Cerebral Oxygen Saturation and Negative Postoperative Behavioral Changes in Pediatric Surgery: A Prospective Observational Study

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Objective To evaluate if an intraoperative cerebral regional oxygen saturation ($crSO_2$) decrease, less pronounced than 20% below baseline (the current threshold believed to be associated with cognitive dysfunction in adults), is associated with negative postoperative behavioral changes (NPOBC) in the pediatric population after noncardiac surgeries.

Study design A prospective observational study was conducted with 198 children aged 2-12 years old scheduled for noncardiac procedures under general anesthesia. Intraoperatively, $crSO_2$ was monitored with a cerebral oximeter. On postoperative day 7, the Post-Hospital Behavior Questionnaire was used to diagnose NPOBC.

Results The incidence of NPOBC was 38.8%. Logistic regression analysis revealed that with every 1% reduction of $crSO_2$ from the baseline value, the odds of developing NPOBC were 1.199 higher. Likewise, preoperative anxiety (OR 2.832, P = .006), duration of surgery (OR 1.026, P < .0001), and being between the ages of 2 and 3 years (OR 2.604, P = .048) were associated with NPOBC incidence. The multivariable logistic regression model receiver operating characteristic curve showed an area under the curve (95% CI) = 0.820 (0.759-0.881).

Conclusions During noncardiac surgeries in the pediatric population, an intraoperative decrease in $crSO_2$ less pronounced than 20% from the baseline value is associated with negative postoperative behavior changes on postoperative day 7. The long-term implications remain to be determined, but this supports attention to $crSO_2$ during noncardiac surgeries. *(J Pediatr 2019;208:207-13)*.

Negative postoperative behavioral changes in the pediatric population have a relevant, medical, academic, social, and economic impact; their incidence varies significantly among different studies, reaching up to 60%.[1-3] Although diverse risk factors such as age, female sex, or preoperative anxiety have been associated with negative postoperative behavioral changes (NPOBCs), its etiology remains unclear.[4-9]

Although the central nervous system is the primary end point of most general anesthetics, it is the least monitored organ in clinical anesthesiology. As perfusion and oxygenation are essential for proper cerebral function, monitoring of these measures may prove beneficial. In clinical practice, these factors are usually measured by indirect indicators such as blood pressure, heart rate (HR), pulse oximetry, and end-tidal CO_2. However, cerebral near-infrared spectroscopy (NIRS) oximetry, which is used less frequently than these vital signs, may be a better method of monitoring cerebral perfusion and oxygenation, as NIRS displays both the relative cerebral blood flow and the oxygen metabolic rate in a noninvasive, continuous way, without any associated risk.[10,11] The main limitation of this method is the lack of a simple, uniform, universal value to define pathologic cerebral oximetry.

It is widely accepted that a 20% or more intraoperative decrease of the basal cerebral regional oxygen saturation ($crSO_2$) value is detrimental and is related to postoperative cognitive dysfunction in adults.[12] However, the extent to which an intraoperative decrease in $crSO_2$ impairs the brain function in pediatric patients is not known. We might speculate that because of cerebral immaturity, regional cerebral oxygen desaturation of less

ASA	American Society of Anesthesiologists
$crSO_2$	Cerebral regional oxygen saturation
HR	Heart rate
NIRS	Near-infrared spectroscopy
NPOBC	Negative postoperative behavioral change
PHBQ	Post-Hospital Behavior Questionnaire
ROC	Receiver operating characteristic

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pronounced than 20%, may be associated with the deterioration of brain functions and, therefore, lead to the development of NPOBC in children.

Hence, the main objective of this study was to evaluate whether a decrease in $crSO_2$ of lesser magnitude than 20% from the baseline value is associated with an increase in the incidence of NPOBC in pediatric patients undergoing noncardiac surgery.

Methods

This prospective observational study was conducted at the University Clinic Hospital of Valladolid, Spain over a 12-month period between 2014 and 2015. The study was approved by the Institutional Review Board and conducted in accordance with guidelines established for experiments involving humans by the Hospital's Ethic Committee and the Code of Ethics of the World Medical Association, Declaration of Helsinki. This observational study was registered at clinicaltrials.gov (NCT02773186).

