) and a used a varying dose (1 to 4 µg/kg)[7]. Hence in this study we made an effort to compare oral administration of midazolam with two different doses of dexmedetomidine as premedication in pediatric patients to find out its effectiveness and the best oral dose of dexmedetomidine for premedication. The primary endpoint of this study was to analyze sedation score in children on premedication with oral midazolam(0.5mg/kg), oral dexmedetomidine (2µg/kg) and oral dexmedetomidine (4µg/kg), thirty minutes after giving the drug.

Materials and methods

This department supported, prospective, randomized, controlled, double blind study was registered with Clinical Trials gov, India (CTRI/2017/09/009943) after ethical clearance by institutional ethical committee. Enrollment was started following these approvals. Study initiation and completion dates were October 03, 2017 and May 6, 2019 respectively.

Children 1-7 years old with American Society of Anesthesiologists (ASA) physical status classification of I or II scheduled to undergo any surgical procedure of at least two hours duration with expected postoperative stay of at least 12 hours were eligible for enrollment.

Children who had any contraindication to preoperative sedation or had a known allergy or sensitivity to the study medications as well as children with weight for age below the 5th percentile or above the 95th percentile according to the published Center for Disease Control and Prevention clinical growth charts at the time of the study were excluded. Children with any neurodevelopmental disorders were also excluded.

Written informed consent was obtained from parents or legal guardians prior to study participation. Randomization was done in three groups by a computer – generated random number on the central computer, and group allocation was concealed in an opaque envelope with sequence written on the top of envelope. The envelopes were kept in a sequence and locked with trial coordinator. The trial coordinator was informed to open the envelope and convey the group allocation once a patient was enrolled for the study. The study drug was given according to group allocation, group M – received midazolam (0.5mg/kg), group D2 – received dexmedetomidine (2µg/kg) and group D4 - received dexmedetomidine (4µg/kg).

Drugs were mixed with honey and the total volume of the mixture was kept constant at 5ml. Drugs were prepared by a nursing staff not involved in clinical study. Study medication was administered 45 minutes before the anticipated time of separation from patients.

In the preoperative room, patients were monitored for hemodynamic parameters every 15 minutes until patient was transferred to the operating room and side effects such as hypotension (decrease in blood pressure below 20% of baseline) and bradycardia (decrease in heart rate below 60) were noted. In the postoperative room parameters were also recorded untill the patient was transferred to the ward. Other side effects such as respiratory depression (decrease in respiratory rate below 10), fall in saturation (decrease in saturation below 90%), shivering, vomiting, and hiccups if any were noted both in preoperative room and in PACU.

The anesthesiologist who monitored the patient, scored the patient's behavior, and collected the data was blinded to the study drug administered.

The primary outcome was to assess sedation score, 30 minutes after administration of premedication drug.

The secondary outcomes were parental separation score, and mask acceptance at the time of induction, postoperative agitation score in post anesthesia care unit, hemodynamic changes and any other adverse effect in all three group.

Level of sedation was assessed by using a 4-point scale: 1 = anxious depressed/ agitated/crying, 2 = awake, calm, quiet, 3 = drowsy, responds to verbal commands/gentle stimulation, 4 = asleep. Sedation scores of children were assessed half an hour after giving study medication. If no satisfactory sedation level was achieved for parental separation after the maximum time interval of 45 min, still the child was separated from parents. The response of the child at parental separation was recorded. It was graded as 1 = crying, cannot be reassured, 2 = awake, anxious, can be easily reassured, 3 = good separation, awake, calm, 4 = asleep.

After placement of routine monitoring (electrocardiogram, pulse oximetry, capnogram, and noninvasive blood pressure), anesthesia was initiated with sevoflurane 8% in an oxygen-nitrous oxide mixture via a face mask. If the child came to the induction room already asleep, a steal induction was performed. Mask acceptance was assessed using a 5-point scale: 1 = combative, crying, 2 = moderate fear of mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative, and 5 = asleep, steal induction. Mask induction scores of 1

and 2 were considered unsatisfactory while a score of 3-5 was regarded as a successful response to premedication.

