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Down Syndrome and Dementia: A Randomized, Controlled Trial of Antioxidant Supplementation

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Abstract

Individuals with Down syndrome over age 40 years are at risk for developing dementia of the Alzheimer type and have evidence for chronic oxidative stress. There is a paucity of treatment trials for dementia in Down syndrome in comparison to Alzheimer disease in the general (non-Down syndrome) population. This 2-year randomized, double-blind, placebo-controlled trial assessed whether daily oral antioxidant supplementation (900 IU of alpha-tocopherol, 200 mg of ascorbic acid and 600 mg of alpha-lipoic acid) was effective, safe and tolerable for 53 individuals with Down syndrome and dementia. The outcome measures comprised a battery of neuropsychological assessments administered at baseline and every 6 months. Compared to the placebo group, those individuals receiving the antioxidant supplement showed neither an improvement in cognitive functioning nor a stabilization of cognitive decline. Mean plasma levels of alpha-tocopherol increased ~2-fold in the treatment group and were consistently higher than the placebo group over the treatment period. Pill counts indicated good compliance with the regimen. No serious adverse events attributed to the treatment were noted. We conclude that antioxidant supplementation is safe, though ineffective as a treatment for dementia in individuals with Down syndrome and Alzheimer type dementia. Our findings are similar to studies of antioxidant supplementation in Alzheimer disease in the general population. The feasibility of carrying out a clinical trial for dementia in Down syndrome is demonstrated.

Keywords

Down syndrome; Alzheimer disease; antioxidants; clinical trial

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INTRODUCTION

By age 40 years, virtually all individuals with Down syndrome (DS) have the characteristic neuropathology of Alzheimer disease (AD) [Zigman and Lott, 2007; Lott and Dierssen, 2010]. The prevalence of dementia increases with age in DS, rising from approximately 15% after age 45 years to approximately 75% after age 65 years [Tyrrell et al., 2001; Coppus et al., 2006]. Individuals with DS as well as those with AD in the general population share a common predisposition towards oxidative stress. Oxidative stress resulting from an imbalance in the metabolism of free radicals such as reactive oxygen species (ROS) is thought to have a direct role in the development of neuropathological changes of AD in DS [Kedziora and Bartosz, 1988; Busciglio et al., 1998].

Mitochondria are recognized as the most susceptible target of ROS formation and mitochondrial control region mutations occur in demented individuals with DS as well as those with AD in the general population [Coskun et al., 2010]. Mitochondrial membrane potentials measured in blood mononuclear cells from individuals with DS are more susceptible to damaging agents than controls [Roat et al., 2007]. Functional genomic analysis of amniotic fluid cell-free mRNA suggests that oxidative stress is significant even in fetuses with DS [Slonim et al., 2009]. Oxidative stress and antioxidant systems have been implicated in the cognitive dysfunction associated with the pre-demented state in DS but the relationship to genes and gene products is not yet clear [Strydom et al., 2009]. Glycation end products that are known to be associated with cellular oxidation are increased in brains from fetuses with DS, suggesting that oxidative stress may begin before birth [Odetti et al., 1998].

Oxidative stress is also increased in mouse models for DS. In the trisomy 16 mouse, which has genetic homology to human chromosome 21, decreased respiration has been noted for Complex 1 in mitochondria [Bambrick and Fiskum, 2008]. Lipid peroxidation, a measure of oxidative stress, is increased in the brain [Ishihara et al., 2010]. Oxidative stress has been identified as a possible therapeutic target in mouse models for DS [Gardiner, 2010]. Alpha-tocopherol, an antioxidant, delayed the onset of cognitive and morphological abnormalities in the Ts65Dn mouse [Lockrow et al., 2009], providing a rationale for the use of antioxidants in individuals with the disorder. In the same mouse model, alpha-tocopherol reduced the oxidation state of S100-beta protein and subsequently its influence on the neuroinflammatory process [Bialowas-McGoey et al., 2008].

Within AD in the general population, oxidative stress has been associated with increased brain concentration of lipid peroxidation products such as malondyaldehyde and 4-hydroxynnonenal [Markesbery and Carney, 1999]. Oxidized proteins such as carbonyls are increased in the hippocampus as well as other brain regions in AD and mild cognitive impairment [Butterfield et al., 2006]. Oxidative modifications of nucleic acids have been reported in brain of patients with AD type dementia [Ding et al., 2005; Wang et al., 2006].

