



## CLINICAL RESEARCH ARTICLE

## Cerebral oxygenation in preterm infants during maternal singing combined with skin-to-skin care

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**BACKGROUND:** Our aim was to investigate the effect of music therapy in combination with skin-to-skin care (SSC) on regional cerebral oxygenation (rSO<sub>2</sub>) measured with near-infrared spectroscopy (NIRS) in premature infants and to study physiological stability during the interventions.

**METHODS:** This was a prospective single-center observational cohort study conducted in a tertiary neonatal intensive care unit. The study consisted of four phases: (1) baseline measurements in an incubator for 30 min; (2) quiet SSC for 30 min (SSC-Pre); (3) SSC with live maternal singing accompanied by live guitar music for 20 min (SSC-Music); (4) final quiet SSC for another 30 min (SSC-Post).

**RESULTS:** The primary outcome measure of mean rSO<sub>2</sub> for the 31 preterm infants analyzed showed a significant increase from baseline during SSC-Music (76.87% vs 77.74%,  $p = 0.04$ ) and SSC-Post (76.87% vs 78.0%,  $p = 0.03$ ) phases. There were no significant changes observed in heart rate (HR), peripheral oxygen saturation (SpO<sub>2</sub>), and cerebral fractional tissue oxygen extraction (cFTOE). The coefficient of variation (CV) of rSO<sub>2</sub> and SpO<sub>2</sub> decreased during each intervention phase.

**CONCLUSION:** Combining music therapy with SSC appears to be safe in preterm neonates. The impact of the small increase in rSO<sub>2</sub> and reduced variability of SpO<sub>2</sub> and rSO<sub>2</sub> warrants further investigation.

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**IMPACT:**

- Music therapy combined with skin-to-skin care (SSC) is safe in clinically stable premature infants and could be encouraged as part of developmental care.
- This is the first report where near-infrared spectroscopy (NIRS) was used to detect the simultaneous effect of music therapy and SSC on cerebral rSO<sub>2</sub> in preterm infants.
- Music therapy with SSC caused a modest increase in rSO<sub>2</sub> and decreased the coefficient of variation of rSO<sub>2</sub> and peripheral oxygen saturation (SpO<sub>2</sub>), which suggest short-term benefits for preterm infants.

**INTRODUCTION**

Although recent advances in neonatology have led to significant improvements in the survival of very preterm infants, the consistently high morbidity has created further challenges. Substantial efforts have been made to better understand the early neuro-behavioral processes and environmental factors that may help to improve long-term outcomes. A variety of interventions, collectively called developmental care, have been introduced with the aim to minimize stressful stimuli for the baby.<sup>1</sup> Reduced ambient noise and light, positioning, care bundling, and skin-to-skin care (SSC) have been shown to positively influence outcomes.<sup>2</sup> Music therapy has a recognized role in maternal bonding in nearly every culture<sup>3</sup> and has recently re-emerged as an attractive intervention being both safe and inexpensive.<sup>4</sup>

It has been demonstrated that infants recognize their mother's voice and language as early as at the time of birth.<sup>5,6</sup> Encouraging parents to choose their songs of kin leads to a more harmonized

parent–child interaction, which is further enhanced by the presence of a professional music therapist.<sup>7,8</sup> Live infant-directed singing allows mothers to continuously interact with and respond to their infant's behavior.

Maternal singing has been shown to reduce the incidence of adverse cardiorespiratory events and maternal stress, increase peripheral oxygen saturation (SpO<sub>2</sub>), heart rate (HR), and improve the feeding habits of infants.<sup>9–12</sup> The Perinatal Music Program “I know your voice” has been introduced on our NICU in 2014. We found that parents do not require any specific training and offering them the ability to be actively involved in their child's care and psychological wellbeing overcomes their initial reluctance to sing.

