Magnitude and Factors Associated with Preoperative Anxiety Among Pediatric Patients: Cross-Sectional Study

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Background: Anesthesia and surgery are common sources of anxiety and stressful experiences in children. This unpleasant sensation depends on several factors. This study aimed to determine the magnitude of preoperative anxiety and associated factors in pediatrics patients at the University of Gondar Comprehensive Specialized Hospital North West Ethiopia 2020.

Methods: An institutional-based cross-sectional observational study was conducted from March to September 2020 at the University of Gondar Comprehensive Specialized Hospital. After obtaining ethical approval from the institutional review board. All consecutive ASA physical status I & II boys and girls with the age of 2–12 years scheduled for a variety of elective (general, urologic, ENT, ophthalmic and other surgical) operations were included. The level of anxiety was measured using the Modified Yale Preoperative Anxiety Scale short form (m-YPAS-SF) observational tool. Parental anxiety was assessed using Spielberger’s short version of state-trait anxiety. Binary logistic regression analysis was performed to identify the association between preoperative children’s anxiety and independent variables. The strength of the association was present by adjusted odds ratios.

Results: The magnitude of preoperative anxiety in children in the operation room was 75.44% (95% confidence interval (CI): 68.36, 81.34). Age (AOR: 3.83; 95% CI: 1.58, 9.30), previous surgery and anesthesia (AOR: 6.73, 95% CI: 1.25, 36.19), outpatient surgery (AOR: 5.16, 95% CI: 1.32, 20.23) and parental anxiety (AOR: 3.26, 95% CI: 1.30, 20.23) were significantly associated with preoperative children anxiety.

Conclusion: The magnitude of preoperative anxiety in pediatric patients was considerably high in our setup. Younger age, previous surgery and anesthesia, outpatient surgical setting, and parental anxiety were the independent risk factors for preoperative anxiety. Therefore, the operating staff should assess the child’s anxiety and should consider appropriate anxiety reduction methods during the preoperative visit of pediatric patients and their families.

Keywords: preoperative, anxiety, children, anesthesia, surgery

Introduction

Anxiety is a feeling of worry, nervousness, or unease about something with an uncertain outcome. Surgery and anesthesia is one of the most stressful and anxiety-provoking medical procedures that a child can experience. Pediatric patients undergoing medical procedures commonly feel extreme uneasiness or anxiety due to a lack of understanding and limited control over their environment and the situation.1

Preoperative pediatric anxiety is associated with several psychological and physiological adverse effects. Most children demonstrate anxiety through
a behavioral change such as trembling, being silent, restlessness, or crying and only a few can verbalize their fear either because they are not yet developmentally capable of such communication or are hindered in doing so because of their anxious state. Preoperative children’s anxiety (POCA) is also responsible for increased surgical morbidity. It has several negative impacts on anesthesia management; requiring large doses of induction and maintenance anesthetics, prolong induction time, delay the recovery, cause postoperative delirium, increased pain, and analgesic requirements, and delayed hospital discharge. A high level of POCA is also associated with post-operative negative behaviors, a greater level of postoperative anxiety, which negatively affects patients’ satisfaction with postsurgical analgesia. All these conditions might have cost implications for the parent and the institution; which also affect surgical outcome.

The magnitude of preoperative pediatric anxiety differs in different patient conditions and previous experiences. It has been reported higher in several studies; which ranges 50–75% patients in studies done from USA and Brazil but studies done in Greek and Brazil reported relatively smaller (42% and 39%). Younger age children, female gender, past bad hospital experience, past anesthetic, and surgical exposure, intravenous mode of anesthetic induction, increased number of people during induction, and low socioeconomic status of the parent are known to experience preoperative anxiety more frequently.

Children are influenced by parental advice and guidance in coping with new or stressful situations; on the other hand, parents may be anxious varying with the information given regarding anesthesia and associated risks, which may result in fear and anxiety for their children. Well-prepared parents, in turn, will be able to support their children and help themselves and their children suitably for an upcoming surgery. Therefore, parents play a critical role in preparing and helping children cope with their surgery. Thus, it becomes the responsibility of healthcare professionals working in pediatric surgical units to prepare children as well as their parents for the surgery.

Several preoperative strategies (ie, pharmacological, behavioral/psychological) have been used to reduce anxiety and negative responses of children so that to increase the cooperation and compliance during induction of anesthesia and to improve the postoperative recovery.