These and other observations have prompted studies of anti-oxidants to decrease oxidative damage and improve cognition. In the non-DS AD population, the results of trials utilizing either a single antioxidant such as vitamin E or combinatorial antioxidants have been mixed with some studies showing beneficial effects [Sano et al., 1997; Engelhart et al., 2002; Morris et al., 2002; Maxwell et al., 2005] and others absence of therapeutic efficacy [Luchsinger et al., 2003; Yaffe et al., 2004; Fillenbaum et al., 2005; Petersen et al., 2005; Kang et al., 2006]. Neither has the efficacy of antioxidant usage been clarified in DS, where there is a paucity of clinical trials. An international Phase III trial for alpha-tocopherol in adults with DS is nearing completion (clinical trial #NCT 00056329). This trial has utilized several neuropsychological outcome measures in common to those reported in the current study [Sano et al., 2005]. Coenzyme Q10 (CoQ10) was used to treat oxidative damage to

DNA but no significant differences were found in treated participants with DS compared to placebo [Tiano et al., 2009]. In infants with DS aged 7 months or younger, administration of folinic acid and a combination of antioxidants did not result in an improved developmental quotient [Ellis et al., 2008] but in a slightly older cohort (ages 3–30 months) a different form of folinic acid (leukovorin) resulted in a small improvement of developmental quotient, particularly for those infants on thyroid supplementation [Blehaut et al., 2010]. Physical training lowered the lactate level and approved pro-oxidant status in adults with DS [Aguiar et al., 2008]. In another study of pro-oxidant state in children with DS, the CoQ10 ratio was normalized by supplementation with ubiquinol-10 administration [Miles et al., 2007]. Because these studies have not provided a unifying outcome, further investigation of oxidative stress for the treatment of dementia in DS is needed.

The current clinical trial was designed to test the hypothesis that a combination of antioxidants with a mitochondrial cofactor would lead to either to stabilization or improvement in cognitive functioning for demented adults with DS. The rationale for the selection of the components was based upon work using a canine model of aging that accumulates beta-amyloid neuropathology and oxidative damage along with cognitive decline similar to middle-aged adults with DS [Cotman and Head, 2008]. An antioxidant diet consisting of cellular antioxidants (alpha-tocopherol and ascorbic acid, fruits and vegetables) along with mitochondrial cofactors (alpha-lipoic acid and L-carnitine) resulted in improved cognitive ability and evidence for maintenance of cognition over a 2-year period of time [Head et al., 2002; Milgram et al., 2005]. In parallel, antioxidant-treated dogs showed improved mitochondrial function and reduced oxidative damage [Opii et al., 2008; Christie et al., 2009] and interestingly, reduced amyloid plaque loads [Pop et al., 2010]. However, lipoic acid, while decreasing oxidative stress markers in mice overexpressing APP, did not result in cognitive improvement or a reduction in endpoint beta-amyloid load [Siedlak et al., 2009].

The current pilot trial was intended to determine the feasibility, tolerability, safety, and efficacy of using alpha-tocopherol, ascorbic acid, and alpha-lipoic acid to treat dementia in individuals with DS.

METHODS

This clinical trial was a randomized, double-blind, placebo-controlled study of selected antioxidants over a 2-year treatment period.

Eligibility Requirements for Participants

Inclusionary criteria for this study included a karyotype diagnosis of trisomy 21 or the Robertsonian translocation form of DS. In addition, participants were required to have existing psychological test records indicating their pre-dementia level of intellectual function. The diagnosis of dementia was made by employing DSM-IV criteria [Strydom et al., 2007]. The diagnosis of dementia required a clinical and neurological examination showing deficits in 2 or more areas of cognitive functioning, and progressive worsening of cognitive performance compared to the potential participant's baseline functioning. Potential participants were required to have a stable medical condition for at least 3 months prior to the study and to have an absence of systemic disorders that might confound a diagnosis of dementia. Medication usage including psychotropic and Parkinsonian drugs was required to be stable for 3 months prior to study. Any potential participant needed to be willing and able to take an acetylcholinesterase inhibitor for the treatment of dementia along with the study medication. English speaking skills to facilitate neuropsychological testing was required. The final inclusionary decision was based upon a consensus opinion following a comprehensive evaluation of collected data.

