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ABSTRACT

The aim of the present study was to compare the reduction of subjective complaints by 3 treatment strategies in 90 "amalgam patients" whose complaints could not be explained by a medical or psychological disorder. The individuals were randomly assigned either to removal of dental amalgam only (removal group), or removal in combination with a "biological detoxification" therapy with high doses of vitamins and trace elements (removal-plus group), or participation in a health promotion program without removal of dental amalgam (no-removal group). Between baseline and month 12, the sum score of main complaints decreased by 3.5 (SD = 2.2) points on average in the removal group as well as in the removal-plus group, and by 2.5 (SD = 2.4) points in the no-removal group ($p = 0.152$). Both removal groups showed a significant decrease in steady-state levels of inorganic mercury compared with the no-removal group. Thus, all 3 interventions were associated with clinically relevant improvements.

KEY WORDS: Dental amalgam, mercury, subjective health complaints, controlled trial.

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Treatment of Health Complaints Attributed to Amalgam

INTRODUCTION

Dental amalgam is still widely used as a filling material in the treatment of dental caries, but safety concerns relating to its mercury content have been a topic of discussion for many years (Hörstedt-Bindslev *et al.*, 1991; LSRO, 2004; Bates, 2006). This and the known toxicity of methylmercury for the developing brain have recently initiated two randomized longitudinal studies on the neuropsychological effects of amalgam in children (Bellinger *et al.*, 2006; DeRouen *et al.*, 2006). Some amalgam-bearers with chronic, subjective, non-specific health problems suspect that their complaints are caused by mercury released from their amalgam fillings. Typically, these so-called "amalgam patients" report a large number and variety of symptoms (Yontchev *et al.*, 1986; Melchart *et al.*, 1998). Some of the reported symptoms correspond well with the major toxic effects on the nervous and immune systems that are considered to be associated with chronic subtoxic exposure to mercury (Molin, 1990; Eneström and Hultman, 1995).

In 1995, approximately 1500 persons filed a law suit against the Degussa company (former main manufacturer of amalgam in Germany), claiming health injury by dental amalgam. The ensuing settlement generated funds which were allocated by an independent research funding organization for investigation of controversial questions such as the detrimental potential of amalgam, diagnosis of injury by amalgam, and treatment of persons who relate their health problems to amalgam. As part of the research program, we conducted a controlled trial to investigate the effectiveness of 3 treatment strategies for "amalgam patients" in reducing subjective health complaints that could not be explained by other medical or psychological disorders. Thus, the underlying null hypothesis assumed no differences among the treatment regimens.

MATERIALS & METHODS

Design

The study was randomized and controlled, comparing removal of dental amalgam (removal group), removal of dental amalgam combined with a 'biological detoxification' therapy (removal-plus group), and participation in a health promotion program without removal of amalgam (no-removal group). Participants were not blinded to treatment. Randomization was done by telephone according to a random list generated in advance, and stratified according to the number of amalgam restoration surfaces. The protocol was approved by two university ethics committees. All study participants provided written informed consent.

Participants

Inclusion criteria were: persons with dental amalgam restorations who suspected that their health complaints were caused by dental amalgam; having reported at least 10 symptoms (including at least 3 of strong intensity); and age 20 to 50 yrs.

Exclusion criteria were: persons with bridges, crowns, or gold inlays; persons having undergone unsuccessful endodontic treatment; having relevant

