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Dental Amalgam and Psychosocial Status: The New England Children's Amalgam Trial

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Abstract

High-dose exposures to elemental mercury vapor cause emotional dysfunction, but it is uncertain whether the levels of exposure that result from having dental amalgam restorations do so. As part of the New England Children's Amalgam Trial, a randomized trial involving 6- to 10-year-old children, we evaluated the hypothesis that restoration of caries using dental amalgam resulted in worse psychosocial outcomes than restoration using mercury-free composite resin. The primary outcome was the parent-completed Child Behavior Checklist. The secondary outcome was children's self-reports using the Behavior Assessment System for Children. Children's psychosocial status was evaluated in relation to three indices of mercury exposure: treatment assignment, surface-years of amalgam, and urinary mercury excretion. All significant associations favored the amalgam group. No evidence was found that exposure to mercury from dental amalgams was associated with adverse psychosocial outcomes over the five-year period following initial placement of amalgams.

Keywords

dental amalgam; children; psychosocial function; randomized trial

INTRODUCTION

Among dental professionals, higher mercury body burden has been associated with increased self-reported psychiatric symptoms (Aydin *et al.*, 2003). It is uncertain whether mercury vapor released by dental amalgam produces similar effects in patients. A study of twins discordant for amalgam exposure failed to find significant differences in mental health (Bjorkman *et al.* 1996). In some studies, individuals with self-identified "amalgam disease" had more symptoms than did control individuals, but symptom prevalence was not strongly associated with mercury biomarker levels (Herrstrom and Hogstedt, 1993; Bagedahl-Strindlund *et al.*, 1997; Bratel *et al.*, 1997; Langworth, 1997; Bailer *et al.*, 2001; Gottwald *et al.* 2001, 2002; Langworth *et al.*, 2002; Zimmer *et al.*, 2002). In one study, however, women with amalgam restorations had significantly higher levels of mercury in the oral cavity than women who did not; moreover, they reported more symptoms (Siblerud *et al.*, 1994). In persons with multiple sclerosis, those with amalgam restorations reported more symptoms than those whose amalgam restorations had been removed (Siblerud, 1992). Improvement in psychiatric symptoms following amalgam removal was reported in a retrospective study (Lindh *et al.*, 2002), but in a randomized trial of

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amalgam and psychosocial health, chelated and non-chelated groups did not differ in symptom severity or frequency (Grandjean *et al.*, 1997).

Few data are available on dental amalgam restorations and psychiatric symptoms in children. As part of the New England Children's Amalgam Trial (NECAT), a randomized trial comparing the health effects of dental amalgam and mercury-free composite resin (Bellinger *et al.*, 2006, 2007a,b), we evaluated the hypothesis that, by parent- and self-report, the psychosocial health of children in the amalgam group is worse than that of children in the composite resin group.

METHODS

Trial Design

In total, 534 children from Boston/Cambridge (Massachusetts) and Farmington (Maine) were enrolled. Eligibility criteria were: 6 to 10 yrs old; fluent in English; no known prior or existing amalgam restorations; 2 or more carious posterior teeth; and no physician-diagnosed psychological, behavioral, neurological, immunosuppressive, or renal disorders. At baseline visits, children received an examination by a study dentist, including x-rays, and standard preventive dental care. Blood and urine samples were collected, anthropometric measurements were made of height, weight, and body fat, neuropsychological tests were administered to the child and guardian, and a health interview was conducted with the child's guardian (Children's Amalgam Trial, 2003).

After completing baseline visits, children were randomized to a treatment arm: dental amalgam or composite resin (hereafter "non-amalgam"). Randomization was stratified by geographic location (Boston/Cambridge vs. Maine) and number of teeth with caries (2 to 4 vs. ≥ 5), with randomly permuted blocks within each of the four strata.

Children received semi-annual dental examinations throughout the five-year trial period. For children in the amalgam group, a dispersed-phase amalgam was used to restore carious posterior teeth at baseline as well as incident caries. For children in the non-amalgam group, caries in permanent teeth was restored with composite resin, and caries in primary teeth was restored with compomer, a mixture of composite and glass ionomer. In both groups, composite resin was used to restore caries in anterior teeth, and stainless steel crowns were used to restore primary teeth with extensive lesions that could not otherwise be restored. Techniques were standardized across sites and dentists, and the materials used at different sites were obtained from the same manufacturers. (Because the dentists used their own supplies, we are unable to list the manufacturer information in this paper.)