All patients between the ages of 2 and 12 years with American Society of Anesthesiologists physical status I and II (American Society of Anesthesiologists [ASA] I and II) and scheduled for elective noncardiac surgery under general anesthesia with mechanical respiratory assistance, were included in the study. Written informed consent was obtained from the parents or legal guardians before the surgery. A total of 198 children were enrolled in the study.

The exclusion criteria were a previous neuropsychiatric disorder; emergency surgery; inability of parents because of their language or comprehension levels, to understand the questions in the Post-Hospital Behavior Questionnaire (PHBQ); and refusal by the parents to participate.

Anesthetic Management

Anesthesia was induced using a controlled technique with O_2/air/sevoflurane (Sevorane, Abbvie, Madrid, Spain). Once the child was asleep, an intravenous cannula was inserted. In all cases, anesthesia was maintained with a mixture of oxygen and air to achieve a 0.35-0.4 inspired oxygen fraction with 2-4% of sevoflurane, according to the clinical response. Mechanical ventilation was adjusted to maintain end-tidal CO_2 between 35 and 40 mm Hg. The body temperature was monitored using a tympanic thermometer and was kept between 36.5 and 37.5°C using a warm air blanket. Intraoperative analgesia with fentanyl was provided when indicated. The Holliday-Segar method was used to determine the volume of maintenance crystalloid fluids, and boluses of 10-20 mL per kg of either normal saline or lactated ringer solution were administered over 15 minutes if needed.[13]

Monitoring consisted of routine measurements of the HR, noninvasive arterial pressure, pulse oximetry, end-tidal CO_2, sevoflurane minimum alveolar concentration, inspired and expired oxygen concentrations, and temperature. To measure $crSO_2$, cerebral NIRS was performed using the INVOS Cerebral Oximeter 5100 (Somanetics, Troy, Michigan) with bihemispherical sensors. This device works through a near-infrared light source with wavelengths that can be absorbed by hemoglobin (730-810 nm) and 2 sensors located on a sticker placed on the patient's forehead, and measures the oxygen saturation of the arterial and venous blood of the cerebral region under the forehead-sticker in a continuous and noninvasive way.[11] The cerebral oximeter sensors were placed bilaterally on the patient's forehead before the induction of anesthesia. To reduce artifacts, the child's forehead was covered with a flexible adhesive bandage. Both physiological variables and $crSO_2$ levels were recorded in the operating room prior to induction of anesthesia (baseline) and every 5 minutes thereafter, as well as at the most important stages of the surgical intervention: induction, intubation, surgical incision, end of surgery, and extubation. The $crSO_2$ values of the right and left frontal monitors were recorded simultaneously. The most pronounced of $crSO_2$ between the sides was used for analysis.

Cerebral desaturation was defined as a decrease in $crSO_2$ of 20% or more from the basal value for at least 1 minute. When cerebral desaturation occurred, the protocol was as follows: the position of the head and ventilator were inspected, inspiratory oxygen fraction was increased, and the mean arterial pressure was restored if it had dropped by more than 20% from the baseline value.

Neurologic Assessment

Preoperative anxiety was evaluated using the modified Yale Preoperative Anxiety Scale,[14-16] which has 22 items divided into 5 sections: the child's activity, emotional expressivity, state of arousal, vocalization, and use of parents. Each section has either 4 or 6 items. As is normally done with the modified Yale Preoperative Anxiety Scale, the score obtained in each section was divided by the number of items contained in it to get partial scores, and, later, the partial scores were added up to reach a total score, which ranged from 0 to 100.[15] When the total score was ≥30, the child was considered to have preoperative anxiety.

The diagnosis of NPOBC was made using the PHBQ which, having good test-retest reliability, has been widely used to assess negative behavioral changes following hospitalization.[7,9,17,18] Parents had to compare the child's behavior before and after hospitalization for each item in the questionnaire. There were 5 possible responses: 1 (much less than before) to 5 (much more than before). The total score was calculated by adding all the responses. Parents completed the PHBQ on postoperative day 7 but not earlier to avoid the influence of pain, first day agitation, nausea, or vomiting on questionnaire response. Data were collected via a follow-up phone call, as previously reported.[19] When 7 or more negative behavioral changes were present on the PHBQ, the child was considered to be NPOBC positive. Children were dichotomized into the classifications of NPOBC or non-NPBOC.