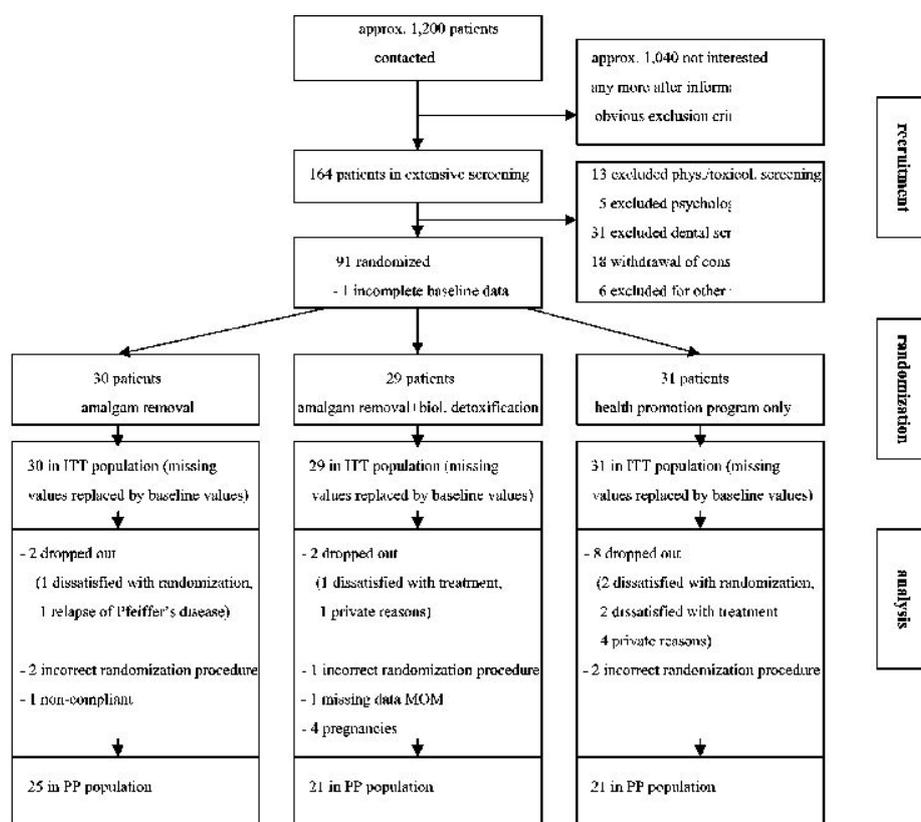


Figure 1. Trial flow chart (ITT = intention to treat, MOM = main outcome measure, PP = per protocol).

organic, allergic, or mental disorders; inability to understand the study; alcohol or drug abuse; pregnancy or lactation; participation in any clinical research study in the preceding 3 months.

Treatments

Removal of amalgam and replacement by other restoration materials were performed by the University Unit of Dentistry, including provisions for protecting both participant and physician during treatment. Amalgam was removed by quadrant, with at least 1 wk between visits; underlying restorations and carious dentin were removed completely. Calcium hydroxide was used as a liner in cases of very deep restorations (caries profunda) before being restored with ceramic or gold inlays, or a composite restoration.

In the removal-plus group, participants were additionally treated with high doses of vitamins and trace elements (following the recommendations of the International Association for Holistic Dental Medicine), intended to support the excretion of mercury from the body. Biological detoxification therapy lasted for 12 wks, beginning 4 wks before amalgam removal, and consisted of the daily intake of tablets containing: vitamin B6 (100 mg), vitamin C (1 g), vitamin E (300 mg), calcium (500 mg), selenium (200 µg as sodium selenite), zinc orotate (2 x 40 mg, *i.e.*, 2 x 6.3 mg zinc), and a garlic preparation (1 x 100-300 mg). Participants were not allowed to take vitamin C and selenium at the same time of day, to avoid neutralization.

Those in the no-removal group participated in a health promotion program, aimed at developing health-related lifestyle management skills suitable for individuals' everyday life (Wunderlich and Melchart, 2002). The program consisted of 14 two-hour group sessions (up to 12 participants) and was conducted initially selected complaints at visits 1, 2, 6, 12, and 18

by professionals from the Centre for Complementary Medicine Research.

Outcomes

Initially, extensive toxicological, psychiatric, and dental screenings were performed. Concomitant treatment, compliance with the medication regimen in the removal-plus group and participation in the health promotion sessions in the no-removal group, and the occurrence of serious adverse events were documented by the physician at each visit. Total and inorganic mercury levels were determined in plasma and erythrocytes by cold-vapor atomic absorption. Total mercury was also determined by urinalysis (Halbach *et al.*, 1998, 2003).