The NECAT trial was approved by the institutional review boards of the New England Research Institutes, the Forsyth Institute, and the clinics from which children were recruited. All parents provided informed consent, and all children provided assent.

Psychosocial Status Measurements

The primary psychosocial outcomes are scores on the Child Behavior Checklist (CBCL) (Achenbach, 1991), completed by a parent at baseline prior to dental treatment and 5 yrs later, at the completion of the trial. It yields four global T-scores: Competence, Internalizing Behavior Problems, Externalizing Behavior Problems, and Total Problem Behaviors. Three subscales contribute to the Competence score: Activities, Social Adaptation, and School. Eight subscales contribute to the Behavior scores: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behaviors, and Aggression.

Secondary outcomes were children's self-reports at the five-year evaluation on the Behavior Assessment System for Children (BASC-SR) (Reynolds and Kamphaus, 1992). The BASC-SR yields four global scores: Clinical Maladjustment (derived from scores on the Anxiety, Atypicality, Locus of Control, and Social Stress scales), School Maladjustment (derived from scores on Attitude to School and Attitude to Teachers), Personal Adjustment (derived from scores on Relations with Parents, Interpersonal Relations, Self-reliance, and Self-esteem), and the Emotional Symptoms Index, a global indicator of emotional disturbance (derived from scores on Social Stress, Anxiety, Interpersonal Relations, Self-esteem, Depression, and Sense of Inadequacy).

Mercury Exposure Measurements

The primary index of a child's exposure was treatment group assignment. Two secondary indices were also considered. One was surface-years of amalgam, calculated from a child's dental records, prospectively assembled over the course of the trial. The other was urinary mercury excretion. Urine samples were collected annually and analyzed for elemental mercury by cold vapor atomic absorption. Values were expressed as μg mercury/gram creatinine ($\mu\text{g/g Cr}$). In analyses, we used the mean urinary mercury concentration in samples collected at 3, 4, and 5 years of follow-up. Samples with a mercury concentration below the detection limit were assigned a value of $0.45/\sqrt{2}$ (Hornung and Reed, 1990).

Statistical Analyses

Using analyses of covariance, we evaluated the associations between children's CBCL change scores and treatment group, adjusting for baseline score, age, gender, race, socio-economic status, primary caregiver's marital status, birth weight, maternal exposure during pregnancy to tobacco, alcohol, and drugs, family stress, baseline child Full-Scale IQ, and randomization stratum (*i.e.*, the four strata defined by geographic location and number of teeth with caries at baseline). In secondary analyses, change scores on the four global CBCL scales were evaluated in relation to surface-years of amalgam and urinary mercury excretion. In total, 395 children (197 in the amalgam group, 198 in the non-amalgam group) had complete data and were included in the CBCL analyses. Over the course of the trial, 42 children withdrew from the amalgam group, and 43 from the non-amalgam group. The remaining 54 children were missing data on baseline or five-year CBCL scores.

Because the BASC-SR is normed for children older than 8 yrs, children who were 6 or 7 yrs old at baseline did not complete it. Because all children were older than 8 yrs at the five-year evaluation, the BASC-SR analyses evaluated treatment group differences at 5 yrs. Analysis of covariance models were used, adjusted for the same covariates used in the CBCL analyses. These analyses involved 426 children (213 in each treatment group).

Sample Size Calculations

The sample size was determined on the basis of the primary outcome of the trial, the change in children's IQ scores over 5 yrs. For the analyses of CBCL scores, the available sample size of 395 children provided 80% power, at $p < 0.05$, to detect a difference of 0.2 points between treatment groups in the change in CBCL scores over the trial.

RESULTS

Treatment groups were similar in terms of most baseline characteristics, but differed in terms of race, primary caregiver's marital status, alcohol use during pregnancy, and family stress (Table 1). Therefore, group comparisons were adjusted for these factors.

