

# Scientific Article



## Formocresol Blood Levels in Children Receiving Dental Treatment under General Anesthesia

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**Abstract: Purpose:** The purpose of this study was to determine the presence of formocresol in the plasma of children undergoing oral rehabilitation involving pulp therapy under general anesthesia. **Methods:** Thirty 2- to 6-year-old preschool children were enrolled in the study. Preoperative, intraoperative, and postoperative peripheral venous samples were collected from each child. All samples were analyzed for formaldehyde and cresol levels using gas chromatography with mass spectrometry detection. **Results:** Eighty-five pulpotomies were performed ranging from 1 to 5 per child. Three hundred twelve blood samples were collected. Analysis revealed that formaldehyde was undetectable above baseline plasma concentration and cresol was undetectable in all samples. Benzyl alcohol (a byproduct of cresol metabolism) was present in all samples except the baseline preoperative samples. Benzyl alcohol concentrations ranged from 0 to 1 mg/ml. **Conclusions:** Formaldehyde was undetectable above baseline plasma concentration, and cresol was undetectable in subjects receiving pulpotomy treatment under general anesthesia. Benzyl alcohol was detected in the plasma of all subjects receiving pulpotomy treatment. The levels present were far below the Food and Drug Administration's recommended daily allowance. It is unlikely that formocresol, when used in the doses typically employed for a vital pulpotomy procedure, poses any risk to children.

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Formocresol has been utilized by dentists for over 100 years as a medicament in the treatment of primary teeth requiring therapeutic pulpotomies.<sup>1-3</sup> Even today, most dentists use formocresol manufactured at the same composition recommended in 1904 (Buckley type formula, 19% formaldehyde, and 35% cresol in a vehicle of 15% glycerin and water).<sup>1</sup>

Some concern has been expressed in the last 25 years regarding the use of formocresol for vital pulpotomy treatment of primary molars due primarily to its mutagenic, carcinogenic, and toxic potential when used in high concentrations and under specific conditions.<sup>4-8</sup> The controversy stems from animal studies, which demonstrated that formaldehyde and tricesol diffuse through the apical foramen within minutes of a formocresol pulpotomy.<sup>9-12</sup> The systemic exposure to

formocresol after a 5-minute pulpotomy ranges from 1% to 30% of the formocresol dose used in animal models.<sup>11,13-15</sup> Studies using radio-labeled paraformaldehyde in rhesus monkeys and dogs demonstrated distribution to regional lymph nodes, blood, kidney, and liver following formaldehyde application to radicular pulp stumps.<sup>11,13,14</sup>

Nevertheless, further studies demonstrated that high systemic doses (0.0285 mg/kg of formaldehyde, which is approximately 500 times the expected dose from 1 pulpotomy in a 10-kg test subject) administered intravenously (IV) to dogs can lead to liver, kidney, and cardiac pathology.<sup>16,17</sup> Despite the controversy, formocresol use continues to be the standard of care for vital pulpotomies in children primarily because of its high clinical success rate (defined as absence of pain, fistulas, mobility, and radiographic evidence of pathology) and failure to show any systemic effects when used in much lower concentrations.<sup>18</sup>

Formocresol proponents cite the fact that there are no documented cases of systemic distribution or pathologic tissue changes associated with the use of formocresol in humans.<sup>19</sup> These proponents also argue that the doses used in animal models far exceed those used in clinical practice and that normal clinical doses carry little risk for patients.<sup>4,5,19</sup> It would be unethical to treat children with radio-labeled paraformaldehyde. Therefore, determining the distribution of formaldehyde following exposure to formocresol in human

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test subjects would be difficult. If formocresol concentrations in the plasma of subjects undergoing pulpotomy treatment could be determined, however, comparison to *in vivo* models would be more clinically relevant.