At baseline, participants were given a pre-defined symptom list with 50 items (scoring from 0 = not present to 3 = strong intensity) and additionally were asked to rank their three main complaints (rating scale from 0 = not present to 9 = extreme), resulting in a weighted sum score. This procedure was repeated for the

mos after the start of treatment.

The number of complaints as well as a total symptom score were also determined. At baseline and 6, 12, and 18 mos after the start of treatment, participants completed the SF-36 to assess health-related quality of life (Ware *et al.*, 1993), the Symptom Checklist SCL-90-R, providing a general index of symptom severity as a measure for overall psychological distress (Derogatis, 1992), and the KKG questionnaire to estimate the participant's health-related locus of control (Lohaus and Schmitt, 1989). At baseline, participants completed two additional psychometric instruments: the SAM questionnaire, assessing dispositional self-consciousness (Filipp and Freudenberg, 1989); and FPI-R, an inventory assessing basic personality traits (Fahrenberg *et al.*, 1994).

The main outcome measure was the difference in the main complaints sum score between baseline and 12 mos. Pre-defined secondary outcomes included: total symptom score after 18 mos, quality of life, psychic symptoms and signs, and mercury levels in blood and urine after 12 and 18 mos.

Statistics

Since there were no data to estimate the expected effect sizes for each treatment group, mean reductions for the main outcome measure were assumed as: 2.5 in the removal group, 3.0 in the removal-plus group, and 1.0 in the no-removal group, with a common standard deviation of 2.5 ($\alpha = 5\%$, two-sided). A minimum sample size of 29 participants *per* group met these conditions, showing an 80% power to reject the null hypothesis (Elashoff, 2000).

All randomized participants with baseline data on symptom score and dental status were defined as the intention-to-treat (ITT) population, while protocol violators (see Fig. 1) until month 12

were excluded from the *per-protocol* (PP) population.

Statistical testing of the main outcome measure was performed on the ITT population, with missing data replaced with baseline values (thus setting the differences compared with baseline to zero) by analysis of variance. In case of rejection of the null hypothesis, posteriori pair-wise comparisons were planned. In addition, sensitivity analyses were performed for the main outcome measure, with all available data or replacement of missing data by the 'last value carried forward' method. Exploratory analyses (without adjustment for multiple testing) were done for pre-defined secondary outcome measures. All data were analyzed descriptively (mean values with standard deviations, 95% confidence intervals), and percentages were provided. In case of baseline differences ($p < 0.1$), analyses of covariance with the baseline values as covariates were carried out. Additional sensitivity analyses were performed excluding participants who had expressed a preference for a specific treatment at baseline, since there was some concern about whether one of the study physicians had followed the correct randomization procedure (see Fig. 1).

Participants

Persons were included in the study between April, 1998, and July, 2002. Most participants were recruited through reports in local newspapers. Approximately 1200 persons expressed interest in participating in the study (Fig. 1), 164 entered at baseline, and 91 were randomized. One individual randomized to the removal group dropped out before treatment without complete baseline data on dental status (90 people in the ITT population). Two people in the removal group, two in the removal-plus group, and eight in the no-removal group withdrew or were lost to follow-up at month 12 ($p = 0.041$, χ^2 test).

RESULTS

Disposition of Participants

As their most important complaint, 64% of the participants reported either skin disease, headache, mental complaint (*e.g.*, nervousness, sleeplessness), general tiredness/weakness, or an infection/low resistance to infections. Complaints like allergies, sensory disturbances, and urological, gastrointestinal, or cardiovascular symptoms were reported less frequently.

At baseline, groups were comparable for most variables. No statistically significant differences between the treatment groups could be found (APPENDIX Table).