For children in both treatment groups, the mean scores on the CBCL composites and subscales at both baseline and year 5 were similar to those of children in the CBCL standardization sample (Table 2). Children in the amalgam and non-amalgam groups were compared in terms of the changes in their CBCL scores over time, adjusted for randomization stratum, baseline score, as well as baseline covariates (Table 3). Significant group differences were noted on Internalizing and Total Problem Behaviors, with the scores of the amalgam group decreasing more than the scores of the non-amalgam group. This reflects greater improvement in the amalgam group. The expected standard deviation is 10. Therefore, the improvements in the scores of the amalgam group correspond to 36% and 46% of a standard deviation for Internalizing and Total Problem Behaviors, respectively, compared with 16% and 20% for children in the non-amalgam group.

A significant treatment group difference in change score was found on one Competence subscale, Activities. The scores of the children in the amalgam group improved more than did the scores of the children in the non-amalgam group. Significant treatment group differences were also noted on two Behavior subscales, Anxious/Depressed and Delinquent Behaviors. For both, greater change in the positive direction was found for children in the amalgam group.

Total Problem Behaviors was the only global CBCL score with which surface-years of amalgam was significantly associated. Greater amalgam exposure was associated with greater improvement. Mean urinary mercury excretion between years 3 and 5 of follow-up was not significantly associated with any CBCL global score.

With regard to the four composite scales of the BASC-SR, treatment groups differed on the Emotional Symptoms Index and Personal Adjustment (Table 4). The score of the amalgam group was significantly lower (better) on the Emotional Symptoms Index and significantly higher (better) on Personal Adjustment.

DISCUSSION

The NECAT provides no evidence that the psychosocial status of children exposed to dental amalgam was less optimal than that of the children whose caries was treated with mercury-free composite resin. The scores of children in both groups were similar to those of the CBCL and BASC-SR standardization samples. Some differences were noted between treatment groups in the time-course of children's scores, but none was in the direction that suggest an adverse effect of dental amalgam. Consistent results were obtained when we examined the associations between CBCL global scores and two alternative indices of exposure to mercury vapor, surface-years of amalgam and urinary mercury excretion. Similarly, children in the amalgam group had significantly better outcomes on two of the four global scores on the BASC-SR.

Our directional hypothesis—that use of amalgam is associated with worse psychosocial outcomes in children—was clearly not confirmed, since all significant associations favored the amalgam group. This could reflect chance, residual confounding, beneficial effects of amalgam, or detrimental effects of composite and/or glass ionomer on these outcomes. A role for chance can never be eliminated with certainty. The use of random assignment to treatment groups reduced the likelihood of residual confounding by measured or unmeasured factors. While we consider it implausible that exposure to elemental mercury confers health benefits, concerns have recently been raised regarding possible toxicities of dental resin materials (Schweikl *et al.*, 2006). Data germane to this issue were not collected in our study, which was designed a decade ago when this information was not available. Therefore, the explanation for our findings is uncertain, but the possibility that the dental materials used as replacements for

amalgam are associated with toxicities should be considered in future studies, especially when these materials are placed in posterior teeth on contact surfaces.

Several features of the NECAT increase the confidence that can be placed in our findings. First, the experimental design, involving random assignment to treatment groups, provides the optimal design for drawing causal inferences. An observational design cannot support such inferences. Second, the primary outcome instrument, the Child Behavior Checklist, is widely used and has been shown to be sensitive to chemical exposures such as lead (Needleman *et al.*, 1996), pre-natal cocaine (Sood *et al.*, 2005), pre-natal alcohol (Lee *et al.*, 2004), and polychlorinated biphenyls (Lai *et al.*, 2002). Third, these results are consistent with those reported previously for the primary outcomes of NECAT, which were neuropsychological test scores (Bellinger *et al.*, 2006). For those outcomes, the amalgam group showed greater, albeit not statistically significant, improvement over the trial period than the non-amalgam group. Fourth, these results are consistent with those of the similar Casa Pia trial, which found no adverse neuropsychological effects of amalgam (DeRouen *et al.*, 2006).