It is important to note that, for this study's purposes, there are many potential sources of formaldehyde, both man-made and natural. Man-made sources include, but are not limited to, cigarettes and tobacco products, automobile exhaust emissions, building materials and furniture containing formaldehyde-based resins, adhesives containing formaldehyde, formaldehyde used for plastic surfaces and parquet, carpets, paints, disinfectants, gas cookers, open fireplaces, soaps, deodorants, shampoos, and preservatives used in dried foods and processed fish.<sup>20-22</sup> There is also some formaldehyde naturally present in raw foods (fruits, vegetables, fish, milk products, pork, poultry, and sheep) and drinking water.<sup>20-22</sup> The World Health Organization has estimated the daily intake of formaldehyde from food to be 1.5 to 14 mg/day.<sup>23</sup> Other recent data and discussion have estimated the daily intake of formaldehyde to be 9.4 mg/day from food, 1 mg/day from inhalation, and 0.15 mg/day from water—resulting in a daily adult intake of 10.55 mg/day.<sup>24,25</sup> Formaldehyde also exists in all mammals as a normal part of cellular metabolism. Biological pathways in which formaldehyde is formed include oxidative demethylation, amino acid metabolism, and purine and pyrimidine metabolism.<sup>26</sup> Endogenous levels of metabolically produced formaldehyde range from approximately 3 to 12 ng/g of tissue.<sup>27</sup>

Given all these sources of formaldehyde, one would assume that the prevalence of mutation and toxicity in the general population would be high. This would be true if not for 2 reasons:

1. Formaldehyde exists in a bound (unavailable) form in most of these sources.
2. The human body is well equipped to handle formaldehyde exposure via multiple pathways for conversion of formaldehyde and its oxidation product formate.

Formaldehyde that enters the body is rapidly metabolized (half life=1-1.5 minutes).<sup>28,29</sup> Degradation has been demonstrated via the enzymes cytosolic alcohol dehydrogenase, mitochondrial aldehyde dehydrogenase, and glutathione-dependent and glutathione-independent dehydrogenase in hepatocytes,<sup>30</sup> oral mucosa,<sup>31</sup> and nasal respiratory mucosa.<sup>32</sup> Formaldehyde metabolites are incorporated into macromolecules via one-carbon pathways. They are then used in the biosynthesis of purines, thymidine, and other amino acids that are incorporated into RNA, DNA, and proteins during macromolecular synthesis, or are eliminated in the expired air (CO<sub>2</sub>) and urine.<sup>33,34</sup>

Of primary concern is the belief that formaldehyde that escapes metabolism can react with macromolecules, particularly form DNA-protein cross links, and thereby cause mutations. There is *in vivo* evidence that, at high concentrations,

formaldehyde can cause DNA-protein cross links at the initial site of contact in rodent models.<sup>35-38</sup> More recent evidence demonstrates that these DNA-protein cross links do not persist for more than a few hours before undergoing spontaneous hydrolysis or active repair by proteolytic degradation of cross linked proteins.

Evidence that formaldehyde could potentially induce DNA-protein cross links at low concentrations is lacking. To date, there is no direct human evidence that formaldehyde can induce mutations. Worldwide concern over formaldehyde's classification as carcinogenic in humans<sup>39</sup> is largely based on extrapolation from laboratory animal studies using very high doses of formocresol.<sup>25</sup> Given the milligram quantity of formaldehyde that humans are exposed to on a daily basis, it is unlikely that the microgram quantities of formaldehyde utilized in the vital pulpotomy procedure could overwhelm the aforementioned biological pathways and escape into circulation. If this did occur, however, it could potentially be detected as a rise in the plasma concentration of formaldehyde. No data exist as to the mean plasma concentration of formaldehyde in the pediatric population. The mean formaldehyde concentration (baseline plasma concentration) in the blood of 6 adult volunteers, however, was determined to be 2.61±0.14 µg/100 ml.<sup>40</sup>

Cresol, the second active ingredient in formocresol, has received little attention in biological circles, probably because it has no other dental or medical applications.<sup>5</sup> The assumption in the literature has been that, due to its poor solubility, cresol most likely does not enter systemic circulation. Cresol is lipophilic and has been shown to completely destroy cellular integrity.<sup>5</sup> It has also been shown to produce irreversible damage to connective tissues and delayed recovery of normal biological activities of the affected connective tissue cells in rats.<sup>41</sup> No data currently exist regarding cresol's metabolism, environmental sources, or mean plasma concentration in the pediatric or adult population.

This study's purpose was to determine the existence, if any, of formocresol in the plasma of children undergoing comprehensive oral rehabilitation involving vital pulp therapy under general anesthesia.