Statistical Analyses

No similar studies were available for power analysis for this study. The sample size was calculated using the number of pediatric surgeries performed the previous year at the University Clinic Hospital and assuming the incidence of NPOBC to be 20%. We accepted an α error of 0.05 and a β error of 0.2 in a bilateral contrast, and it was estimated that 64 patients who developed NPOBC and 118 patients who did not would be required to detect a minimal OR of 2.8.

The Kolmogorov-Smirnov test was used to check the normality of the data distribution. Data were presented as proportions or medians with IQRs. The χ^2 test or the Fisher exact test (when the expected frequency was found to be less than 5) were used to assess differences in the categorical variables between the 2 groups (NPOBC/non-NPOBC). For continuous variables the Mann-Whitney U test was used. The hemodynamic variables (HR and mean arterial pressure) and pulse-oximetry were collected at different stages and studied using ANOVA of repeated measurements, considering behavioral disorders for Gaussian distribution, or using the Friedman test for non-Gaussian distribution. Univariate analyses were performed with potential predictor variable for negative postoperative behavioral changes.

The aggregate influence of predictor variables was assessed using stepwise multivariable logistic regression analysis, with $crSO_2$ as a continuous variable. The results were expressed as ORs with 95% CI. Multicollinearity was assessed using the variance inflation factor. Model calibration was done using the Hosmer-Lemeshow test, and the diagnostic performance was confirmed by the receiver operating characteristic (ROC) curve and the area under the ROC curve. The Spearman rho was used to assess the relationship between the $crSO_2$ decrease and PHBQ total score. The Mann Whitney U test and Kruskal Wallis test were also used to look for a relationship between minimally invasive techniques and age ranges with NIRS values, respectively. The level of significance was set at $P < .05$. Statistical analyses were performed using the SPSS v 24.0 software (SPSS Inc, Chicago, Illinois).

Results

The enrollment data and patient demographics of the 198 patients included in this study are summarized in Table I. On postoperative day 7, NPOBC was reported in 38.8% (77/198) of patients, who were found to be younger ($P < .001$) and with a higher incidence of preoperative anxiety ($P < .001$) than patients who did not develop NPOBC. No

Table I. Sociodemographic and clinical characteristics of children on postoperative day 7

	Total (n = 198)	NPOBC (n = 77)	Non-NPOBC (n = 121)	*P* value
Age				**.010**
Toddler (2-3 y)	48 (24.2)	26 (33.8)	22 (18.2)	
Preschool age (4-6 y)	88 (44.4)	35 (45.5)	53 (43.8)	
School age (7-12 y)	62 (31.4)	16 (20.7)	46 (38.0)	
Sex				.602
Male	153 (77.3)	58 (75.3)	95 (78.5)	
Female	45 (22.7)	19 (24.7)	26 (21.5)	
Weight (kg)	15.0 [13.0-18.5]	15.0 [13.0-18.5]	18.0 [15.0-24.5]	**<.001**
Preoperative anxiety	119 (60.1)	57 (74.0)	62 (51.2)	**<.001**
Surgery type				.192
General	65 (32.8)	22 (28.6)	43 (35.5)	
Inguinal hernia repair	40	14	26	
Umbilical hernia repair	25	8	17	
Urologic	62 (31.3)	31 (40.2)	31 (25.6)	
Phimosis surgery	25	14	11	
Hypospadia repair	8	3	5	
Hydrocele surgery	17	9	8	
Cryptorchidism surgery	12	5	7	
ENT	49 (24.7)	17 (22.1)	32 (26.4)	
Adenoidetomy	12	3	9	
Amygdalectomy +	18	10	8	
Transtympanic ventilator tubes	19	4	15	
General + urologic	22 (11.1)	7 (9.1)	15 (12.3)	
Inguinal/umbilical repair	10	3	7	
Hydrocele/cryptorchidism surgery	12	4	8	
Laparoscopic surgery	8 (4.0)	5 (6.4)	3 (2.4)	.266
Locoregional blockade	113 (57.1)	45 (58.4)	68 (56.1)	.756
Duration of surgery (minutes)	55.0 [40.0-70.0]	60.0 [47.5-90.0]	50.0 [40.0-65.0]	**<.0001**
Previous hospitalization	33 (16.7)	16 (20.7)	17 (14.0)	.173
Basal $crSO_2$ (%)	80.5 [80.0-84.0]	81.0 [80.0-85.5]	80.0 [79.0-83.5]	.238
Intraoperative crSO2*, n (%)				
decrease ≥20%	4 (2.0)	4 (5.1)	0 (0)	**.021**
decrease ≥15%	17 (8.5)	14 (18.1)	3 (2.4)	**<.001**
decrease ≥10%	43 (21.7)	27 (35.0)	16 (13.2)	**<.001**
decrease ≥5%	103 (52.0)	55 (71.4)	48 (39.7)	**<.001**