The mean total numbers of treatment sessions were 10.3

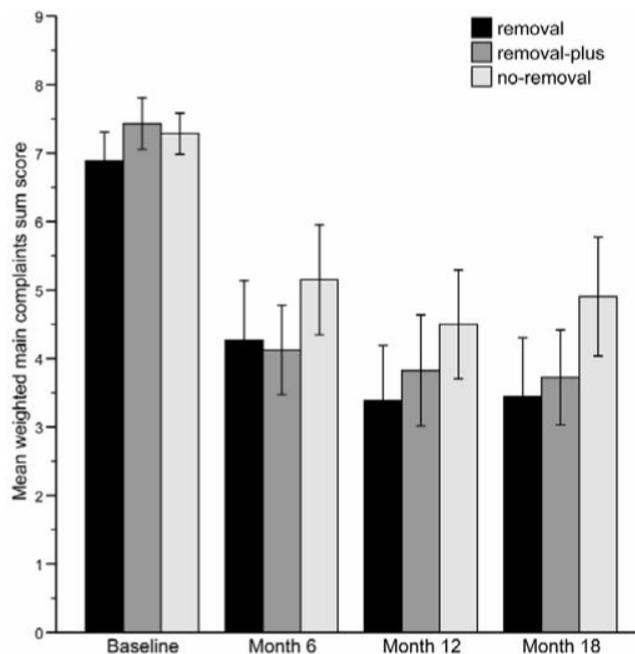


Figure 2. Course of mean weighted main complaints sum score (means and 95% CI; ITT with missing values replaced by baseline values) for all three groups.

(SD = 6.1) in the removal group, 13.4 (SD = 7.4) in the removal-plus group, and 9.9 (SD = 2.9) in the no-removal group ($p = 0.058$). In both removal groups, an average of 4.1 (SD = 1.4) and 4.4 (SD = 1.3) sessions was needed purely for amalgam removal; the remaining sessions were preparations due to the final restoration therapy. In the no-removal group, 19% of the participants participated in fewer than 8 sessions, and 31% attended at least 12 sessions, but only two people complied with the full program.

Primary and Secondary Outcomes

Between baseline and month 12, the 'main complaints' sum score decreased by an average of 3.5 (SD = 2.2) points each in the removal and removal-plus groups, and by 2.5 (SD = 2.4) in the no-removal group ($p = 0.152$; ITT population; see Fig. 2). The sensitivity analyses confirmed the main result (Table 1).

Table 1. Main Outcome Measurement: Mean Differences (standard deviations) between Baseline and Month 12 and Sensitivity Analyses, Unadjusted (ANOVA), and Adjusted for Baseline Values (ANCOVA)

| | Group A Removal of Dental Amalgam | | Group B Removal Plus Biological Detoxification | | Group C Health Promotion Program without Removal | | p ² | p ³ |
|---|---|-------------------------|--|-------------------------|--|-------------------------|----------------|----------------|
| | n | Mean (SD ¹) | n | Mean (SD ¹) | n | Mean (SD ¹) | | |
| Missing values replaced by baseline value | 30 | -3.5 (2.2) | 29 | -3.5 (2.2) | 31 | -2.5 (2.4) | 0.152 | 0.091 |
| Missing values replaced by last value carried forward | 30 | -3.5 (2.2) | 29 | -3.6 (2.0) | 31 | -2.8 (2.3) | 0.286 | 0.194 |
| No replacement of missing values | 28 | -3.8 (2.1) | 26 | -3.9 (2.0) | 23 | -3.4 (2.1) | 0.683 | 0.557 |
| Per protocol population (no missing values) | 25 | -3.6 (2.1) | 21 | -3.9 (1.8) | 21 | -3.3 (2.2) | 0.626 | 0.597 |

1 Standard deviation. 2 p-value for ANOVA among groups. 3 p-value for ANCOVA among groups adjusted for baseline values.

Table 2. Mean Differences (standard deviations) between Baseline and Month 12 in Secondary Outcomes for the Three Treatment Groups