## Methods

Following approval by the Colorado Multiple Institutional Review Board, 30 2- to 6-year-old preschoolers were enrolled. These children were undergoing comprehensive dental rehabilitation under general anesthesia at The Children's Hospital, Denver, Colo, with an expected need for pulpotomy treatment in primary teeth. Written informed consent was obtained from the parents or legal guardians. We limited enrollment to healthy children rated physical status 1 or 2, per the American Society of Anesthesiologists. All subjects fasted 8 hours for solids and 2 hours for clear liquids, per standard practice.

Formocresol pellets were prepared by weighing 50 sterile cotton pellets before placement in 2 mL of Buckley's

formocresol (Buckley type formula, 19% formaldehyde and 35% cresol in a vehicle of 15% glycerin and water, Sultan Chemists Inc, Englewood, NJ). Full-strength formocresol, as provided by the manufacturer, was used instead of a 1:5 dilution. These pellets were blotted using gauze to remove excess solution. The pellets were then weighed again to determine the average milligram dose of formocresol per pellet. Pellets were stored at room temperature in glass bottles prior to use in the study.

After induction of general anesthesia, 2 peripheral intravenous lines were inserted: one for fluid and drug administration, the other for blood sampling. Pulpotomies were performed on primary teeth isolated with a rubber dam. After pulpal access and coronal pulp extirpation, hemostasis was achieved by placing a sterile dry cotton pellet in the pulp chamber for 1 to 5 minutes. The radicular pulp stumps were then treated with 2 previously prepared sterile pellets that had been placed in formocresol solution, as aforementioned. The pellets were removed after 5 minutes, the pulp chambers were sealed, and the teeth were restored.

Up to 12 blood samples per subject were drawn for the study, with a maximum of 24 mL of blood drawn. Quantity of blood drawn was 2 mL per sample and no more than 3 mL/kg (5% of total blood volume) total. A baseline blood sample (sample no. 1) was obtained before dental treatment began. Once treatment had been further initiated, sampling was performed immediately after the first formocresol pulpotomy had been completed and then at 30-minute intervals (no more than 4 interval samples were taken; sample nos. 2-5) until the last pulpotomy was complete. At that time, pulpotomy samples were taken at 5, 15, 30, 60, 90, and 120 minutes (sample nos. 6-11 in the operating room and recovery area). A final sample was taken immediately prior to patient discharge from the recovery unit (sample no. 12). Collected samples were then sent to the University of Colorado Health Sciences Center, Denver, for analysis. Variables collected for statistical analysis include age and number of pulpotomies performed. Subjects were categorized as receiving a high dose of formocresol ( $\geq 4$  pulpotomies) or low dose ( $\leq 3$  pulpotomies).

**Laboratory analysis: Materials.** All cresol and formaldehyde standards were purchased from Acros Organics (Morris Plains, NJ). 2,6-dimethylphenol (IS – internal standard), benzyl alcohol, and dichloromethane were obtained from Sigma-Aldrich (St. Louis, Mo). Acetonitrile used in the extraction process was purchased from Fischer Scientific (Fair Lawn, NJ). Blank human plasma was acquired from healthy volunteers. All stock solutions were made in chromatographic quality water and methanol at a ratio of 70:30 (v/v), respectively. Calibration curves for each assay were made in blank human plasma (plasma not previously exposed to formocresol) using the stock solutions of formaldehyde, mixed cresols, and benzyl alcohol. If not mentioned otherwise, chemicals were purchased from Fisher Scientific.

**Formaldehyde measurement sample preparation and analysis.** The procedure used to determine the formaldehyde concentration in the blood samples was essentially identical to that previously published by Dong et al.<sup>42</sup> Briefly, 2,4-dinitrophenylhydrazine (DNPH) derivitizing agent was prepared by dissolving 310 mg of DNPH in 100 mL of 2M HCl. Plasma (0.1 mL) was then mixed in a 10 mL screw cap glass polytetrafluoroethylene lined tube, with 0.33 mL of deionized water containing the internal standard and 6.7 mL of DNPH derivitizing agent. The solution was mixed for 15 minutes, after which 6.7 mL of pentane was added. The solution was again mixed intermittently for 15 minutes, and the organic phase was removed. The remaining aqueous phase was re-extracted with another 6.7 mL of pentane. The second organic phase was combined with the first and dried in a speed-vac. The resultant pellets were reconstituted with dichloromethane analyzed for formaldehyde and compared to the standard.

