Acquisition of Mutans Streptococci and Caries Prevalence in Pediatric Sickle Cell Anemia Patients Receiving Long-term Antibiotic Therapy

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Abstract

Purpose: The purpose of this study was to: (1) evaluate the prevalence of mutans streptococci (MS) and dental caries in sickle cell anemia (SCA) patients receiving long-term prophylactic penicillin therapy; and (2) determine changes in MS colonization and dental caries upon discontinuing the antibiotic.

Methods: Sixty subjects with SCA and 60 age- and race-matched control subjects participated in this study. The SCA subjects were divided into 2 separate age groups: (1) group 1 subjects were under 6 years of age and received penicillin twice a day; and (2) group 2 subjects were 6 to12 years old and received no daily prophylactic antibiotics, although up to age 6 they had received daily penicillin before it was discontinued. DMFS/dmfs scores for all subjects were obtained through a comprehensive dental examination including bitewing radiographs. Stimulated salivary samples to assess MS levels were obtained on all subjects. Data on medical, dental, fluoride, and dietary history were obtained on all patients through a written parental questionnaire.

Results: No group 1 patients had positive cultures for MS. In contrast, 70% of matched controls cultured positively for MS ($P<.01$). The DMFS/dmfs score for group 1 was 0.21 vs 5.1 for the control group ($P<.01$). Differences in surfaces affected were also noted, with no group 1 patients having interproximal lesions compared to 47% of control subjects having these lesions ($P<.01$). Group 2 also had significantly lower levels of MS than matched controls (47% vs 97%, $P<.01$), although there was no statistically significant difference in caries prevalence or surfaces involved.

Conclusions: These findings demonstrate that long-term penicillin prophylaxis in SCA patients likely prevents the acquisition of MS, resulting in significantly lower caries rates in these patients. This benefit occurs only during active administration of the drug, however, and only delays the acquisition of MS. (Pediatr Dent 2005;27:186-190)

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In 1993, Caufield et al described a discrete "window of infectivity" during which infants acquired mutans streptococci (MS) from their maternal host.[1] This "window" opened at 19 months and extended to 31 months, with a mean of 26 months. During this period, the prevalence of MS was seen to rise from 0% to 82%. Caufield hypothesized that the discrete nature of initial MS acquisition was directly related to the presence of nondesquamated hard surfaces, namely newly erupted teeth.

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Empirically, if the acquisition of these cariogenic bacteria could be blocked during this period, an individual may never acquire these organisms and thereby experience lifelong immunity from dental caries. Other authors have suggested a less discrete window, which opens far earlier, even before the eruption of the primary dentition but with a less well-defined closure.[2-5]

Testing these hypotheses requires a model in which the acquisition of MS could be blocked during the discrete window of infectivity, as described by Caufield.[1] Antibiotics effective against MS provide such a mechanism. Finding a model to test this hypothesis proves much more difficult. The initiation and duration of antimicrobial therapy is inconsistent for such disorders as chronic respiratory disease, rheumatic fever, and immune deficiencies, making these patient groups a poor choice for study. Sickle cell

anemia (SCA) patients, however, may represent a more ideal model.

Neonatal screening allows SCA child patients to be identified early in life. Because of their high susceptibility to infection and the high morbidity and mortality associated with septicemia or meningitis secondary to streptococcus pneumoniae, SCA children are placed on prophylactic penicillin as soon as they are diagnosed.[6,7] Oral penicillin dosages of 125 mg twice a day are prescribed for children under 3 years, and 250 mg is prescribed twice a day for children between the ages of 3 and 6. Typically, prophylactic administration of penicillin ceases at age 6 years, well after the so-called window of infectivity closes.

If the discrete window of infectivity hypothesis is correct, then blocking the normal colonization of the dentition by MS during this period with penicillin should provide lifelong protection against the acquisition of this organism. The purpose of this cross-sectional study was to evaluate the prevalence of MS and dental caries in SCA patients receiving long-term prophylactic penicillin therapy and to determine changes in MS colonization and dental caries upon discontinuing the antibiotic.

Methods

SCA children between the ages of 3 and 12 were recruited from the Department of Hematology at Children's Hospital Boston, Boston, Mass. Following approval by the hospital's Institutional Review Board, letters were sent to their parents requesting their participation in the study. Follow-up calls were made to individuals who failed to respond to the initial request. Sixty children with SCA were entered into the study and divided into 2 groups. All SCA subjects were diagnosed prior to age 3 months and immediately placed on daily oral penicillin (dosage=125 mg BID).