After the establishment of an IV access, glycopyrrolate 5µg/kg and fentanyl 2µg/kg were given intravenously. The airway was maintained with an endotracheal tube or laryngeal mask airway throughout the surgery. Anesthesia was maintained with sevoflurane in a 40-60% mixture of oxygen-nitrous oxide and analgesia was provided by caudal neuraxial block if indicated. At the end of surgery as soon as a patent airway was maintained, the child was placed in the recovery position and allowed to wake up naturally in the post anaesthesia care unit (PACU). In the PACU, agitation was assessed as 1 = agitated, crying, 2 = crying, but easily consoled, and 3 = calm. Any episode of hypoxemia (SpO2<90%) or any other adverse hemodynamic events were recorded.

A preliminary study was conducted in 30 patients (10 in each group). Mean sedation score observed in group M was 2.66±0.57, 1.66± 0.577 in group D2 and 3.66± 0.577 in group D4. The sample size was calculated at a power of 95% and a significance level of 5%. The analysis showed that 90 patients would be required for each group in order to obtain significant statistical value. Hundred patients for each group were included to the study against the possibility of patient dropouts.

All statistical analyses were performed using SPSS for Windows version 18.0 software (SPSS Inc., Chicago, USA). The Kolmogorov Smirnov test was used to test the normality of data distribution. Continuous variables were expressed as mean ± standard deviation, and median values (25th–75th percentiles), and categorical variables were expressed as counts (percentages). Ordinal variables were expressed as median (interquartile range). Non-normally distributed continuous variables were compared between the groups using the Krusal-Wallis Test. Categorical variables were compared between the groups using Fisher's exact chi square test. Two-sided p values<0.05 were considered statistically significant.

Results

Subject enrollment occurred between October 2017 and May 2019. A total of 300 subjects were enrolled (Fig. 1). 21 subjects dropped out of the study: seven subjects spit out the study medication and sixteen due to postponement of surgery. Study was completed in 279 subjects: 93 received midazolam, 94 received dexmedetomidine 2 µg/kg and 90 received dexmedetomidine 4 µg /kg (Fig. 1). Sevoflurane was used for general anesthesia cases. Caudal anesthesia was the only regional anesthesia procedure utilized in the study. Surgical procedure

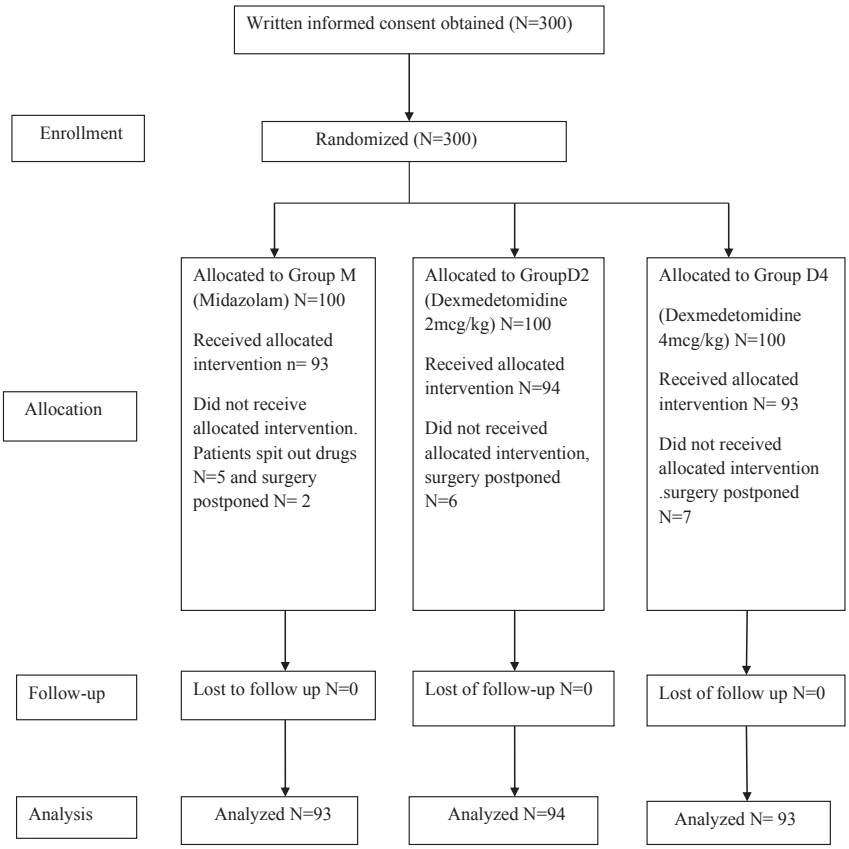

Fig. 1 — Consort diagram.