Given that high-dose exposure to elemental mercury is known to produce emotional disturbances, it is important to consider factors that might explain our failure to find evidence of increased morbidity among children in the amalgam group. First, perhaps the mercury doses were not sufficient to produce such adversities. Although NECAT eligibility criteria ensured the enrollment of children with greater numbers of caries than most US children (Beltran-Aguilar *et al.*, 2005), exposures to elemental mercury would be greater among individuals who require more extensive restorative work than the children in NECAT. However, children enrolled in the Casa Pia trial had more caries and higher urinary mercury excretion than did children in the NECAT, but showed no adverse effects of amalgam. Nevertheless, we might have detected adverse effects of amalgam exposure on psychosocial function had the follow-up interval been longer. Second, although we studied children within the age interval in which the incidence of caries, and thus potential mercury exposure, is greatest, this might not be the period of greatest susceptibility to elemental mercury. The results of NECAT cannot be generalized to children younger than 6 yrs, particularly to the fetus, a population subgroup known to be particularly sensitive to other forms of mercury (National Research Council, 2000). Third, recent studies have identified polymorphisms that modify elemental mercury neurotoxicity (Echeverria *et al.*, 2005, 2006). Children enrolled in NECAT were not genotyped, and it is possible that a small subgroup of children in the amalgam group experienced adverse psychosocial effects, but that the number was too small to produce a significant treatment group difference in mean scores.

In summary, in NECAT, a randomized trial, the psychosocial status of children in the dental amalgam group was not worse and, in some respects, was better than that of children in the non-amalgam group.

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Table 1
Baseline Characteristics of Trial Participants Included in Analyses

	Amalgam Group (N = 197)	Non-amalgam Group (N = 198)
Age in yrs (mean, SD, range)	7.9, 1.4, 6.1-11.5	7.8, 1.3, 6.0-11.2
Sex (N, %)		
Female	96, 48.7%	106, 53.5%
Male	101, 51.3%	92, 46.5%
Race (N, %) ^a		
Non-Hispanic white	144, 73.1%	146, 73.7%
Non-Hispanic black	40, 20.3%	23, 11.6%
Hispanic/Other	13, 6.6%	29, 14.6%
Education of primary caregiver (N, %)		
< High school	19, 9.62%	23, 11.6%
High school graduate	89, 45.2%	103, 52.0%
College graduate	63, 32.0%	59, 29.8%
Post-college degree	26, 13.2%	13, 6.6%
Socio-economic status (mean, SD)	53.3, 6.9	52.2, 6.1
Marital status of primary caregiver (N, %)		
Single, never married	32, 16.2%	52, 26.3%
Married	132, 67.0%	123, 62.1%
Separated/divorced/widowed	33, 16.8%	23, 11.6%
Birth order (mean, SD)	1.6, 0.9	1.6, 0.8
Birth weight (g) (mean, SD)	3305 (577)	3331 (632)
Child full-scale IQ (mean, SD)	96.9, 13.4	97.4, 11.7
Pregnancy exposures (N, %)		
Any alcohol	30, 16.3%	17, 8.8%
Any smoking	65, 35.3%	76, 39.2%
Any drug use	7, 3.8%	6, 3.1%
Family stress (mean, SD)	10.3, 10.2	6.9, 8.1
Randomization stratum (N, %)		
Boston, 2-4 caries	40, 20.3%	31, 15.7%
Boston, ≥ 5 caries	48, 24.4%	62, 31.3%

	Amalgam Group (N = 197)	Non-amalgam Group (N = 198)
Maine, 2-4 caries	62, 31.5%	63, 31.8%
Maine, ≥ 5 caries	47, 23.9%	42, 21.2%

^aRace was self-reported by parents.

Table 2
CBCL T-scores of Children in Amalgam and Non-amalgam Treatment Groups at Baseline and Five-year Follow-up