ENT, ear-nose-throat.
Quantitative data are expressed as medians with IQRs (IQR = [Q1-Q3]) and qualitative data as absolute numbers and percentages.
Bold values were considered statistically significant ($P \leq .05$).
*A single patient could be included in several groups, depending on the amount of $crSO_2$ decrease (ie, a patient with a decrease of 12% is included in both the group of a decrease ≥5% and the group of a decrease ≥10%).

Table II. Multivariate analysis of risk factors associated with the development of NPOBC on postoperative day 7

NPOBC (yes)*	β	SE	OR (95% CI)	*P* value
Duration of surgery (min)	.026	.007	1.026 (1.012-1.041)	**<.0001**
Preoperative anxiety	1.041	.379	2.832 (1.349-5.946)	**.006**
$crSO_2$ decrease (per 1%)†	1.181	.035	1.199 (1.120-1.283)	**<.0001**
Toddler age (2-3 y)*	.957	.485	2.604 (1.007-6.733)	**.048**
Preschool-age (4-6 y)*	.485	.423	1.624 (0.709-3.719)	.089

β, standardized regression coefficient.
Hosmer-Lemeshow χ^2_8 = 14.496; *P* = .07.
The variables included in the regression model were age stage, duration of surgery, preoperative anxiety, and cerebral regional oxygen saturation decrease.
Bold values were considered statistically significant ($P \leq .05$).
*Age reference: 7-12 years old.
†$crSO_2$ has been considered as a continuous variable.

statically significant differences in the surgical approach (*P* = .266) and basal cerebral oxygen saturation values (*P* = .238) were seen between patients with and without NPOBC. There was a significant difference ($P < .0001$) in the median of $crSO_2$ decrease between the NPOBC (11.25% [3.14-13.67]) and non-NPOBC group (3.41% [1.19-6.94]). The incidence of NPOBC was also significantly higher in patients with cerebral oxygen desaturation defined as a ≥5% ($P < .001$), ≥10% ($P < .001$), ≥15% ($P < .001$), and ≥20% (*P* = .021) decrease in $crSO_2$ from baseline value during general anesthesia. Regional cerebral oxygen desaturation ≥20% from baseline value was present in 4 (5.1%) patients of the NPOBC group and none of the non-NPOBC group despite acceptable systemic saturation ($SatO_2$ ≥98%) in both groups during the entire period of surgery. Patients were admitted to hospital the day of surgery or the day before, and all of them were discharged on the first postoperative day. Blood transfusions were not required.

Comparison of the hemodynamic variables and pulse oximetry between the NPOBC and non-NPOBC patients revealed a decrease in systolic and diastolic arterial pressure values from basal to intubation time in both groups, and no significant differences in blood pressure, HR, or SpO_2 values between the groups during the different stages of the surgery. No association between surgical approach, age range, and a decrease in $crSO_2$ was found either.

Multivariable logistic regression analysis (Table II) showed that every 1% decrease in $crSO_2$ (OR 1.199, $P < .0001$), every additional minute in duration of surgery (OR 1.026, $P < .0001$), presence of preoperative anxiety (OR 2.832, *P* = .006), and age under 3 years old (OR 2.604, *P* = .048) were independent risk factors for developing NPOBC. The ROC curve of the logistic regression model, measured using $crSO_2$ as a continuous variable, showed an area under the curve (95% CI) = 0.820 (0.759-0.881) (Figure 1). Figure 2 (available at www.jpeds.com) shows the relationship between $crSO_2$ decrease and PHBQ total score.