Table I. — There were no differences in demographic characteristics between pediatric subjects who received midazolam, dexmedetomidine (2µg/kg) or dexmedetomidine (4µg/kg) premedications.

	Group M	Group D2	Group D4
Age(yr)	4.3±2.2	4.1±2.3	4.1±2.2
Weight(kg)	14±2	14±3	14±1
Sex–male/ female*	72/21	73/21	80/13
ASA grade –I/ II*	89/4	90/4	86/7
Duration of surgery (minutes)	186±78	206±85	192±70
Data expressed in means with standard deviation *ratio.			

Table II. — Sedation score measures in children ages 1-7 years given premedications midazolam, dexmedetomidine(2µg/kg) or dexmedetomidine (4µg/kg). The data expressed as number (percentage) and analyzed with Fisher exact test.

	Sedation score	GroupM(n= 93)	Group D2(n=94)	Group D4(n=90)
A	1-2{n(%)}	47(50.5%)	83(88.3%)	24(26.7%)
B	3-4{n(%)}	46(49.5%)	11(11.7%)	66(73.3%)
Comparing A & B	Z-Statistic	0.147	10.5	6.261
	P-Values	0.82	0.002	0.003
A – sedation score 1 and 2, B – sedation score 3 and 4.				
The level of sedation was assessed by using a 4-point scale: 1 = anxious depressed/ agitated/crying, 2 = awake, calm, quiet, 3 = drowsy, responds to verbal commands/gentle stimulation, 4 = asleep.				

Table III. — Intergroup comparison of sedation score, parental separation score, mask acceptance score and post operative agitation score. The data expressed in median (interquarantile range), for intergroup comparison kruskal –wallis test was used; $p<0.05$ is clinically significant.

	Group M (n=93)	Group D2(n=94)	Group D4(n=90)	
Sedation score	2(3,2)	2(2,2)	4(4,3)	P<0.00001
Parent separation score	2(3,2)	1.5(2,1)	3(4,3)	P<0.00001
Mask acceptance score	2(3,1)	1(2,1)	3(4,2)	P<0.00001
Postoperative agitation score	2(2,2)	3(3,3)	2(3,2)	P<0.00001
Patient separation score: 1 = crying, cannot be reassured, 2 = awake, anxious, can be easily reassured, 3 = good separation, awake, calm, 4 = asleep; Mask acceptance was assessed using a 5-point scale: 1 = combative, crying, 2 = moderate fear of mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative, and 5 = asleep, steal induction; Agitation was assessed as 1 = agitated, crying, 2 = crying, but easily consoled, and 3 = calm.				

Table IV. — Parental separation score measures in children ages 1-7 years given premedication midazolam, dexmedetomidine(2µg/kg) or dexmedetomidine (4µg/kg). The data expressed as number (percentage) and analyzed with Fisher exact test.

	Parental Separation score	Group M (n=93)	Group D2 (n=94)	Group D4 (n=90)
A	1-2{n(%)}	53(57%)	76(80.9%)	16(17.8%)
B	3-4{n(%)}	40(43.0%)	18(19.1%)	74(82.2%)
Comparing A & B	Z-Statistics	1.906	8.46	8.646
	P-Values	P=0.58	P=0.004	P=0.003
A – Parental Separation score 1 and 2, B – Parental Separation score 3 and 4. Patient separation score: 1 = crying, cannot be reassured, 2 = awake, anxious, can be easily reassured, 3 = good separation, awake, calm, 4 = asleep.				

Table V. — Mask Acceptance Separation score measures in children ages 1-7 years given premedications midazolam, dexmedetomidine(2µg/kg) or dexmedetomidine (4µg/kg). The data expressed as number (percentage) and analyzed with Fisher exact test.

	Mask Acceptance Score	Group M (n= 93)	Group D2(n= 94)	Group D4(n=90)
A	1 – 2{n(%)}	67(72%)	82(87.2%)	32(35.6%)
B	3 – 4{n(%)}	25(26.9%)	12(12.8%)	40(44.4%)
C	5{n(%)}	1(1.1%)	0	18(20%)
Comparing A & B	Z- Statistics	6.16	10.211	1.217
	P- Values	P=0.005	P=0.003	P=0.002
Comparing B & C	Z- Statistics	Not computed	Not computed	2.33
	P- Values			P=0.004
Comparing A & C	Z- Statistics	Not computed	Not computed	3.509
	P- Values			P=0.005

A-Mask Acceptance Score 1and 2, B- Mask Acceptance Score 3 and 4, C - Mask Acceptance Score 5. Mask acceptance was assessed using a 5-point scale: 1 = combative, crying, 2 = moderate fear of mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative, and 5 = asleep, steal induction.

included in the study included yeloplasty, hernia surgery, urethroplasty, ureteral reimplants and hypospadiasis. No events occurred that required unblinding for clinical treatment decisions.