For the chromatographic analysis, a gas chromatography-mass spectrometry (GC-MS) system, (Agilent Technologies, Palo Alto, Calif) equipped with a Supelco Equity-5 (30 m $\times$ 0.32 mm id, 0.25  $\mu$ m) column was used. The injector temperature was 230°C, and a Marlin microseal septa (Agilent Technologies) was used to avoid leaks caused by the relatively high column head pressure. The injection was done in the splitless mode with a splitless injection glass liner that was deactivated and contained no glass wool. The separation was done under a constant flow of 3.8 mL/min. The GC oven was programmed with an initial temperature of 100°C for 0.1 minute, followed by a ramp of 18°C/minute, up to 330°C. A solvent delay of 4.5 minutes preceded the MS spectra acquisition, which covered a mass range of 50 to 450 amu (atomic mass unit). The total run time was 12.88 minutes.

**Sample preparation and analysis for cresol and benzyl alcohol measurement.** Plasma (0.1 mL) was mixed with 0.2 mL of internal standard (1  $\mu$ g/mL 2,6-dimethylphenol in acetonitrile) in an Eppendorf tube and vortexed for 5 minutes. The tubes were then centrifuged for 10 minutes at 13,000 rpm at 4°C. The 0.25 mL of supernatant was removed from the Eppendorf tube and placed in a glass test tube. Solvent extraction was then performed. Dichloromethane (0.2 mL) was added to each glass tube and then vortexed for 5 minutes. The organic layer was carefully removed and placed into an HPLC (High Performance Liquid Chromatography) vial. Analysis was then performed and compared to each standard.

For cresol analysis, a new method was developed<sup>43</sup> using a network GC system (model no. 6890N, Agilent Technologies) with an inert mass selective detector (model no. 5973, Agilent Technologies). The GC was fitted with a split/splitless injector and operated in the pulsed splitless mode. The initial column head pressure was 11 psi. The inlet temperature was held at 200°C, and the pulse time was 1 minute at a pressure of 25 psi.

The column flow rate was 1.2 mL/minute in constant flow mode. Following injection, the oven temperature program was as follows: 70°C for 2 minutes, then ramp at 40°C/minute to a final temperature of 325°C for 1 minute. The total run time was 9.4 minutes.

The GC column (model no. 10901S-433, Agilent Technologies) was directly coupled, via transfer line heated to 325°C, to the ion source of the mass spectrometer. Effluent cresols and benzyl alcohol were fragmented and ionized by electron impact ionization. The detector was operated in the selected ion monitoring mode using m/z (mass to charge ratio) 108 for cresol, m/z 122 for 2,4-dimethylphenol (IS), and m/z 108 for benzyl alcohol. This was interfaced to and controlled by a data system using Agilent Chemstation software D.00.01 (ACCTA, Inc, St. Paul, Minn).

**Results**

The final study sample consisted of 30 children. The ages of the children at treatment ranged from 2 to 6.4 years, with a mean age of 3.7 years (±1.2 years SD, median=3.7 years). We performed 85 pulpotomies. The number of pulpotomies performed per patient ranged from 1 to 5, with a mean of 4 (±1.3 SD), and a median of 2.8). Nine subjects fell into the high-dose pulpotomy group, and 21 subjects fell into the low-dose group.

**Laboratory analysis.** We collected 312 blood samples for the study. The assays were validated using spiked human plasma samples, including interday performance and stability. The size of the initial blood samples allowed for preparation of multiple aliquots of the same sample to be used as a measure for internal control. The lower limit of quantitation (LOQ) for formaldehyde was 14 ng/mL. The lower limits of detection (LOD) were determined to be 2 ng/mL formaldehyde, 50 ng/mL cresols, and 100 ng/mL for benzyl alcohol. During formaldehyde analysis, peaks were seen in the 2 to 2.5 ng/mL range (presumably physiologic concentrations). Thus, formaldehyde was “detectable.” Because this was below the LOQ, however, we were unable to quantify the concentration. Formaldehyde was undetectable above 2 to 2.5 ng/mL (physiologic concentration). Cresol was undetectable in all samples.

Coincidentally, benzyl alcohol was present in all samples except the preoperative samples (baseline samples). The concentration of benzyl alcohol ranged from 0-1 mg/mL (Table 1). Graphical analysis of this data revealed a dose-response like curve with peaks appearing to be concurrent with placement of formocresol pellets at multiple times (Figure 1).