Discussion

The main finding of the present study was that a decrease in $crSO_2$ of lesser magnitude than 20% from baseline value in children undergoing noncardiac surgery under general anesthesia, is associated with NPOBC on postoperative day 7.

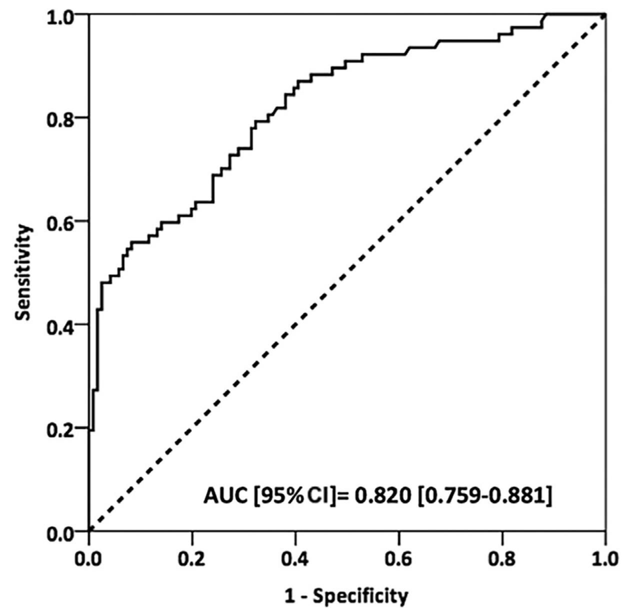

Figure 1. ROC curve of the logistic regression model, used to predict the risk factors for the development of NPOBC. $crSO_2$ was included as continuous variable. *AUC*, area under the curve.

There is no uniform, universal absolute value for defining pathologic cerebral regional desaturation,[11,20,21] perhaps partially attributable to the wide interindividual variability in the baseline $crSO_2$ values, the comorbidities, and the different populations and scenarios included in other studies.

Most studies have been conducted on very specific categories of patients, such as adults, pediatric patients undergoing cardiac surgery, and newborns in intensive care units.[22-28] Our study was conducted on a more general pediatric population than those above, children who were ASA I and II undergoing more general operations, such as urologic, gastrointestinal, and otorhinolaryngological surgeries.

Fenton et al conducted a study with the objective of establishing the basal value of cerebral oxygen saturation of 143 pediatric patients undergoing cardiac surgery, and observed a mean basal value of $crSO_2$ of 64%.[21] The mean baseline $crSO_2$ value in our study was greater than that present in Fenton et al (81.34 ± 4.95), perhaps because the pediatric population chosen for our study was different, having no described cardiac anomalies and a lesser probability of arteriovenous shunts.

In adults, cerebral NIRS measures the cerebral oxygen saturation of the region under the forehead-stickers.[11] In children, however, this regional cerebral oxygen saturation may reflect the balance between the consumption and the supply of oxygen of not only a local area under the forehead, but of most of the brain due to a more immature self-regulating cerebral system.[29] This may explain why, in our study, a decrease from baseline $crSO_2$ values was associated with an increased odds of developing NPOBC on postoperative day 7 (OR 1.199) even if the decrement did not reach the threshold of ≥20% commonly used in adults. Cerebral oxygen desaturation of ≥20% from baseline occurred in only 4 patients of the NPOBC group. Our findings suggest that use of intraoperative $crSO_2$ monitoring may be useful in a broader audience than those undergoing cardiac surgery, as is common practice now. This is particularly the case because in our study there were no differences in blood pressure, HR, and pulse oximetry between patients with and without NPOBC.

Cerebral perfusion index, systemic oxygenation, and cerebral metabolism, which may be affected by anesthesia, influence the $crSO_2$ value.[10,11,30,31] In addition, cerebral neuronal oxygen extraction affects $crSO_2$ values with impaired extraction manifested by normal or increased $crSO_2$ values. The fractional oxygen extraction represents the relationship between the systemic oxygenation and $crSO_2$. Although it may be more informative than $crSO_2$ alone, it has not been used in many studies.[32,33] We did not use this measure either, as our patients maintained an adequate and stable systemic saturation ($SatO_2$ ≥98%) at all times. Our patients were unlikely to have impaired oxygen extraction as they were in generally good baseline physical condition (ASA I-II), they had a constant body temperature, they did not undergo prolonged surgery, and the surgical procedures were neither critical nor emergent. We preferred to use $crSO_2$ as it is more directly and quickly obtained than fractional oxygen extraction using readily available cerebral oximetry devices. We did not examine an increase in $crSO_2$ from the basal value, which is also related to cognitive deterioration,[32] as our study focused on the implications of decreased $crSO_2$.