Near-infrared spectroscopy (NIRS) is a non-invasive, portable, silent, and relatively inexpensive optical imaging technique that is used in developmental neuroscience research and is increasingly

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available in neonatal units.<sup>13</sup> Cortical activity is associated with an increase in localized cerebral blood flow, which is described as neurovascular coupling.<sup>14</sup> Changes in brain activity can be observed indirectly by measuring the changes in tissue concentrations of oxygenated and deoxygenated hemoglobin.<sup>15</sup> In a clinical setting, monitoring regional cerebral oxygenation (rSO<sub>2</sub>) with NIRS may help to avoid hypoxic episodes, although its ability to influence long-term clinical outcomes is yet to be established.<sup>16</sup>

To date, there are no publications describing the cortical response to music therapy in preterm infants with NIRS. A potential increase in mean cerebral oxygenation would suggest a favorable response to music, while a decreased variability of these parameters during SSC and music therapy could imply greater physiological stability. We therefore designed a study to compare rSO<sub>2</sub> and other physiological parameters during incubator care, SSC and subsequently during music therapy in preterm infants.

## METHODS

### Study design and oversight

This was a prospective single-center observational study conducted between March 2017 and January 2019 in the Neonatal Intensive Care Unit of the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary. Written informed parental consent was obtained after a detailed verbal discussion. The study was approved by the Ethics Committee of the National Medical Research Council (ETT-TUKEB 13030-1/2017/EKU).

### Participants

The patient population consisted of outborn infants referred for tertiary neonatal care. Clinically stable preterm infants (gestational age 23–36 weeks) who were at least five days old, with or without non-invasive respiratory support were eligible. The availability and willingness of the mother to participate and provide SSC was required. Exclusion criteria were on-going requirement for mechanical ventilation via endotracheal tube, cardiorespiratory instability, and any congenital cerebral malformation potentially affecting auditory perception. All infants subsequently had a normal hearing test performed by brainstem evoked response audiometry. Sample size calculation demonstrated that a total of 32 infants would achieve a power of 80%, with type I error of 5%, for an effect size of 0.45% change in rSO<sub>2</sub> using one-tailed matched pairs *t*-test. A total of 34 patients were approached. One parent declined participation, one infant was excluded due to unexpected clinical deterioration before the intervention, and one patient's data could not be analyzed due to a recording error. There were no adverse events observed during the study period.

### Equipment

NIRS monitor (SenSmart® Model X-100, Nonin Medical Inc., Plymouth, MN, USA) was used to monitor HR, SpO<sub>2</sub>, and rSO<sub>2</sub>. Cerebral fractional tissue oxygen extraction (cFTOE) was calculated as an indicator of the balance between oxygen delivery and oxygen consumption. The rSO<sub>2</sub> sensors were positioned over the temporal region bilaterally, 1 cm above the ears. Investigators and participants were blinded to the NIRS monitor during the study.

### Study intervention

The study consisted of four phases of continuous recordings for each infant. Baseline measurements were performed with the infant in the incubator at rest for 30 min (Baseline). This was followed by 30 min of skin-to-skin contact with the mother, when the child was wearing a nappy, was covered with a blanket, and was placed prone and upright on mother's chest (SSC-Pre). The third phase consisted of 20 min of live maternal singing accompanied by live guitar music with the infant remaining in the same position as before (SSC-Music) (Fig. 1). This was followed



**Fig. 1 Music therapy session.** Live maternal singing during skin-to-skin care with the help of a professional music therapist. Image is reproduced with permission from the participants.

by the fourth post intervention phase, when the skin-to-skin contact was continued for another 30 min (SSC-Post). This design ensured that each infant served as his/her own control. The transition time between each phase was kept to a minimum. The head position of the infants was recorded to note which ear was resting on the mother's chest. During all sessions the ambient noise in the unit was kept to the minimum (<45 dB). In patients where respiratory support was required, there were no alterations in the ventilation settings throughout the study period. Mothers were encouraged to remain silent during the SSC-Pre and SSC-Post phases. The sessions were held in the afternoon, between cares and feedings, commencing at least 20 min after feeding. Music therapy consisted of maternal singing of simple pentatonic repetitive soothing songs, accompanied by a guitar played by a professional music therapist with the overall volume kept between 55–65 dB. The presence of trained musicians ensured that music therapy sessions were structured similarly, allowing for comparison between infants for study purposes.

### Outcome measures

Primary outcome was the difference in mean rSO<sub>2</sub>, while secondary outcomes were changes in HR, SpO<sub>2</sub>, and cFTOE among the study phases. The coefficient of variation (CV) of each parameter within every intervention phase was also calculated to compare the variability of different data sets and to assess physiological stability. We also tested the effect of covariates on the outcome, including birth weight, age at measurement as continuous variables and sex, the presence of intraventricular hemorrhage grade III/IV, or the need for respiratory support as binary variables.