| | Group A Removal of Dental Amalgam | | Group B Removal Plus Biological Detoxification | | Group C Health Promotion Program without Removal | | p ² |
|---|---|------------------------|--|------------------------|--|------------------------|----------------|
| | n | Mean (SD) ¹ | n | Mean (SD) ¹ | n | Mean (SD) ¹ | |
| Participant questionnaires | | | | | | | |
| Total symptom score (0-150) | 27 | - 21.8 (17.6) | 25 | - 24.0 (16.5) | 23 | - 16.3 (12.2) | 0.230 |
| No. of complaints (0-50) | 27 | - 9.7 (8.4) | 25 | - 10.5 (9.2) | 23 | - 7.6 (7.7) | 0.487 |
| No. of strong complaints (0-50) | 27 | - 4.5 (3.2) | 25 | - 4.7 (3.0) | 23 | - 3.6 (2.5) | 0.437 |
| SF-36 physical health ^{3,4} | 26 | 3.9 (8.5) | 24 | 2.4 (11.5) | 21 | 1.0 (6.9) | 0.546 |
| SF-36 mental health ^{3,4} | 26 | 3.5 (8.3) | 24 | 4.4 (10.6) | 21 | 5.0 (9.1) | 0.858 |
| SCL-90-R Global Severity Index ⁴ | 26 | - 5.5 (7.4) | 26 | - 4.9 (8.9) | 22 | - 6.9 (5.4) | 0.633 |
| KKG internal locus of control ⁵ | 26 | - 0.2 (9.3) | 26 | 2.3 (7.8) | 22 | 4.1 (7.2) | 0.197 |
| KKG external locus of control ⁵ | 26 | 1.1 (11.8) | 26 | 0.2 (10.4) | 22 | 0.7 (8.9) | 0.947 |
| KKG fatalistic externality ⁵ | 26 | 0.8 (12.1) | 26 | - 0.4 (9.2) | 22 | - 1.8 (11.0) | 0.711 |
| Mercury concentrations | | | | | | | |
| Total in blood plasma (ng/mL) | 26 | - 0.43 (0.39) | 26 | - 0.46 (0.63) | 23 | - 0.16 (0.27) | 0.049 |
| Inorganic in blood plasma (ng/mL) | 26 | - 0.44 (0.38) | 26 | - 0.45 (0.57) | 21 | - 0.12 (0.17) | 0.013 |
| Total in erythrocytes (ng/mL) | 26 | 0.06 (1.77) | 26 | - 0.42 (1.69) | 23 | - 0.73 (1.57) | 0.259 |
| Inorganic in erythrocytes (ng/mL) | 26 | - 0.41 (0.38) | 26 | - 0.43 (0.49) | 22 | - 0.12 (0.19) | 0.012 |
| In urine (ng/mL) | 26 | - 1.15 (1.42) | 26 | - 1.86 (2.71) | 23 | - 0.48 (1.43) | 0.054 |
| In urine excretion (ng/8 hrs) | 25 | - 0.44 (1.04) | 26 | - 1.18 (10.4) | 23 | - 0.33 (1.04) | 0.022 |

1 Standard deviation.

2 p-value for ANOVA among groups.

3 Positive differences indicate improvement.

4 t-values.

5 Stanine values.

The groups did not differ significantly with regard to mean differences in secondary outcomes between examinations at baseline and 12 mos later (Table 2). Descriptive analyses indicated persistent improvements up to month 18.

With the exception of total mercury in erythrocytes, mercury concentrations of all measured blood and urine parameters were significantly lower after amalgam removal as compared with concentrations in the no-removal group (Table 2). In all three groups, the concentrations of inorganic mercury in erythrocytes and plasma, of total mercury in plasma, and of the urine parameters hardly changed between months 12 and 18.

Safety and Tolerability

Three serious adverse events (in-patient surgical treatments considered unrelated to study condition and intervention) were documented; all three persons continued the trial.

During the study, 43 participants (12/14/17, respectively, for the three groups) reported 73 complaints as 'new'. Overall, 16% of the complaints were gastrointestinal symptoms, 15% arthralgia/back pain, 11% dental problems due to the replacement of restorations (only in the removal groups), 10% skin diseases, 7% infections, 7% sensory disturbances, and 34% other complaints. Four women (all in the removal-plus group) became pregnant.