The incidence and time of presentation of behavioral changes after surgery have been shown to be highly variable in previous studies[1,34] perhaps because of the small sample sizes selected, variations in the time that the behavior was assessed, and differences in the tools used to diagnose NPOBC. Kain et al, in a study involving 91 children undergoing major abdominal surgery, reported incidences of NPOBC of 67%, 45%, and 23% of patients on day 1, day 2, and 2 weeks after surgery, respectively.[34] In our study, 38.8% of children developed NPOBC on postoperative day 7, which is concordant with results found by these authors. The latest 27-item validated version of the PHBQ, used in most research on this subject, was the method used to diagnose NPOBC.[1,2,6]

The duration of cerebral oxygen desaturation may influence the incidence of NPOBC, but very few studies have taken this into account. Orihashi et al observed that length of desaturation was positively associated with adverse postoperative neurological events in adults undergoing aortic surgery with selective cerebral perfusion.[35] In addition, Suehiro et al observed that the duration of brain desaturation in adults was inversely related to the Mini-Mental Examination score on postoperative day 4.[36] In our study, we took into account the duration of any drop in $crSO_2$ >20% from the basal value, which was corrected in less than 2 minutes, as done by other authors.[37] Further studies should be carried out to assess the impact of the duration of desaturation of <20% on the development of NPOBC in children.

In this study, apart from intraoperative $crSO_2$ decreases, preoperative anxiety, surgery duration, and age less than 3 years, were also related to the development of NPOBC. The association between preoperative anxiety and later behavioral problems has previously been reported in children.[4,5,7] There are also some studies conducted on animals and children, which associate the duration of exposure to general anesthetics with posterior neurologic disturbances.[38-40] Similar to Razlevice et al, we have not observed any association between age and $crSO_2$ decrease from baseline value.[30] However child's age is one of the most closely related factors associated with the development of NPOBC. This was also shown for the first time by Levy,[41] and was confirmed in other studies.[1,42-44] All of above could be explained as the more immature the brain is, the more susceptible it might be to aggressions (oxygen decrease, anesthetics, etc). Similar to Tuna et al, we have not found any association between the surgical approach and the decrease in $crSO_2$, despite variations in the partial pressure of arterial carbon dioxide and in the intra-abdominal pressure that can occur during laparoscopic surgery.[45] More studies should be performed on this topic because we had very few patients who received a laparoscopic approach. We have not found any relationship between the type of procedure or having been previously hospitalized with the development of NPOBC, as other authors have.[1,7,19]

Our findings should be interpreted in light of the limitations that we cannot assert causality in this observational cross-sectional study; that our study includes a single-center regional database, and it is likely that the selection of patients and the management of the perioperative period may be important determinants of developing NPOBC; and that we used only 1 tool for behavioral evaluation. In addition, we only assessed NPOBC once so we cannot report on the time course of the development of, nor the resolution of behavioral changes, nor can we speak to any long-term implications and the patients included underwent a variety of surgeries, although they did receive similar anesthesia, and comparable degrees of surgical complexity. We did not evaluate other factors that may influence the development of NPOBC, such as intraoperative and postoperative pain. In addition, we are underpowered for more robust analysis of surgical approaches, such as differentiating laparoscopic vs open approaches.

In conclusion, during noncardiac surgeries in the pediatric population, an intraoperative decrease in $crSO_2$ less pronounced than 20% from the baseline value is associated with negative postoperative behavior changes on postoperative day 7. The long-term implications remain to be determined, but this supports attention to $crSO_2$ during noncardiac surgeries. ■

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50 Years Ago in *The Journal of Pediatrics*