Different anxiolytic premeditations have been routinely used to treat anxiety in children with several studies supporting its benefit. On the other hand, some studies argue against the use of premedication because of its possible side effects and extra costs. Some studies showed parental presence has a good effect on relieving anxiety in children during the induction of anesthesia. On the other hand, a systematic review concluded that parental presence has no effect on preoperative pediatric anxiety during induction. However, parental presence during induction of anesthesia varies in different settings, which is not practiced in our settings.

Even though preoperative anxiety has several negative consequences both during and after surgery, it has been given less attention by the clinicians in our hospital. As per my information, there is no study conducted on this topic in Ethiopia as well as in Africa. Therefore, this study aimed to determine the magnitude and factors associated with preoperative anxiety among pediatric patients in our hospital using the modified Yale preoperative scale-short form (m-YPAS-SF anxiety scale).

Methods

Study Design and Setting

An observational cross-sectional study was conducted from March – September 2020. The study was conducted at University of Gondar Comprehensive Specialized Hospital pediatric operation theatres. The UGCSH is a teaching and referral hospital located in northwest Ethiopia, 738 km from the capital, Addis Ababa. The hospital provides a variety of pediatric surgical services in two operation theaters; in the major operation theaters and ophthalmic pediatric operation theater.

Before conducting the study, ethical clearance was obtained from the University of Gondar College of Medicine and Health Science, School of Medicine ethical review committee (Ref. No. 1933/03/2020), and voluntary informed written consent was taken from each parent or guardian after a brief explanation about the benefit, and risk of participating in the study.

Participants

All consecutive ASA physical status I & II pediatric patients with the age of 2–12 years, scheduled for elective surgical operation during the study period were included. Children who have ASA status III and above, known history of neuropsychiatric disorder or developmental delay and children whose parents’ care or giver refused to participate were excluded from the study.
Sample Size
A single population proportion formula was used to determine the sample size. Since there was no previous similar study done, the sample size was calculated by taking the assumption of a proportion of preoperative anxiety in children is 50%; with a 95% confidence, and a 5% margin of error. Finally, the sample size of this study was calculated as:

\[ n = \frac{\left( \frac{Z_{a/2}}{\rho(1 - \rho)} \right)^2}{\epsilon^2} \]

\[ n = \frac{(1.96)^2 \times 0.5(1 - 0.5)}{(0.05)^2} \]

\[ n = 384.16 \]
\[ n \approx 385 \]

Since the total number of pediatric patients getting an operation in our hospital annually was below 10,000. The correction factor formula was used to get the exact sample size. Here at the University of Gondar Comprehensive Specialized Hospital, an average of 88 pediatrics patients have undergone pediatric surgeries per month. By considering this, a total number of 264 pediatrics patients have been considered to operate during the data collection period. By considering this data, the sample size corrected as:

\[ nF = \frac{n}{1 + n/N} \]

\[ nF = \frac{385}{1 + 385/264} \]

\[ nF = 157 \]

Considering 10% of non-response rates the total number of study participants was 173.

Data Collection Procedures
Data collection was carried out by two trained staff nurses; both have experience in pediatric nursing, using a pre-tested semi-structured questionnaire. Socio-demographic data were collected from parents and medical charts. The annual income of the participant was evaluated using a scale developed by the 2013 report of the federal democratic republic of Ethiopia, ministry of finance and economic development. The questionnaire additionally composed the Face Leg Activity Cry Consolability score of pain parameters.

The assessment of anxiety was made through direct observation using the modified Yale Preoperative Anxiety Scale-short form (m-YPAS-SF). The m-YPAS-SF was used, for quicker assessment and greater clinical applicability with strong validity and reliability was appeared in 2014. \(^{25-29}\) The tool consists of 18 items divided into four domains: general activity,\(^{1-4}\) emotional expressivity,\(^{1-4}\) state of arousal,\(^{1-4}\) and vocalization.\(^{1-6}\) Scores range from 22.92 to 100, with scores ≥ of 30 points indicates a state of anxiety. The data collectors were standing at a distance to observe the child’s behavior in the operation room before the induction of anesthesia. The Spielberger short version state-trait anxiety inventory (STAI)\(^{30}\) translated to Amharic was used to evaluate parent’s situational anxiety. STAI is scored is based on a 4-point Likert scale (1= almost never to 4 = almost always) with a total score of 20–80. STAI score of ≥44 indicates anxiety.