The demographic data of three groups were comparable (p>0.05) (Table I).

All the children in the Dexmedetomidine 2mcg/kg, and Dexmedetomidine 4mcg/kg groups accepted the oral drug mixed with honey. Seven children in midazolam group did not accept the premedication.

In group M 47 (50.5%) patient had sedation score 1-2 and 46 (49.5%) patient had sedation score 3-4 (Z- statistics – 0.147, p-value 0.82). Group D2 maximum 83(88.5%) patients had a lower sedation score 1-2 with only 11 (11.7%) patients having sedation score3-4 (Z- statistics – 10.5, p-value 0.002) and was statistically significant. Group D4 had maximum patients 66(73.3%) with higher sedation score 3-4 and only 24 (26.7%) patients with lower sedation score (Z- statistics – 6.261, p-value 0.003). (Table II) For intergroup comparison sedation score in median (interquartile range) for group M, group D2 and group D4 was 2(3,2), 2(2,2) and 4(4,3) respectively and difference was statistically significant (H-statistic-80.47, p value <.00001) (Table III).

Parental separation score 1-2 and 3-4 was 53 (57%) and 40 (43%) in group M respectively and the difference was statistically insignificant. Group D2 maximum patient 76 (80.9%) had a lower a lower sedation score with only 18 (19.1%) patients with sedation score 3-4 (Z- statistics – 8.46, p-value 0.004). Group D4 had maximum patients with higher sedation score 74(82.2%) and only 16 (17.8%) patients with lower sedation score 1-2(Z- statistics – 8.646, p-value 0.002) (Table IV). Comparing the three groups parental separation score (median (interquartile range)) was 2(3,2), 1.5(2,1) and 3(4,3) for group M, group D2 and group D4 respectively and difference was clinically significant (H-statistic-94.1751, p value <.00001) (Table III).

Maximum patients in group D4 had higher mask acceptance score 40(44.4%) with 3-4 and 18(20%) with 5. The values were significantly high than patients with lower mask acceptance score1-2(Z-statistics – 2.33, p-value 0.013). (Table V) On intergroup comparison group D4 had a higher score than other two group [2(3,1), 1(2,1) and 3(4,2) for group M, D2 and D4 respectively in median and interquartile range, p value <.00001] (Table III). Group D4, most of the patients had postanaesthesia agitation score 3 83(92.2%) with only 7 (7.8%) had PACU score 2 (Z- statistics – 11.261, p-value 0.000) (Table VI). Group D4 also had significantly higher value than other two groups [2(2,2), 3(3,3) and 2(3,2) for group M, D2 and D4 respectively in median and interquartile range, p value <.00001] (Table III).

The haemodynamics and SpO_2 was comparable in all three group (p>.05) and there was no episode of hypotension, bradycardia or desaturation reported in any patient.

Discussion

There are various time points of perioperative anxiety in paediatric patients most important being separation of the child from the parent. The sedation achieved by premedication should be effective enough to provide smooth parental separation and favorable mask induction. Children age <1years will readily accept parental surrogates and are less likely to experience anxiety on separation from parents. They respond to soothing voices, gentle

rocking and being held. Children age 1–7 years are prone to separation anxiety.10The children having high preoperative anxiety experience increased postoperative pain, analgesic consumption, general anxiety and sleeping problems[11,12]. In the immediate postoperative period also these children show high incidence of emergence delirium.

Oral midazolam has proved effective in treating preoperative anxiety. The dose ranges from 0.25 to 1.0 mg/kg to a total dose of 20mg.13,14 A dose of 1.0mg/kg produces more sedation over other dose but has shown to delay recovery thus may compromise safety. Thus we chose the dose 0.5mg/kg, the commonest dose used in most published reports[13,14].