Group 1 was composed of 30 SCA subjects between the ages of 3 and 6 and receiving 250 mg of penicillin twice a day. Group 2 was composed of 30 SCA subjects between 6 to 11 years of age who stopped receiving prophylactic penicillin at age 6. A control group of well children was recruited from the dental department at the same institution. Controls were matched for age, race, and socioeconomic background based on income levels and residence (own vs rent, zip code). Exclusion criteria for the control group included a prior history of antibiotic therapy greater than 2 weeks in the preceding 3 years or an underlying systemic illness.

A questionnaire was administered to the parents of all subjects. Data was collected on maternal level of education, medical history, dental history, home oral hygiene practices, fluoride history, and diet history. Parents of SCA children were also asked about compliance with daily dosing of antibiotics and scored as poor (missing more than 4 doses a week) and good (missing 4 or less doses a week). Analysis of diet histories included exposure frequencies to highly cariogenic foods per day and recorded as high (>10 exposures/day), moderate (6 to 10 exposures/day), or low (≤5 exposures/day). Maternal education level was recorded as "completed secondary education" or "didn't complete secondary education."

All subjects underwent a comprehensive dental examination by 1 of 2 examiners. Examiners were not calibrated prior to the study's onset. The clinical examination utilized a dental mirror, a new No. 23 dental explorer, and dental light. Tooth surfaces were considered carious if there was a stick of the explorer with tug-back resistance. Bitewing radiographs were exposed on all patients to detect interproximal caries. Radiographs were analyzed on a standard dental light box with diminished room lighting utilizing ×2 magnification by a single examiner.

A tooth surface was considered carious if a radiolucency extended up to or beyond the dentoenamel junction. Subjects were scored for the presence of caries and type of tooth surface involved (smooth surface and/or fissural). DMFS/dmfs scores were determined for each patient. Teeth extracted for orthodontic reasons were excluded from scoring.

Dentocult SM Strip mutans (Orions Diagnostica, Finland) was used to estimate the presence of *Streptococcus mutans*. This commercially available method is based on the use of a selective culture broth and adherence of MS to a test strip. Per the manufacturer's instructions, samples of stimulated saliva were obtained and placed in a bacitracin-treated culture medium and incubated for 48 hours at 95˚F to 99˚F. Following incubation, cultures were examined for the presence of mutans colonies. Patients were scored as either 0 for no growth (0 colonies) or 1 for visibly detectable mutans colonies. Fisher exact test was used for statistical analysis.

Results

Sixty SCA subjects and 60 age- and race-matched controls were entered into the study. All 60 SCA subjects had started penicillin prophylaxis twice a day by the age of 3 months. Those SCA subjects over the age of 6 had ceased prophylactic antibiotics by age 6. Ninety-six percent of subjects' parents reported good compliance with their prophylactic antibiotics.

The study group was composed of 37 males and 23 females; the control group had 34 males and 26 females. There were 30 SCA patients under the age of 6 years receiving daily prophylactic antibiotic and 30 patients between the ages of 6 and 12 years who were no longer receiving antibiotics. Likewise, the control group had 30 patients under the age of 6 years and 30 patients between the ages of 6 and 12 years. There were no statistically significance differences in home dental hygiene practices, fluoride exposure, diet, maternal education, or frequency of dental visits between any of the groups.

The results of the MS cultures revealed that none (0/30) of the group 1 subjects had positive cultures, while 70% (21/30) of the control group had detectable MS ($P<.01$; Table 1). There was also a statistically significant difference observed in caries prevalence between group 1 and controls. While no group 1 subjects had interproximal caries, 13%

Table 1. Comparison of Control and Group 1 (Sickle Cell Anemia [SCA] Patients) Between Ages 3 and 6

	Group 1: SCA (N=30)	Controls (N=30)*
Maternal education (completed secondary education)	80% (24)	87% (26)
Diet: cariogenic exposures	30% (9)=high 47% (14)=moderate 23% (7)=low	37% (11)=high 43% (13)=moderate 20% (6)=low
Detectable mutans streptococci	0% (0)	70% (21)†
Interproximal caries	0% (0)	47% (14)†
Fissural caries	13% (4)	17% (5)
DMFS/dmfs	0.21	5.1†

*All SCA group patients receiving 250 mg of prophylactic penicillin by age 3 months.
†Statistically significant at $P \leq .01$.

had fissural caries. Fifty-seven percent of the matched controls had caries. Forty-seven percent of caries observed in the control group was smooth surface lesions ($P<.01$). The mean DMFS/dmfs scores were 0.21 in group 1 and 5.1 in the control group ($P<.01$).