Statistical Methods
The content validity was checked by seven experts from different disciplines (2 anesthetists, 2 pediatricians, 1 pediatric surgeon, and 2 pediatric nurses). The scale level content validity index by universal agreement was 0.83 and the scale level content validity index by average was 0.97; which was excellent and in line with many other studies. The internal validity of the tool was also checked (Cronbach alpha = 0.85), which ensures the internal consistency of the instrument. The inter-rater reliability between two data collectors with an interclass correlation coefficient was 0.92; which also indicates good inter-rater reliability.

The completed data were coded and entered into Epi-data 4.1 version, and then transferred to STATA version 14 statistical software for analysis. Descriptive statistics were used to summarize socio-demographic characteristics, child-related factors, and clinical-related factors of the child and the parent. Association between predictor variables and outcome of interests using binary logistics regression and fisher’s exact test was performed to identify variables associated with preoperative pediatric anxiety. According to Hosmer Lemeshow assumptions, the variables with a p-value < 0.2 in univariate analysis were included in the final model of multivariate logistic regression analysis. Multivariate analysis was performed to compute the adjusted odds ratio (AOR). Statistical significance was set at a one-sided P value < 0.05 in the multivariate analysis.

Results
Socio-Demographic Characteristics
In this study, a total of 173 children (92 boys and 81 girls), aged 2 to 12 years who underwent surgical operations under general anesthesia were included. Hundred fifty-one
(88.3%) were ASA I and the remaining twenty (11.7%) were ASA II. The distribution by surgical field comprised forty-seven (27.5%) ophthalmic, forty (23.39%) general, and the rest other surgical procedure. More than 50% of parents were uneducated and from a rural area (Table 1).

**Table 1** Socio-Demographic Characteristics of the Study Participant and Their Parent in UOGCSH, Gondar, Northwest Ethiopia, 2020. (n=173)

| Variables                  | Category          | Frequency(N) | Percentage (%) |
|----------------------------|-------------------|--------------|----------------|
| Age of the child in years  | 2–6               | 88           | 50.87          |
|                            | 7–12              | 85           | 49.13          |
| Sex of the child           | Male              | 92           | 53.18          |
|                            | Female            | 81           | 46.82          |
| School enrollment          | Enrolled          | 80           | 46.24          |
|                            | Not enrolled      | 93           | 53.76          |
| Birth order                | First             | 55           | 31.79          |
|                            | Second            | 62           | 35.84          |
|                            | Third and above   | 56           | 32.37          |
| Residency                  | Urban             | 80           | 46.24          |
|                            | Rural             | 93           | 53.76          |
| Parent level of education  | No formal education | 80         | 46.24          |
|                            | Up to 8(primary)  | 23           | 13.29          |
|                            | 9–12(high school) | 32           | 18.50          |
|                            | College and above | 38           | 21.97          |
| Annual parent income(ETB)  | No income         | 36           | 20.81          |
|                            | <3781             | 65           | 37.57          |
|                            | ≥3781             | 72           | 41.62          |

Magnitude of Preoperative Pediatric Anxiety Using m-YPAS

The study finding showed that 130 (75.14%) of children experienced anxiety with (95% CI: 68.36, 81.34) in the operation room before induction of anesthesia.

Child, Parental, and Clinical Related Factors, and Preoperative Anxiety

The majority of children who had experienced anxiety 76 (86.4) were the age of 2–6 years old. Sixty-four (69.6%) patients who had experienced anxiety were males. The majority of children 80 (86.8%) who had anxious parents were experienced preoperative anxiety. Also, 87.5% of the children from those who have been previous surgical events were anxious. Among 54 children who were admitted in outpatient 50 (92.6%) of them were experienced preoperative anxiety in the operation room. The majority of children (158) who undergone intra-veins anesthesia induction, 119 (75.3%) of them were had observed preoperative anxiety in the operation room. The distribution by surgical field comprised 47 (27.5%) ophthalmic, 40 (23.39%) general, and the rest other surgical procedure (Table 2).