Exclusionary criteria were comprised of inability to meet all of the above inclusionary criteria in addition to known hypersensitivity to any of the study supplements, or unwillingness to follow the protocol.

Study Setting

The study took place at two ambulatory clinic sites of the General Clinical Research Center at the University of California, Irvine-one at the Medical Center in Orange, CA and the other in Irvine, CA. Participants were recruited from Orange County and contiguous areas. Study participants lived semi-independently in their family home or within community care residential facilities. No participants were recruited from residential developmental institutions. The study was approved by the Institutional Review Board at the University of California, Irvine. An independent Data and Safety Monitoring Board consisting of a research nurse, pharmacist, neurologist, and biostatistician monitored the study.

Interventions

Participants were randomly assigned to either an oral placebo or an oral form of the study compounds. The daily dose of the study compounds consisted of 900 IU of alpha-tocopherol, 200 mg of ascorbic acid along with 600 mg of alpha-lipoic acid to be taken as one capsule at breakfast and two capsules at the evening meal. Each participant received a standard multivitamin tablet once daily. All participants received an acetylcholinesterase inhibitor as standard treatment for dementia.

Outcomes

The neuropsychological outcome assessments consisted of both informant and performance based measures. The primary informant measure was *The Dementia Questionnaire for Mentally Retarded Persons* (DMR) [Evenhuis, 1992, 1996] which was administered as a questionnaire by means of a structured interview. Simple “yes,” “no,” or “sometimes” answers are given to 50 items. The questionnaire is designed for longitudinal measurements but absolute cut-off scores are provided for diagnosis on the basis of a single administration. For our primary outcome measure we used the sum of cognitive scores (DMR SOC) that measured the functional domains of short-term memory, long-term memory, spatial and temporal orientation. The sum of social scores was used as a secondary outcome measure (see below). The primary performance measure was *The Severe Impairment Battery* (SIB) [Panisset et al., 1994] which is a 57 item scale with a range of scores between 0 and 100 points developed to assess participants with moderate to severe dementia. The scale assesses nine domains: attention, language, orientation, memory, praxis, visuospatial ability, construction, social interaction and orientating to name. Since items are single words or one-step commands combined with gestures, non-verbal responses are allowed thus decreasing the need for language output. Lower scores indicate greater cognitive impairment. The SIB has been shown to both test and re-test and criterion validity in an adult population with DS.

In addition to the above primary endpoints we also considered several secondary outcome measures. The Sum of Social Scores on the DMR (DMR SOS) was used to measure the functional domains of speech, practical skills, mood, activity and interest as well as behavioral disturbance. The *Vineland Adaptive Behavior Scales* (VABS) [Sparrow and Cicchetti, 1984] is an informant-based scale covering domains of communication, daily living skills, socialization, motor skills, and maladaptive behavior. The VABS provides a composite score reflecting an individual’s overall functioning. It has been widely used and validated in the DS population. While not developed as a measure of dementia, the importance of adaptive behavior deficits in the early manifestations of AD in DS warrant its inclusion in this study. The scales are administered by a trained observer to the parent or care-giver. Domain raw scores for the communication, daily living skills, socialization, and

motor skills domains were used in the secondary outcome analysis. *The Bristol Activities of Daily Living Scale* (BADLS) was administered as an informant based interview. The measure provides an assessment of the abilities of demented participants to complete every day activities. This measure is brief and sensitive to change [Bucks et al., 1996]. *The Brief Praxis Test* (BPT) [Dalton and Fedor, 1997] which uses 20 items to assess major cognitive symptoms with sensitivity to a wide range of dementia severity, high inter-rater and test–retest reliability and sensitivity to changes over time. The BPT has been chosen as the primary outcome measure in a multicenter trial of alpha-tocopherol for adults with DS with or without dementia [Sano et al., 2005].

Randomization and Blinding

At the end of the baseline visit, each participant received either treatment or placebo preparations. A simple one to one randomization scheme (computerized random numbers) was used to assign participants to either the treatment or placebo group. The antioxi-dant supplements for the treatment group were manufactured in capsule form and were identical in appearance to the placebo capsules. They were dispensed in numerically coded bottles. The allocation sequence was concealed from participants and all members of the research team for the entire duration of the study.