### Data collection

NIRS data were recorded separately on both sides at 4 s intervals and were averaged for each phase. The overall rSO<sub>2</sub> was calculated as the average of these left- and right-sided mean values. HR and SpO<sub>2</sub> were recorded with 0.25 Hz sampling rate and averaged over each phase. The cFTOE was calculated from rSO<sub>2</sub> and SpO<sub>2</sub> for each time point as follows:  $cFTOE = (SpO_2 - rSO_2) / SpO_2$ .

### Statistical analysis

Descriptive statistics are presented as median with interquartile range (IQR) or as a numerical value and percentage (%). For the primary and secondary outcomes, we analyzed the effect of the

interventions using repeated measures one-way ANOVA with the Geisser–Greenhouse correction (to adjust for lack of sphericity) or nonparametric Friedman test depending on the data distribution. We calculated the difference in physiological parameters among the four study phases using a repeated measures one-way ANOVA with Dunnett’s or Friedman test with Dunn’s multiple comparison post hoc test as appropriate (for normally distributed or skewed data, respectively). We used Spearman’s rank correlation to test correlation between covariates and response to music. Regression modeling was performed on the  $rSO_2$  dataset to see if left or right ear exposure had any effect by using a repeated measures linear mixed-effect model with first-order autoregression within-group correlation structure.

The coefficient of variation (CV) was calculated as the ratio of the standard deviation to the mean (SD/mean) for each parameter and was expressed as a percentage. To demonstrate the pattern of variability we generated Poincaré plots (also known as return maps), which illustrate the correlation between consecutive data points in time-series data.<sup>17</sup> In brief, consecutive data points are plotted against each other and an ellipse is fitted over the values, centered on the mean. The short and long semi-axis represent short-term (SD1) and long-term (SD2) variability, respectively. R Statistical Software, Version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism, Version 8.2.1. (GraphPad Software, San Diego, CA, USA) were used for data analysis and plotting. We accepted  $p < 0.05$  as a level of significance.

## RESULTS

A total of 31 preterm infants’ data were analyzed. Demographic and clinical characteristics of the participants are shown in Table 1.

**Table 1.** Clinical characteristics of study participants.

Clinical data	<i>n</i> = 31
Gestational age, weeks	30 [26; 32]
Birth weight, grams	1210 [840; 1850]
Female sex, <i>n</i> (%)	16 (51.6)
Apgar 1 min	6.5 [4.0; 8.0]
Apgar 5 min	8.0 [7.0; 9.0]
Corrected gestational age, weeks	34 [33; 36]
Weight during the study, grams	1630 [1420; 2070]
Respiratory support, <i>n</i> (%)	9 (29.0)
IVH stage III or IV, <i>n</i> (%)	7 (22.6)
Previous surgery, <i>n</i> (%)	17 (54.8)

Values are shown as median [IQR] or count, *n* (%); IVH intraventricular hemorrhage.

**Table 2.** Physiological parameters during the four study phases.

	Baseline	SSC-Pre	SSC-Music	SSC-Post	ANOVA
$rSO_2$ (%)	76.87 (2.97)	77.72 (3.50)	77.74 (3.08)	78.00 (3.04)	$p = 0.02^a$
$SpO_2$ (%)	93.07 (4.11)	94.34 (4.19)	94.34 (3.31)	94.10 (3.77)	$p = 0.17^b$
HR (bpm)	154.3 (16.7)	153.9 (14.3)	154.4 (14.8)	155.6 (13.7)	$p = 0.59^a$
cFTOE	0.17 (0.04)	0.17 (0.05)	0.17 (0.04)	0.17 (0.03)	$p = 0.72^a$

Data are shown as mean (SD).  $rSO_2$  regional cerebral oxygen saturation,  $SpO_2$  peripheral oxygen saturation, HR heart rate, bpm beat per minute, cFTOE cerebral fractional tissue oxygen extraction, SSC skin-to-skin care, ANOVA analysis of variance.

<sup>a</sup>ANOVA with Geisser–Greenhouse correction.