Factors Associated with Preoperative Children Anxiety in Multiple Regression Analysis

In the bi-variable logistic regression age, sex, ASA-status, parental education level, parental anxiety, surgical setting, previous hospitalization, and previous surgery, and preoperative pain were positively associated with children’s preoperative anxiety. But, finally, age, surgical setting, previous surgery and anesthesia, and parental anxiety were significantly associated with children’s preoperative
anxiety in the operation room in multi-variable logistic regression.

The odds of being anxious in the operation room among children who had aged 2–6 years were 3.83 (AOR: 3.83; 95% CI: 1.58, 9.30) times higher as compared to children who had aged 7–12 years. The odds of being anxious in the operation room among children who had anxious parents were 3.43 (AOR: 3.54; 95% CI: 1.50, 8.33) higher as compared to children who had not an anxious parent.

The odds of being anxious in the operation room among children who were admitted in the outpatient base were 5.67 (AOR: 5.67; 95% CI: 1.73, 18.55) times higher as compared to patients admitted in the inpatient base. The odds of being anxious in the operation room among children who had previous surgery and anesthesia were 5.96 (AOR: 4.79; 95% CI: 1.16, 30.49) times higher as compared to those who had no previous surgery and anesthesia exposure (Table 3).

**Discussion**

The main purpose of this study was to find out the magnitude of preoperative anxiety in children and factors associated with it. The magnitude of preoperative anxiety in children was considerably high in our hospital. Younger age, previous surgery and anesthesia, outpatient surgical

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**Table 2** Child, Parental, and Clinical Related Factors and Preoperative Anxiety of Children in UOGCSH, Gondar, and North West Ethiopia, 2020. (n=173)

| Variables                        | Category | Frequency (%) | Anxious n (%) |
|----------------------------------|----------|---------------|---------------|
| **Age of child in year**         | 2–6      | 88(50.9)      | 76(86.4%)     |
|                                  | 7–12     | 85(49.1)      | 54(63.5%)     |
| **Sex of the child**             | Male     | 92(53.2)      | 64(69.6)      |
|                                  | Female   | 81(46.8)      | 66(81.5)      |
| **ASA status**                   | ASA I    | 149(86.1)     | 110(73.8)     |
|                                  | ASA II   | 24(13.9)      | 20(83.3)      |
| **Previous hospital admission**  | Yes      | 46(26.6)      | 35(76.1)      |
|                                  | No       | 127(73.4)     | 95(74.8)      |
| **Previous surgery and anesthesia** | Yes    | 35(20.2)      | 30(85.7)      |
|                                  | No       | 138(79.8)     | 100(72.5)     |
| **Preoperative pain**            | Yes      | 32(18.5)      | 27(84.4)      |
|                                  | No       | 141(81.5)     | 103(73.1)     |
| **Parental anxiety**             | Yes      | 93(53.8)      | 80(86.8)      |
|                                  | No       | 80(46.2)      | 50(62.5)      |
| **Surgical sitting**             | Inpatient| 117(67.6)     | 79(67.5)      |
|                                  | Outpatient| 56(32.4)     | 51(91.1)      |
| **Type of induction**            | Intravenous| 158(91.3)   | 119(75.3)     |
|                                  | Inhalational| 15(8.7)      | 10(76.9)      |
| **Surgical type**                | General  | 40(23.1)      | 31(77.5)      |
|                                  | Ophthalmic| 47(27.2)      | 42(89.4)      |
|                                  | ENT      | 37(21.4)      | 22(62.2)      |
|                                  | Urology  | 22(12.7)      | 13(59.1)      |
|                                  | Other    | 27(15.5)      | 17(77.8)      |
setting and parental anxiety were the independent risk factors for preoperative anxiety.

The Magnitude of preoperative anxiety was found in 75% of children undergoing surgery in our study. This result is consistent with recent studies reported that the prevalence of pediatric preoperative anxiety 50–75%. However, our result was considerably high compared to other studies, which reported 35.8% in Portugal, 41.7% in Chile, 50.2% in Australia and 42% in Brazil. This variation in the current study can be explained by the inclusion of younger age and because their parents are separated from them when they enter the operating theatre in our sitting. Whereas, in all of the above studies reviewed that parents remain with their children until the moment of anesthetic induction. Parental presence in the operation room during the induction of anesthesia makes the child happier and cooperative.