Clinical Trial Protocol

Screening took place 2–4 weeks prior to the baseline examination. At the screening visit, a neurological examination and history was carried out to confirm that each potential participant met the DSM-IV criteria for dementia as defined above. Demographic data was obtained and the inclusion/exclusion criteria were applied. At the baseline visit, the neuropsychological battery was administered, baseline alpha-tocopherol levels were obtained and the antioxidant supplement or placebo was given to the participant/care-giver. Return study visits were carried out at 6, 12, 18, and 24 months. At each visit, the following assessments were carried out: general and neurological examination, alpha-tocopherol levels, and the neuro-psychological battery. Standard pill counts of remaining capsules from returned bottles were conducted at each visit post baseline. Medication compliance was assessed by calculating the number of removed capsules and then dividing the number of capsule taken by the number prescribed. A 70% adherence rate was required at each visit for participants to be included in the efficacy analysis. Alpha-tocopherol levels in plasma were determined using High Performance Liquid Chromatography analysis and outsourced to a commercial laboratory [Hess et al., 1991]. Ascertainment of adverse events and serious adverse events (SAE) was carried out at each of the study visits and during interim phone calls from study entry through 30 days post end of study visit. Adverse events were graded on a 3-point scale indicating a mild, moderate, or severe event. Mild was defined as discomfort but no disruption of daily activity. A moderate adverse event resulted in discomfort sufficient to reduce or affect daily activity. A severe event was defined as incapacitation and/or inability to sustain daily activities. For each potential adverse event, causality related to study participation was evaluated by the temporal course in relation to the initiation of the trial, the actual course of the adverse event, whether the potential adverse event was known to be associated with study treatment, and the evaluation of risk factors that could contribute to the event. At regular intervals throughout the study, a meeting of the Data and Safety Monitoring Board was convened to evaluate serious adverse events and any association with group assignment. This analysis was carried out by an independent statistician with investigators blinded as to the groups. Adherence to supplement regimen was assessed with standard pill counts and measurement of alpha-tocopherol concentration in plasma.

Statistical Methods

To address the a priori hypothesis that taking antioxidant supplements would stabilize or improve cognitive functioning in demented individuals with DS, the primary analysis compared the slope of each primary outcome by treatment group. Generalized Estimating Equations [Liang and Zeger, 1986] was used to estimate the longitudinal effect of treatment by fitting a model that includes an intercept, a time term (measured by 1/2-year), a treatment indicator, and treatment-time interaction. In this case, a test of the interaction between treatment and time is equivalent to a test of equality of slopes in the outcome by treatment group. All reported inference was based upon robust standard error estimation [Huber, 1967]. To further investigate potential non-linear changes in each outcome, we also considered secondary analyses of the 1- and 2-year change from baseline (for DMR SOC or SIB) as the response, adjusting for baseline score, with robust standard errors [Huber, 1967] used for inference. In addition, all secondary endpoints were analyzed using the above approach. Serious adverse events were summarized via frequencies and percents.

Sample Size and Statistical Power

Based on the observed sample size, drop-out rate, and standard errors, the trial was designed to attain 80% power when the true mean difference in 1- and 2-year DMR SOC comparing treatment to control is 6.60 and 12.17, respectively. Similarly, the trial was designed to attain 80% power when the true mean difference in 1-and 2-year SIB comparing treatment to control is 21.12 and 17.34, respectively.

RESULTS

The demographic characteristics of the study population are presented in Table I. The average age of the participants was 50 years in both groups. Based upon a review of psychological testing records, 65% of the controls and 74% of the treatment group were in the mild to moderate range of intellectual disability prior to the onset of dementia. In the control group, 35% were in the severe to profound range of intellectual disability, whereas 22% of the treatment group was in this category; a difference which was not statistically signifi-cant at the 0.05 level. Figure 1 displays a flow diagram that describes participant participation from screening until the end of study. Twenty-seven participants initiated the antioxidant supplement and 26 initiated placebo. 85% of participants in both groups remained on study at the 1-year study visit. Sixteen participants (62%) in the treatment group and 15 participants (56%) in the placebo group remained on study at the 2-year study visit. The reasons for attrition included refusal to participate, use of disallowed concomitant medications, and death.