The mean dose of formocresol was determined to be 0.013 mg per pellet. Laboratory analysis of formocresol used in the study before and after placement on cotton pellets revealed no detectable benzyl alcohol.

**Discussion**

The foundation of the argument against the use of formocresol in dentistry is the belief that, upon placement in the pulp chamber, unmetabolized formocresol (primarily formaldehyde) becomes systemically distributed. Free formaldehyde present in the circulation could react with macromolecules, thereby potentially causing mutagenic and/or cytotoxic changes in muscle, liver, kidney, heart, spleen, and lung tissue.<sup>13,14,17</sup>

Studies have demonstrated that radio-labeled carbon incorporated into paraformaldehyde enters the systemic circulation in animal models.<sup>9-12</sup> Thus, formaldehyde is able to exit the tooth. Other studies demonstrated systemic distribution of this radio-labeled carbon within 5 minutes of placement in the pulp chamber.<sup>15</sup> These studies, however, failed to account for metabolism of the formaldehyde and incorporation of the radio-labeled carbon into urine, carbon dioxide, and macromolecules via normal biochemical pathways. Based on the aforementioned results, the misconception was created that potentially harmful levels of unmetabolized formaldehyde are present in the bloodstream of subjects receiving vital pulpotomy treatment.

As stated earlier, proponents of the use of formocresol in dentistry have argued that there are no documented cases of systemic distribution of formocresol in humans.<sup>19</sup> This is primarily due to the fact that formaldehyde is present in all mammals and is readily metabolized via normal metabolic pathways.<sup>25,26,30-32</sup> Proponents also argue that, given the milligram quantities of formaldehyde that humans are exposed to and metabolize on a daily basis, a microgram exposure from pulpotomy treatment would unlikely have a significant

impact on plasma concentration. The absence of detectable formaldehyde above baseline physiologic concentration in all blood samples collected in this study supports this argument. It also further corroborates the belief that formaldehyde is rapidly metabolized upon exiting the pulpotomy. As such, formaldehyde presents little or no risk to the subjects.

Cresol was also undetectable in all of this study’s blood samples. This would seem to support the prevailing assumption that, due to its poor solubility, cresol most likely never

Table 1. MAXIMUM BENZYL ALCOHOL CONCENTRATIONS

No. of pellets	No. of patients	Maximum benzyl alcohol level µg/mL (mean±SD)	Range of maximum values µg/mL
2	6	535±313	223-1040
4	6	429±340	88-996
6	7	376±168	142-617
8	6	227±146	4-459
10	3	273±51	217-316

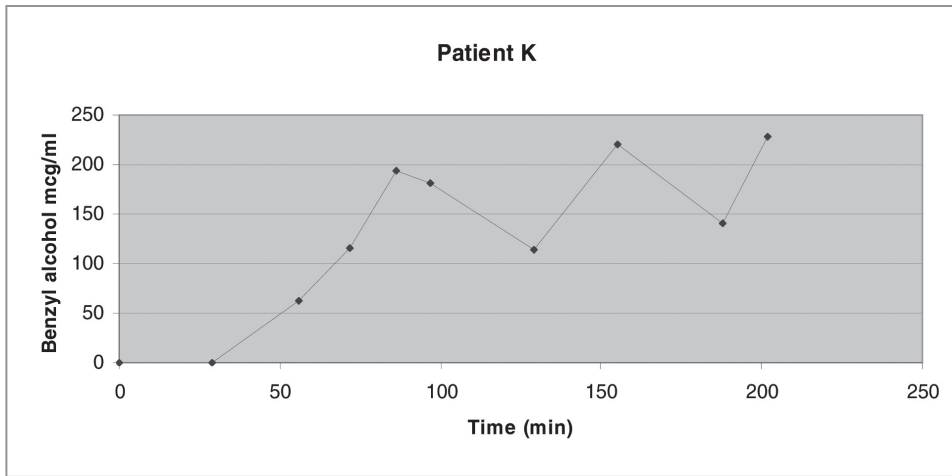


Figure 1. Graphical analysis of benzyl alcohol levels in a single patient.

enters systemic circulation.<sup>5</sup> The coincidental detection of benzyl alcohol in samples taken after vital pulpotomy treatment contradicts this assumption.