	Amalgam Group		Non-amalgam Group	
	Baseline	5 Yrs	Baseline	5 Yrs
Composite Scales				
Competence ^a	44.7 ± 8.0 ^b	45.9 ± 7.8	45.1 ± 7.7	44.2 ± 9.0
Internalizing	48.9 ± 9.4	44.6 ± 9.9	46.2 ± 9.9	45.0 ± 9.9
Externalizing	47.9 ± 9.8	45.9 ± 9.9	47.4 ± 9.0	46.0 ± 10.8
Total problem	48.4 ± 10.7	44.7 ± 10.7	46.7 ± 10.1	45.0 ± 11.0
Subscales				
Activities ^a	45.6 ± 7.0	47.7 ± 7.0	46.7 ± 6.1	45.8 ± 8.4
Social adaptation ^a	45.4 ± 7.4	45.1 ± 7.2	45.3 ± 7.5	44.2 ± 7.7
School ^a	44.1 ± 7.8	44.9 ± 7.9	44.3 ± 7.5	44.5 ± 8.3
Withdrawn	53.1 ± 5.5	51.9 ± 4.3	52.6 ± 5.4	52.0 ± 4.8
Somatic complaints	54.4 ± 6.6	54.0 ± 5.6	53.4 ± 5.5	53.7 ± 5.9
Anxious/depressed	52.9 ± 4.6	51.8 ± 3.9	52.4 ± 5.0	52.1 ± 4.5
Social problems	54.1 ± 7.6	53.5 ± 5.6	53.0 ± 5.6	52.9 ± 5.6
Thought problems	53.3 ± 6.0	52.6 ± 5.1	53.3 ± 5.8	52.4 ± 4.7
Attention problems	53.3 ± 5.6	53.0 ± 4.7	53.8 ± 6.4	52.9 ± 5.2
Delinquent behaviors	53.8 ± 6.4	52.9 ± 5.2	53.1 ± 5.3	52.6 ± 5.4
Aggression	52.8 ± 5.7	52.4 ± 5.0	52.7 ± 5.0	52.6 ± 5.5

^a Lower score is worse on the Competence score and on the subscales that contribute to it; for all other scales, a higher score is worse.

^b Mean ± standard deviation.

Table 3
Treatment Group Comparisons of CBCL Change Scores between Baseline and 5 Years

Scale	Amalgam Group mean (SD) ^a	Non-amalgam Group mean (SD) ^a	P-value
Competence ^b	0.8 (0.6)	-0.9 (0.6)	0.13
Internalizing	-3.8 (0.6)	-2.1 (0.6)	0.03
Externalizing	-1.8 (0.6)	-1.5 (0.8)	0.06
Total problem behaviors	-3.3 (0.7)	-2.1 (0.7)	0.007
Subscales			
Activities ^b	1.7 (0.7)	0.2 (0.6)	0.03
Social adaptation ^b	-0.8 (0.7)	-2.0 (0.7)	0.11
School ^b	0.8 (0.7)	1.3 (0.7)	0.52
Withdrawn	-1.0 (0.4)	-0.3 (0.4)	0.16
Somatic complaints	-0.1 (0.6)	0.0 (0.5)	0.88
Anxious/depressed	-0.8 (0.4)	0.1 (0.4)	0.04
Social problems	-0.4 (0.5)	-0.2 (0.5)	0.72
Thought problems	-1.5 (0.5)	-1.1 (0.5)	0.44
Attention problems	-1.1 (0.4)	-0.6 (0.4)	0.26
Delinquent behaviors	-1.8 (0.6)	-0.2 (0.5)	0.002
Aggression	-0.3 (0.4)	0.2 (0.4)	0.28

^aMean difference between the baseline and five-year scores, adjusted for baseline age, gender, race, socio-economic status, primary caregiver's marital status, birth weight, maternal exposures during pregnancy to alcohol, tobacco, and drugs, family stress, baseline child Full-Scale IQ, and randomization status.

^bLower score is worse on the subscales that contribute to the Competence composite score; for all other scales, a higher score is worse.

Table 4

BASC-SR Composite Scores, by Treatment Group

Score	Amalgam Group	Non-amalgam Group	P-value
School maladjustment ^a	50.8 ± 0.7 ^b	50.4 ± 0.7	0.29
Clinical maladjustment	44.0 ± 0.6	45.7 ± 0.6	0.08
Personal adjustment	53.3 ± 0.6	51.3 ± 0.6	0.005
Emotional symptoms index	44.6 ± 0.6	46.3 ± 0.6	0.05

^a Higher score is worse on School Adjustment, Clinical Maladjustment, and Emotional Symptoms Index; a lower score is worse on Personal Adjustment.

^b Adjusted mean ± standard error; adjustments made for baseline age, gender, race, socio-economic status, primary caregiver's education and marital status, birth order, birth weight, maternal exposure during pregnancy to alcohol, tobacco, and drugs, family stress, baseline child Full-Scale IQ, and randomization stratum.