Currently, the use of topical anesthetics during intravenous (IV) cannula insertion, parental presence in the operating room, visual/auditory distractions, and anxiolytic premedication has been presented as an effective way of helping children to cope with preoperative anxiety.

| Variables                      | Anxiety Status | OR(95% CI) |
|--------------------------------|----------------|------------|
|                                | Yes n (%)      | No n (%)   | COR(95% CI) | AOR(95% CI) |
| Age                            |                |            |            |             |
| 2–6                            | 76(86.4)       | 12(13.6)   | 3.63(1.71,7.71) | 3.83(1.58,9.30)** |
| 7–12                           | 54(63.5)       | 31(36.5)   |            |             |
| Sex                            |                |            |            |             |
| Male                           | 64(69.6)       | 28(30.4)   | 1.92(0.94,3.93) |             |
| Female                         | 66(81.5)       | 15(18.5)   |            |             |
| ASA-status                     |                |            |            |             |
| ASAI                           | 110(73.8)      | 39(26.2)   | 2.09(0.68,6.44) |             |
| ASAIi                          | 20(83.3)       | 4(16.7)    |            |             |
| Parental education level       |                |            |            |             |
| Illiterate                     | 63(78.7)       | 17(21.3)   | 2.16(0.92,5.05) | 2.02(0.72,5.58) |
| Elementary school              | 18(78.3)       | 5(21.7)    | 2.10(0.63,6.09) | 1.68(0.41,6.92) |
| High school                    | 25(78.1)       | 7(21.9)    | 2.08-0.71,6.05 | 2.21(0.58,8.34) |
| College and above              | 24(63.2)       | 14(36.8)   |            |             |
| Parental anxiety               |                |            |            |             |
| Yes                            | 80(86)         | 13(14)     | 3.69(1.76,7.74) | 3.54(1.58,8.33)** |
| No                             | 50(62.5)       | 30(37.5)   |            |             |
| Type of admission              |                |            |            |             |
| Inpatient                      | 79(67.5)       | 38(32.5)   | 4.90(1.81,13.29) |             |
| Out patient                    | 51(91.1)       | 5(8.9)     |            |             |
| Previous hospital admission    |                |            |            |             |
| Yes                            | 35(76.1)       | 11(23.9)   | 1.07(0.48,2.35) | 0.36(0.09,1.47) |
| No                             | 95(74.8)       | 32(25.2)   |            |             |
| Previous anesthesia and surgery|                |            |            |             |
| Yes                            | 30(85.7)       | 5(14.3)    | 2.27(0.82,6.30) | 5.96(1.16,30.49)** |
| No                             | 100(72.5)      | 38(27.5)   |            |             |
| Preoperative pain              |                |            |            |             |
| Yes                            | 27(84.4)       | 5(15.6)    | 1.99(0.71,5.54) | 0.96(0.26,3.43) |
| No                             | 103(73.1)      | 38(26.9)   |            |             |

Note: **Significant variables from multivariate analysis.
Abbreviations: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval.
However, these anxiety alleviating strategies had not ever been practiced in our hospital that could be also the reason for higher prevalence.

The cause of preoperative anxiety in pediatrics is multifactorial. In the current study, age, previous surgery and anesthesia experience, type of surgical sitting, and parental anxiety were significantly associated with preoperative anxiety in multivariable logistic regression. The result of our study showed that younger age children (2–6years) were higher odds of preoperative anxiety in the operation room than older children. This is consistent with the findings from previous literature. In children, the perception of anxiety depends on the developmental stage and cognitive potential of the child; different responses can be observed among those facing the same stressor agent. With increasing age, the cognitive capacity of the child increases, resulting in more awareness, understanding, and more likely to overcome stress than younger children. As such, preoperative anxiety is more prevalent in those of a younger age, and declines as children become older.

The result of this study revealed that children who had previous surgery and anesthesia were higher odds of preoperative anxiety than children who had not previous surgery and anesthesia. This finding is consistent with other similar studies that showed child’s prior experience with surgery and anesthesia has been shown to have an adverse effect on his/her behavior during subsequent anesthesia and surgery. On the contrary, other studies showed that children with previous surgery and anesthesia were significantly less anxious during the preoperative period. The possible explanation for this may be children who had previous negative surgical and anesthetic histories (who suffer pain, light anesthesia) may exacerbate subsequent anesthesia and surgery-related anxiety. However, those who had a previous positive and smooth experience of previous surgeries may favor the sense of safety in the child because he/she already knows what to expect; they are dealing with something known, about the surgery and anesthesia which may attenuate anxiety in the subsequent surgery. These findings may suggest that the overall quality of the previous surgical and anesthetic care of the child could impact on future procedures.