Dexmedetomidine has been used for premedications via parenteral, oral and nasal routes[15,16]. Parenteral routes are generally avoided unless an intravenous cannula has previously been sited. The sensation of burning and nasal irritation is a disadvantage of the nasal route, and sneezing or coughing caused by the nasal irritation could reduce the effects of nasal premedication. Though a meta-analysis has provided evidence that intranasal dexmedetomidine provides more satisfactory sedation at parent separation than other intranasal (midazolam, clonidine, ketamine) or oral premedicants (midazolam) with reduced nasal irritation compared with midazolam[17]. Oral dexmedetomidine as premedicant has also been used but in different study dose ranged between 1 μg/kg to 4 μg/kg[7]. Some studies have reported bradycardia and hypotension with higher doses[7]. We chose two dose 2μg/kg and 4 μg/kg to compare to find the ideal dose providing adequate sedation and not compromising safety. The dose 2 μg/kg of dexmedetomidine was inferior to midazolam for achieving good sedation, good parental separation and favourable mask acceptance. Only postoperative agitation was seen less in this group compared to midazolam group. While dose 4 μg/kg achieved superior sedation, parental separation, mask acceptance compared to other groups. There was no associated hypotension and bradycardia also reported in any of the children. Postoperative agitation was also significantly seen less with dexmedetomidine 4μg/kg consistent with other reported studies[17,18,19]. Kumari et al compared oral midazolam, oral dexmedetomidine and oral clonidine for premedication in paediatrics in 4-12 years old children and concluded that midazolam is superior to the oral clonidine, and oral dexmedetomidine with faster onset of sedation, higher sedation score, lower anxiety score, and greater number of children with easy separation and excellent mask acceptance. The age group of their study subject was very wide as above 7 years incidence of anxiety reduces. Apart from that sample size chosen by them was small (90 patients)[20].

We chose to give premedication 45 minutes prior to anticipated parental separation. Oral midazolam is shown to achieve an adequate sedation within 20 minutes of drug administration[21] while dexmedetomidine takes 30-45 minutes[22]. Thus midazolam has an advantage of having a faster onset. Proper planning and implementation can overcome this problem of dexmedetomidine.

We observed a lower incidence of emergence agitation (EA) in children premedicated with dexmedetomidine. These results are consistent with previous studies as shown by the effective use of either single dose 0.3μg/kg or continuous perioperative infusion 0.2μg/kg/h of IV dexmedetomidine for reduction of postoperative agitation in children treated with sevoflurane[23,24]. However, children premedicated with midazolam had a higher incidence of EA consistent with few published data[25,26].

Duration of surgery has importance as the half-lives of premedicants used is comparatively short. Midazolam has elimination half-life of 1–4 h and dexmedetomidine has elimination half-life of between 2.0 and 2.5 h[24,25].The effect of premedicant has outlasted the surgical time as the mean duration of surgery in both the groups was approximately 1 h, while duration of action of the drugs is much longer (approximately 2–5 h).

We included various surgery (Pyeloplasty, hernia surgery, urethroplasty, ureteral reimplants and hypospadiasis) in the study. Distribution of types of procedures between the groups was not different. The outcome was not different within the group. Hence, it may be concluded that duration, type and heterogeneity of surgical procedures did not affect the outcome of the study. In addition, participant allocation and blinding were strictly adhered to for minimizing the distributive and observer bias.

Off note we observed 7 children in midazolam group spited the drug. The injectable form of midazolam, available as 5 mg/mL, has an extremely bitter taste. Various agents such as honey, pomegranate juice and paracetamol syrup have been used to increase palatability and acceptance. This problem was not observed in dexmedetomidine group.

Limitations of our study includes intravenous formulations of the drugs were used as oral preparations of the drugs were not available. Mixing of the drug with honey could change pH of the drug and its absorption. Separation of children from

parents also depend on how smoothly staff handle the baby, rough handling will awake the patients. Mask acceptance of children at operation table also depend on gentleness of Anaesthesiologist.

Nevertheless we can conclude from the study that dexmedetomidine in dose 4μ/kg is good agent for providing preoperative sedation in paediatric patients. It also facilitate separation of the child from the parents and provide favourable mask acceptance. Dexmedetomidine premedication also lowered the incidence of postoperative agitation. Overall this drug allay anxiety at all required time points during perioperative period.

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The study was cleared by Institutional Ethics committee (Indira Gandhi Institute of Medical sciences, Patna, Bihar, India) by letter no. 860/Aca dated 25/07/2017 with Mr Justice RN Prasad as chairman.

The trial was registered prospectively with clinical trial gov, India (www.ctri.org) with number CTRI/2017/09/009943

Written informed consent was obtained from parents or legal guardians prior to study participation.

Study initiation and completion dates were October 03, 2017 and May 6, 2019 respectively.

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