Benzyl alcohol is a byproduct of tricresol (o-cresol, m-cresol, p-cresol) oxidation, which is facilitated by enzymes in the cytochrome P450 superfamily.<sup>44-46</sup> Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. Benzyl alcohol is present as a bacteriostatic preservative in many multidose intravenous drugs and solutions.<sup>44</sup> Benzyl alcohol occurs naturally in many plants, including raspberries and tea. It is an ingredient in many essential oils, including jasmine and clove. Benzyl alcohol has no mutagenic or carcinogenic potential.<sup>44</sup> The World Health Organization has established an allowable daily intake of 5 mg/kg.<sup>44</sup> The LD50 is 1,000 mg/kg.<sup>44,47</sup>

Benzyl alcohol quantities detected in this study are far below the allowable daily intake and, therefore, pose no known risk to the subjects. Analysis of the formocresol solution before and after placement on the cotton pellet revealed no detectable benzyl alcohol. The presence of benzyl alcohol concurrent with formocresol pellet placement suggests that cresol in the solution becomes oxidized to benzyl alcohol either in the pulp chamber or immediately after entering systemic circulation. Although this finding seemingly demonstrates the potential for cresol to enter systemic circulation, no cresol was detected in any samples, and benzyl alcohol was present only in very small quantities. The cresol doses used in the vital pulpotomy procedure, therefore, present little or no risk to the patients.

Had this been an animal study, acquiring more blood samples and placement of a central vs peripheral venous catheter may have provided more data and a clearer picture of benzyl alcohol metabolism. The use of animal models, however, would have made it less relevant to daily practice. Further study would be required to determine the exact mechanism by which cresol is metabolized to benzyl alcohol after

placement in the pulp chamber and why the concentration of benzyl alcohol appears to continue rising over time (Figure 1). The LOQ for formaldehyde (14 ng/mL) prevented us from determining a baseline concentration for plasma formaldehyde in the pediatric population. The baseline would have presumably been close to the 2.61 ng/mL detected in adult studies.<sup>40</sup> In our method, peaks were indeed seen in the 2 ng/mL range and, therefore, formaldehyde was “detected” within our LOD. This is below the LOQ, however, and statistically insignificant by current analytical limit

standards. The fact that baseline plasma concentrations could not be quantified by our method might be considered a weakness in the methodology.

It is important to note that 20 years ago, LOQ and LOD were considered to be the same in GC-MS. It is possible that, in 1985 when Heck et al quantified the baseline or “normal physiologic” concentration of formaldehyde<sup>40</sup>, they did not make this distinction because it was not the scientific standard at that time.

## Conclusions

Based on this study’s results, the following conclusions can be made:

1. Formaldehyde is undetectable above baseline physiologic concentration, and cresol is undetectable in the plasma of subjects receiving pulpotomy treatment under general anesthesia.
2. Benzyl alcohol was detected in the plasma of all subjects receiving pulpotomy treatment. The levels present were far below the Food and Drug Administration’s recommended daily allowance.
3. It is unlikely that formocresol, when used in the doses typically employed for the vital pulpotomy procedure, poses any risks to children.

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## Abstract of the Scientific Literature

### The prevalence of headaches in children with sickle cell disease

*This cross-sectional study compared the frequency of headaches in 241 children ages 6-21 years with sickle cell disease (SCD) and 141 healthy black controls. Methodology included a standardized headache questionnaire, a supplemental questionnaire about SCD complications, and data from the patients' clinical and radiographic records. Associations between headaches and SCD-related factors such as vaso-occlusive episodes (VOE) and cerebrovascular disease (CVD) were also examined. Results: The prevalence of frequent headaches was 32% in SCD children and was not significantly different from the control group (P=.27). Younger children (<13 years) with SCD reported more headaches (P=.01). Headache prevalence was similar among SCD genotypes. Children with frequent headaches were more likely to report VOE and experience headaches and VOE concomitantly. SCD patients with frequent headaches were also likely to have symptoms suggestive of obstructive sleep apnea. No associations were found between headaches and silent cerebral infarctions or history of overt strokes.*

**Comments:** This paper suggests that though headaches in SCD patients were similar to the general population, children with SCD and a history of frequent headaches may benefit from early screening for CVD to assess the presence or progression of vessel stenosis. **AOA**

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22 references