In the current study, children who enrolled in outpatient surgery had higher odds of preoperative anxiety than children who enrolled in an inpatient setting. In contrast to our result children enrolled in outpatient surgery have been reported to be less anxious than inpatients. The variation can be due to the time spent at the hospital is reduced and the opportunities of the healthcare professionals to provide information to children and their parents are limited. Another possible explanation for this finding could be due to the commonest practice of intravenous anesthetic induction in our set-up, children scheduled for outpatient surgery are cannulated in the waiting room without the use of topical anesthetics before the entrance to the operation room which may increase fear of harming the operation room.

Parental anxiety was another major determinant factor for the experiencing of children’s preoperative anxiety in the operation room. The result of our study found that children who have anxious parents had higher odds of being anxious in the operation room than children who did not have an anxious parent. In agreement with our finding, a study done at the University General Hospital of Alexandropoulos, Greece in 2018 showed that parental anxiety influences their children negatively. They have found to be the strongest independent risk factor for children’s preoperative anxiety levels. Similarly, a study conducted in Catholic University of Santiago Chile showed that a significant positive correlation was observed between self-reported parental anxiety in the preoperative holding room and children’s anxiety in the operating room. William and Lopez also showed that parents are an important factor in determining how a child will respond emotionally to the stress of surgery. They found out that parents could play a more active role in helping their children feel less anxious and respond to surgery more positively. Our previous study showed that parents’ gender was most strongly related to higher anxiety levels for their child. Mothers had four to five times greater chances of having high scores on the anxiety scale than fathers did. However, the effects of parents’ level of education on the children’s level of anxiety were reported controversial. This efforts must be taken to decrease parent’s preoperative stress with behavioral or other interventions which would further facilitate reducing their children’s anxiety.

Strength and Limitation of the Study

This study is the first of its type in the study area as well as in the country. We have used a validated tool that has good inter-observer and intra-observer reliability, and excellent internal validity. As a limitation, this study is an institutional-based which could limit its generalizability and the cross-sectional nature of the study would also limit its ability to establish a temporal relationship. Also, preoperative anxiety in pediatric patients is multifactorial. Important variables such as preoperative preparation and information are given days before surgery for both the
parent and child affect the pre-induction emotion and behavior of the child were difficult to investigate due time constraints and variations to identify these factors.

**Conclusions**

The magnitude of preoperative anxiety in children was considerably high in our setup. Younger age, previous surgery and anesthesia, outpatient surgical setting and parental anxiety were the independent risk factors for preoperative anxiety. Therefore, the operating staff should assess the child’s anxiety and should consider appropriate anxiety reduction methods during the preoperative visit of pediatric patients and their families.

**Abbreviations**

AOR, Adjusted Odds Ratio; ASA, American Society of Anesthesiologist; COR, Crude Odds Ratio; EAA, Ethiopian association of anesthetists; M-YPAS, Modified-Yale Preoperative Anxiety Scale; M-YPAS-SF, Modified – Yale Preoperative Anxiety Scale – Short Form; POCA, preoperative children anxiety; STAI, State-trait anxiety inventory; S-TAIC, State-trait anxiety inventory for children; STATA, Software for statistics and data sciences; UOG, University of Gondar; UOGCSH, University of Gondar compressive specialized hospital.

**Data Sharing Statement**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics Approval and Consent to Participate**

This study was conducted in accordance with the Declaration of Helsinki. To conduct the current research, the ethical approval was obtained from the Ethical Review Board of School of Medicine, College of Medicine and Health Sciences, University of Gondar (Ref. No. SOM/1933/2020), and voluntary informed written consent was taken from each parent or guardian after a brief explanation about the benefit and risk of participating in the study. Potential ethical issues were addressed accordingly during the study period.

**Consent to Publication**

Not applicable (the article did not contain any personal or clinical detail of any individual participant).

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**Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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**Disclosure**

The authors report no conflicts of interest for this work.

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