<sup>b</sup>Nonparametric Friedman test.

## Comparison between intervention phases

Table 2. summarizes the mean of each physiological parameter measured in the four intervention phases. Repeated measures ANOVA showed that cerebral oxygenation significantly increased during the interventions ( $p = 0.02$ ). ANOVA post hoc tests revealed a significant increase from baseline in mean  $rSO_2$  during SSC-Music (76.87% vs 77.74%,  $p = 0.04$ ) and SSC-Post (76.87% vs 78.0%,  $p = 0.03$ ) phases. There was no significant difference in mean  $SpO_2$  ( $p = 0.17$ ), HR ( $p = 0.59$ ), or cFTOE ( $p = 0.72$ ) during the intervention phases.

## Effect of covariates on NIRS changes

We analyzed the effect of potentially relevant covariates on the response to intervention defined as the difference in mean  $rSO_2$  between SSC-Pre and SSC-Music. We included birth weight, sex, postmenstrual age at measurement, the presence of intraventricular hemorrhage grade III–IV and the need for respiratory support (continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC)). We could not identify any correlation between these covariates and the response to intervention (Supplemental Fig. 1).

## Variability of physiological parameters during interventions

The CV was calculated for the measured parameters to study physiological stability in the four study phases (Table 3). Using a linear mixed-effect regression model, we found that the CV of  $rSO_2$  decreased significantly from baseline during both SSC-Pre and SSC-Music phases (mean CV 3.41 vs 2.27 and 2.11,  $p = 0.03$  and  $p < 0.001$ ; respectively). Poincaré plots were used to visualize this decrease in  $rSO_2$  variability. A representative case is shown in Fig. 2. We observed a considerable decrease in the average length of these axes during intervention (Supplemental Table 1), reflecting a reduction in short- and long-term variation of the data, respectively. The CV of  $SpO_2$  decreased from baseline during all three SSC phases. Interestingly, the CV of HR decreased significantly only during the SSC-Pre phase (Table 3). In addition, we found that during all three intervention phases the overall mean  $rSO_2$  values measured over the left temporal lobe were higher than those over the right side ( $78.6 \pm 3.2\%$  vs  $77.0 \pm 3.7\%$ ,  $p = 0.02$ ). Regression modeling was used to show that the difference in  $rSO_2$  was most prominent when the left ear was uncovered, and during the SSC-Music phase (mean difference 2.85%,  $p < 0.001$ ).

## DISCUSSION

Our results suggest that music therapy combined with SSC is safe in preterm infants as it has improved regional  $rSO_2$  when compared to incubator care. The modest, but statistically significant changes in  $rSO_2$  in the SSC-Music and SSC-Post phases suggest a response of cortical activity to music. Of note, we investigated the cortical effect of multisensorial stimulation over 20–30 min periods as opposed to functional studies assessing

brain activity and hemodynamic responses within few seconds of isolated stimuli.<sup>18</sup> Although specific rSO<sub>2</sub> values will depend on the type of equipment and sensors used or computational algorithms applied,<sup>19</sup> the changes in these values that we observed are comparable with those reported in similar studies.<sup>20–22</sup> Throughout the study periods rSO<sub>2</sub> values remained in the normal range for neonates (55–85%),<sup>16</sup> which provides a high degree of reassurance regarding the safety of the interventions.

To our knowledge, ours is the first report investigating preterm infants to detect the simultaneous effect of SSC and music therapy on rSO<sub>2</sub>. Previously, Sakatani et al.<sup>23</sup> reported that playing recorded piano music through earphones to infants in their cots increased regional cerebral blood flow, although the vast majority of their patients were not born preterm.

We could not demonstrate any significant change in mean rSO<sub>2</sub> between baseline and SSC-Pre phase (SSC only), which is in line with other published reports.<sup>20–22</sup> Begum et al.<sup>20</sup> found no significant changes in mean regional oxygen saturations; only

when applying power spectral analysis were the changes of total power of rSO<sub>2</sub>, HR, and SpO<sub>2</sub> found to be significant. Lorenz et al.<sup>21,22</sup> reported no significant changes in rSO<sub>2</sub> during SSC in ventilated infants but found a significant reduction of rSO<sub>2</sub> during SSC in those not receiving ventilatory support.