Comments on Current Literature: Bell's Palsy in Children

Blattner RJ. J Pediatr 1969;74:835-7

Idiopathic peripheral facial nerve palsy has been referred to as Bell's palsy since Sir Charles Bell described a unilateral facial paralysis from an intrinsic seventh cranial nerve lesion. As was the case 50 years ago, Bell's palsy is often preceded by an upper respiratory infection, although the differential diagnosis is broad. Typically, facial paralysis and weakness are preceded by a prickly sensation and numbness of the face. In children under the age of 2 years, Bell's palsy is rare and central nervous system causes should be considered. In 1969, similar to today, there was no specific evidence regarding whether steroids should be used to treat Bell's palsy in children. Both the American Academy of Neurology and the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) have published clinical practice guidelines which reach similar conclusions regarding the treatment of Bell's palsy.[1,2] Both organizations recommend oral steroids; the AAO-HNSF specifies that they be started within 72 hours of symptom onset and for patients 16 years and older. The use of antiviral medication to treat presumed herpes simplex virus as the cause of the symptoms is mentioned as an option, but should not be prescribed as monotherapy. The referenced article discusses in detail the use of nerve excitability potential as a tool to predict prognosis for recovery of function in Bell's palsy; however, this testing is not typically performed today. In fact, the AAO-HNSF guidelines recommend against performing electrodiagnostic testing if the facial paralysis is incomplete. One constant recommendation over time is for careful attention to eye care to avoid corneal injury when eye closure is not complete.

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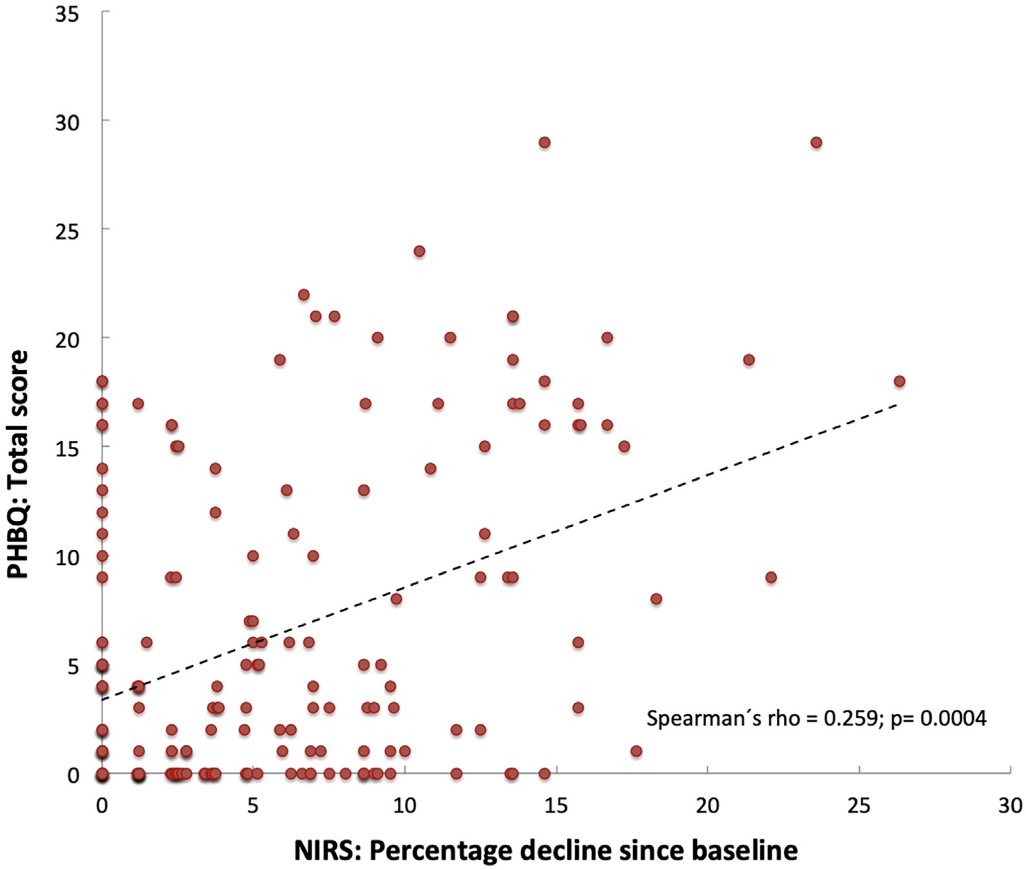

Figure 2. The relationship between $crSO_2$ decrease and PHBQ total score.