DISCUSSION

The focus of this controlled trial was to investigate treatment options for so-called "amalgam patients". Removal of dental

amalgam (with or without biological detoxification therapy) was associated with a marked reduction in the participants' subjective complaints and mental stress. However, a health promotion program without amalgam removal was similarly effective. The improvements observed in all groups were clinically relevant and persisted throughout the follow-up period of 18 mos.

This study is the first comparative randomized controlled trial of treatment strategies for adults with amalgam restorations, and benefited from the cooperation of experts from medical, dental, and toxicological departments. Strengths of the study were extensive screening procedures, strict exclusion criteria, and

high-quality treatment schedules for amalgam removal following generally accepted guidelines. The validity of our results is supported by the consistency of findings from various variables.

The study participants cannot be regarded as representative of all persons with amalgam. Further limitations are that the definition of "amalgam patients" and the measurements of improvements are based on subjective criteria and may be underpowered. Recruitment for the trial turned out to be difficult and required several years of effort, mainly because individuals with other dental materials in combination with amalgam were excluded. Many individuals insisted on amalgam removal and therefore refused randomization. Since blinding was not possible, the relevant effects observed in the removal groups may also be due to the expectations of the person, the natural course of the complaints, or placebo effects. Individuals randomized to the no-removal group showed a high drop-out rate. Due to the unequal drop-out, they tended to benefit less than those in both removal groups in the main analysis (missing values replaced by baseline values), but the results of the sensitivity analyses suggest improvements similar to those reported in the other groups.

The strong effects of the health promotion program on the subjective complaints of "amalgam patients" were unexpected, especially since we observed only a weak relationship between numbers of treatment sessions and symptom relief. A possible explanation may be that by adopting a health-promoting lifestyle, including good nutrition, exercise, and relaxation techniques, the individuals' general health improved, *e.g.*, by strengthening the

immune system and reducing 'amalgam anxiety'. Another reason may be that participants acquired coping strategies for their complaints (Gottwald *et al.*, 2002). Placebo effects in the no-removal group cannot be ruled out as well (Grandjean *et al.*, 1997).

The mercury measurements revealed that, although removal plus biological detoxification therapy tended to result in slightly lower mercury values than amalgam removal alone, participants from both removal groups showed similar improvements in their subjective outcome measurements. Furthermore, a low mercury level was not a precondition for subjective improvement. The strong effects on health observed in the no-removal group are unlikely to be explained by the slight decrease in mercury levels (possibly caused by the participants' avoiding additional mercury uptake by adopting a healthier diet, thereby also ingesting more vitamins and trace elements, similar to what would occur in biological detoxification therapy). As a side-effect, the measurement of total mercury in the erythrocytes showed no significant difference in the three groups at months 12 and 18, while the drop in inorganic mercury in both removal groups was significant. Since the value for total mercury is the sum of inorganic plus organic mercury, a latent increase in organic mercury cannot be excluded for the post-removal data.

A recent review on the health effects of dental amalgam (LSRO, 2004) concluded that, apart from allergic sensitivity, there is insufficient evidence that various non-specific complaints attributed to dental amalgam are actually caused by mercury release from restorations. The review also suggested that "amalgam patients" should be screened for underlying dental, physical, and psychiatric conditions to exclude affective symptoms independent of mercury exposure. The participants in our study met these preconditions exactly.

Removal of dental amalgam and other metal alloys supported by anti-oxidant therapy resulted in improved quality of life in "amalgam patients" in a large retrospective study (Lindh *et al.*, 2002). Several, mainly observational, trials have reported the improvement of various complaints after amalgam removal (Nerdrum *et al.*, 2004; Lygre *et al.*, 2005; Tillberg *et al.*, 2005), while recent randomized trials showed no specific health effects of amalgam restorations in children (Bellinger *et al.*, 2006; DeRouen *et al.*, 2006). In our trial, amalgam removal was associated with a marked reduction in the participants' subjective health complaints. However, similar improvements were observed after a health promotion program without amalgam removal, while mercury levels deviated only slightly from baseline. In conclusion, although the reasons for amalgam-related complaints are still unclear, our results suggest that amalgam removal is not the only treatment option, since all treatments were associated with clinically relevant improvements.

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