The results for group 2 and matched controls also revealed statistically significant differences in MS cultures (Table 2). Forty-seven percent of group 2 cultured positive for MS compared to 97% of controls ($P<.01$). When group 2 was stratified by age, however, differences in MS scores were found to drop below a statistically significant level by age 8 years (Figure 1). Differences in DMFS/dmfs scores remained statistically significant ($P<.01$) until the age of 10.

Discussion

This study's results reveal that SCA patients younger than age 6 receiving daily prophylactic antibiotics had no detectable MS levels as cultured with a commercially available technique. Paralleling this finding, all SCA patients in this group were free of interproximal lesions, although 13% demonstrated occlusal lesions. In contrast, 70% of the control patients in this age group had detectable MS, and 47% demonstrated carious lesions. Forty-seven percent of these lesions were interproximal. After age 6, the number of SCA patients remaining MS and caries free decreased. By age 8, there were no statistically significant differences between SCA patients and the matched controls in MS levels. By age 10, there were no longer any statistically significant differences in caries experience.

This study's results demonstrate that antibiotic therapy in pediatric SCA patients during the so-called "window of infectivity" prevents acquisition or suppression of MS below detectable levels, resulting in a significant decrease in dental caries. The discrete nature of the window of infectivity as proposed by Caufield, however, must be questioned.[1] Although the MS level in SCA patients no longer taking antibiotics remained lower than controls for several years, ultimately these patients had MS levels and experienced caries rates no different than the controls. Consequently, the suggestion that the "window of infectivity" closes at about age 3 may not be valid.

A second mechanism may also contribute to these results. It is possible that those patients receiving prophylactic penicillin did, in fact, acquire MS, but at levels undetectable by this study's culturing methodology. Consequently, the changes observed in MS and caries in these patients upon discontinuation of their prophylactic antibiotics may represent growth of already present MS colonies as opposed to initial acquisition.

A large body of evidence exists showing decreased MS levels following antibiotic administration. Caufield and Loesche reported a reduction in both MS levels and carious lesions in patients receiving short-term treatment with a number of agents including topically applied iodine, chlorhexidene, vancomycin, and fluoride.[8-10] These agents reduced oral MS levels for periods lasting from several days to several months. Staves and Tinanoff found that salivary MS levels were reduced for up to 3 months following a

Table 2. Comparison of Control and Group 2 (Sickle Cell Anemia [SCA] Patients) Between Ages 6 and 12

	SCA (N=30)	Controls (N=30)*
Maternal education (completed secondary education)	83% (N=25)	80% (N=24)
Diet: cariogenic exposures	37% (N=11)=high 43% (N=13)=moderate 20% (N=6)=low	43% (N=13)=high 40% (N=12)=moderate 17% (N=5)=low
Detectable MS	47% (N=14)	97% (N=29)†
Interproximal caries	30% (N=9)	70% (N=21)†
Fissural caries	63% (N=19)	77% (N=23)
DMFS/dmfs	3.89	5.78†
Total caries experience	63% (N=19)	77% (N=23)

*All SCA group patients ceased taking prophylactic penicillin by age 6.
†Statistically significant at $P \leq .01$.

10-day course of antibiotic therapy in a pediatric population.[11] In a similar study utilizing an adult population, Maltz and Zickett reported only a 21-day suppression of MS following antibiotic therapy.[12] Staves and Tinanoff suggested that these differences might be the result of a more mature microflora in the adult being less susceptible to antibiotics or possibly the drug's delivery mode.

To date, all efforts to show a therapeutic link between antimicrobial therapy and reduction in MS and caries activity have met with only partial success. Some investigators have reported conflicting results. Dasanyake found that African American children who received antibiotics, in fact, had more carious surfaces than controls, although this association did not reach statistically significant levels.[13] Sandham also failed at long-term elimination of MS through the application of an antimicrobial varnish in adults.[14]

The central problem encountered by those studies showing some therapeutic success was the difficulty in suppressing or eliminating MS for an extended period of time. After cessation of the antimicrobial agent, these organisms recolonized the dentition. In cases following chlorhexidene gel treatment, where MS levels had been reduced by 99.9%, pretreatment levels were reached after only 2 to 6 months following treatment.[15] Patients with deep grooves or multiple restorations showed the most rapid recolonization rates. Regrowth of bacteria suggests that, despite assayable elimination of MS, transmission between individuals, resistant colonies, or reservoirs exist that are unaffected by chemotherapy.