Interestingly, we found that the mean rSO<sub>2</sub> values measured over the left temporal lobe during every intervention phase were significantly higher than those on the right side irrespective of infant positioning. Although our study was not specifically designed to investigate this phenomenon, the reason for this lateralization raises exciting questions. While music is processed with a right hemispheric dominance, our findings may be explained by the more prominent impact of the mother's voice on the left hemisphere's linguistic processing or the emotional response to multisensorial stimulation.<sup>24</sup>

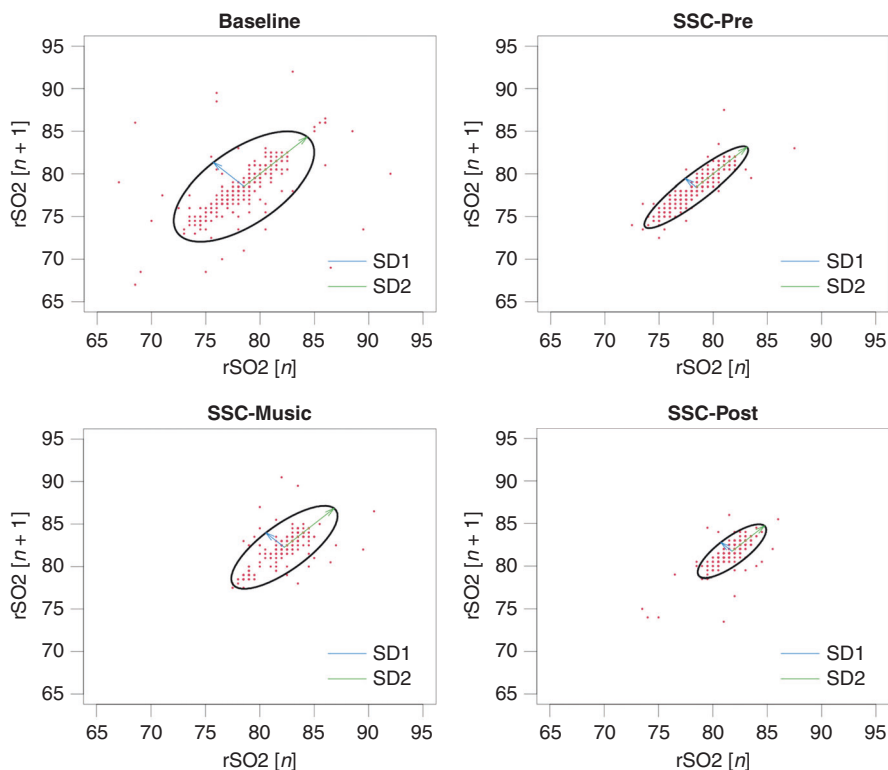
Throughout the intervention the changes in SpO<sub>2</sub>, HR, and cFTOE were not significant, which is in line with other published research using different protocols of combining music therapy with SSC.<sup>25</sup> A study by Teckenberg-Jansson et al.<sup>26</sup> reported a statistically significant change in blood pressure, but there were no significant changes in HR and SpO<sub>2</sub>.

We analyzed the CV of study variables for every intervention phase, allowing us to describe the variability of each measured dataset over time. Our results confirmed a decrease in variability of SpO<sub>2</sub> and rSO<sub>2</sub> during the music therapy phase, suggestive of physiological stability.

The variability of physiological parameters in preterm infants has been an area of interest recently. There is evidence that reduced variability of SpO<sub>2</sub> is beneficial.<sup>27</sup> Heart rate variability (HRV) seems to be associated with the maturity of the autonomic system;<sup>28</sup> however, in some cases an increase in HRV may signal response to sepsis.<sup>29</sup> Previous studies have used HRV to infer autonomic stability in preterm infants.<sup>25</sup> As variability of rSO<sub>2</sub> in

	Baseline	SSC-Pre	SSC-Music	SSC-Post
CV of rSO <sub>2</sub> (%)	3.41	2.27 ( <i>p</i> = 0.03)	2.11 ( <i>p</i> < 0.001)	2.68 ( <i>p</i> = 0.052)
CV of SpO <sub>2</sub> (%)	3.91	2.85 ( <i>p</i> < 0.001)	2.67 ( <i>p</i> < 0.001)	2.83 ( <i>p</i> < 0.001)
CV of HR (%)	5.64	4.08 ( <i>p</i> = 0.04)	4.7 ( <i>p</i> = 0.11)	5.13 ( <i>p</i> = 0.49)

*P* values represent the effect of the study phase on the coefficient of variation using a linear mixed-effects regression model.  
rSO<sub>2</sub> regional cerebral oxygen saturation, SpO<sub>2</sub> peripheral oxygen saturation, HR heart rate, SSC skin-to-skin care, CV coefficient of variation.