Previous intervention studies have failed to identify an optimal time for the administration of antimicrobial agents.

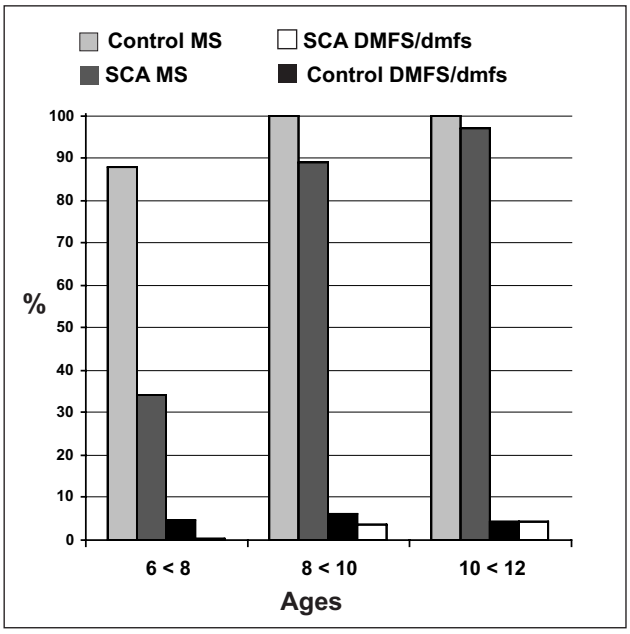

Figure 1. Mutans streptococci (MS) and caries (DMFS/dmfs) for controls and sickle cell anemia (SCA) patients after age 6 years, stratified by age.

Most interventions have been directed at high-risk patients who already harbor high MS levels. Although several studies have reported acquisition of MS prior to the eruption of the primary dentition, this study was unique in that patients received an antibiotic effective against MS from age 2 to 3 months, prior to any reported colonization of the oral cavity with this organism, and continued for approximately 6 years.[5,16] In spite of this protracted therapeutic period, all patients acquired MS after cessation of their antibiotic and reached comparable levels with controls within approximately 2 years. This study's findings are similar to the results reported by Zickert et al, in which children were treated with an aggressive preventive program including antimicrobial therapy. They, too, found that MS counts returned to pretreatment levels approximately 2 years after program discontinuation.[3] The observation that caries activity lagged behind these changes in MS counts is not surprising, as clinically detectable caries often takes several years to manifest itself.

This study's results suggest that, although the "window of infectivity" may open around age 19 months, its closure is less discrete and is certainly later than the 31 months suggested by Caufield.[1]

Conclusions

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

1. SCA patients receiving prophylactic penicillin lack detectable levels of MS and have significantly lower caries rates than matched control subjects.
2. Discontinuation of prophylactic penicillin in SCA patients results in detectable levels of mutans streptococcus and caries rates approaching those of untreated controls after approximately 4 years.

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Abstract of the Scientific Literature

Intervention Designed to Increase Preventive Health Care Seeking Among Adolescents

Sexually active adolescents and young adults have the highest rates of sexually transmitted diseases in the United States, yet they are less likely to seek and receive health care than any other age group. The purpose of this study was to evaluate the effectiveness of an intervention designed to increase preventive health care seeking among adolescents. Adolescents and young adults aged 12 to 21 years, recruited from community-based organizations in 2 different communities, were randomized into either a 3-session intervention or a control condition. Authors estimated outcomes from 3-month follow-up data. Results showed that female intervention participants were significantly more likely than female control participants to have scheduled a health care appointment, undergone a checkup, and discussed with friends or family members the importance of undergoing a checkup. There were no differences between male intervention and male control participants in terms of outcomes. It was concluded that this theory driven, community-based group intervention significantly increased preventive health care seeking among female adolescents.

Comments: If young people delay or avoid seeking health care, they may be at increased risk of transmitting infections to sexual partners and experiencing long-term negative sequelae such as infertility, chronic pelvic pain, and cancer. Therefore, there are many benefits associated with increasing preventive health care seeking on the part of adolescents, including early diagnosis, illness treatment, and the opportunity for preventive health education. Adolescents who use preventive health services have been shown to engage in fewer risk behaviors and more health-promoting behaviors and to be in better health. In addition, establishing the habit of seeking preventive health services during this age period can build health behaviors that may continue throughout adulthood. FSS

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23 references