**Fig. 2** Poincaré plots of rSO<sub>2</sub> changes in the four intervention phases of a study participant. A reduction in rSO<sub>2</sub> variability demonstrated by shorter SD1 and SD2 axes in all three intervention phases and an increase in mean rSO<sub>2</sub> in SSC-Music and SSC-Post phases when compared to Baseline.



preterm infants has not been studied thus far, further studies are clearly need to corroborate our findings.

A strength of our study is that we included preterm infants with significant comorbidities such as IVH grade III–IV or history of surgical procedures. SSC and music therapy had a similar effect on all infants; thus, the heterogeneity of population allows for better generalizability of our findings. Although SSC is increasingly encouraged in our unit for infants who are intubated, we chose to exclude this group of patients for this particular study as we felt the sedation and analgesic requirements could potentially confound our results.

The use of Poincaré plots to analyze NIRS data is currently a novel approach, but we found it to be an informative visual representation of variability when applied to complex physiological data. We believe that combining SSC with live maternal singing had conferred benefits to our study. This multi-sensory experience may have a role in selective attention, cognition, and learning processes.<sup>30</sup>

We would also like to mention a number of potential limitations to our study. Firstly, we lacked statistical power to study a subgroup of infants who received respiratory support. One may speculate that the use of CPAP or HFNC may affect auditory perception of music; however, we could not find any correlation between rSO<sub>2</sub> changes and respiratory support. Secondly, we could not control for the number or frequency of previous SCC and maternal singing sessions each infant took part in prior to the study. Although we did not notice any discomfort or adverse reaction during the study periods, it is plausible that infants who had less exposure to such sessions would have required more time to adapt. Aligning the availability of our volunteer music therapist with stable infants not yet discharged from our unit has admittedly prolonged our recruitment process. We may also have added further strength to our study by monitoring physiological changes in mothers simultaneously with their infants', but technical challenges made this difficult at the time. Randomizing the order in which the four different study phases were performed was considered thoroughly, but during a pilot it was deemed to be unnatural, uncomfortable for the parent, and technically difficult to achieve. Finally, our study analyzed only the immediate effects of a single music therapy session on preterm infants. In coherence with a recent review article,<sup>31</sup> long-term neurodevelopmental outcome studies would be desirable to demonstrate the sustained beneficial effects of maternal singing in this vulnerable group of patients.

In summary, our findings suggest that SSC combined with music therapy is safe in clinically stable premature infants. The potential short- and long-term clinical effects of the observed modest increase in rSO<sub>2</sub> and the decreased CV of rSO<sub>2</sub> and SpO<sub>2</sub> could be the subject of further research. Our results suggest that SSC combined with maternal singing and music therapy can be encouraged for a wide group of preterm infants on NICUs as part of developmental care.

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## AUTHOR CONTRIBUTIONS

Each author has met the *Pediatric Research* authorship requirements. Substantial contributions to conception and design: U.M., T.H., G.B., M.S., and A.J. Acquisition of

data, or analysis and interpretation of data: U.M., E.T., K.K., E.S., A.J.C., T.H., and A.J. Drafting the article or revising it critically for important intellectual content and final approval of the version to be published: U.M., E.T., K.K., E.S., A.J.C., T.H., M.S., G.B., and A.J.

## ADDITIONAL INFORMATION

The online version of this article (<https://doi.org/10.1038/s41390-020-01235-2>) contains supplementary material, which is available to authorized users.

**Competing interests:** The authors declare no conflict of interest.

**Ethics approval:** The study was approved by the Ethics Committee of the National Medical Research Council (ETT-TUKEB 13030-1/2017/EKU). Written informed parental consent was obtained for all participants.

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