From pill counts, mean treatment compliance throughout the study was 91.9% for the treatment group and 90.4% for the placebo group. After 1 year on study, plasma levels of vitamin E increased on average 103.7% and 12.6% from baseline for the treatment group and control group, respectively. At the end of the second year, vitamin E increased on average 87.4% and 14.9% from baseline for the treatment group and control group, respectively. Alpha-tocopherol levels for both groups at each study epoch shown in Figure 2. The results for the primary and secondary analyses of the co-primary endpoints are presented in Table II. No effect of the antioxidant supplement is identified.

Specifically, the estimated change in population trajectory (slope) of DMR SOC comparing treatment to control is 0.34 points per 1/2-year (95%CI: −1.39, 2.07); this difference is not statistically significant ($P = 0.70$). Similarly, the estimated change in slope of SIB comparing treatment to control is 1.10 points per 1/2-year (95%CI: −3.40, 5.59); this difference is not statistically significant ($P = 0.63$). In addition, we estimate the average

difference in 1-year change in DMR SOC to be 1.69 points (95%CI: −2.92, 6.31) comparing the treatment group to the control group, adjusting for baseline DMR SOC score; this difference is not statistically significant ($P = 0.47$). The average difference in 2-year change in DMR SOC is estimated to be 3.71 points (95%CI: −4.81, 12.22) comparing the treatment group to the control group, adjusting for baseline DMR SOC score; this difference is not statistically signifi-cant ($P = 0.39$). The average difference in 1-year change in SIB is estimated to be −9.08 points (95%CI: −23.86, 5.70) comparing the treatment group to the control group, adjusting for baseline SIB score; this difference is not statistically significant ($P = 0.23$). The average difference in 2-year change in SIB is estimated to be −1.51 points (95%CI: −13.65, 10.63) comparing the treatment group to the control group, adjusting for baseline SIB score; this difference is not statistically significant ($P = 0.81$).

A similar analysis for all secondary endpoints is presented in Table III. The difference in slope and adjusted difference between groups at 1- and 2-year can be interpreted similarly to those for the co-primary outcomes of Table II. In summary, no effect of the antioxidant supplement is identified in any of the secondary endpoints except for the 2-year difference of VABS motor skills. The number of subjects used in estimation for each endpoint (test score) and each analysis are not constant due to drop-outs and inability to test as determined by the test giver. For the DMR Cognitive, 45, 31, and 53 participants were used in the 1-year difference analysis, 2-year difference analysis, and time trend analysis, respectively. Similarly, for SIB total score, 26, 18, and 45 participants respectively were used in the 1-year difference analysis, 2-year difference analysis, and time trend analysis, respectively. The disparity in numbers of completed SIB (performance-based) and DMR (informant-based) in both years 1 and 2 is explained by the inability of participants to perform the tests. This is also the case for the secondary endpoints. Disparity in sample size also exists from the secondary analysis presented in Table III.

The number of participants in each group that experienced at least one SAE, along with the type of SAE, is presented in Table IV. The estimated difference in the proportion of participants in each treatment group that experienced at least one SAE is 0.096 (95%CI: −0.210, 0.402); is not statistically significant at the 0.05 level. The estimated difference in the proportion of participants in each treatment group that experienced at least one seizure is 0.191 (95%CI: −0.124, 0.505); and is not statistically significant at the 0.05 level. In the treatment group, among those participants with AD associated seizure disorder, 6 of 12 participants had at least one seizure prior to enrolling the study. While in the control group, five of seven participants had a seizure before entering the study.

DISCUSSION

Brief Synopsis of Findings

This study showed that it is feasible to carry out a 2-year clinical intervention trial using an antioxidant supplement for dementia in DS. There was no therapeutic effect of the supplement based upon multiple endpoints (test scores) and modes of differences (longitudinal, 1- and 2-year differences). We do not draw any conclusions from finding one significant difference in VABS motor skills reported in the secondary analysis. We suspect that this difference cannot be replicated in an independent study. We only present the results for completeness. Alpha-tocopherol levels rose in the treated group indicating compliance with the regimen. Further, no attributable serious safety events were encountered in the course of the trial and attrition occurred non-differentially across study groups.

Possible Mechanisms and Explanation of Results

Despite the strong evidence that oxidative stress is a feature of DS, treatment with a high-potency antioxidant supplement did not result in either clinical improvement or stabilization of the dementia course. Our analysis evaluated both short and long term effects of treatment but did not find significant differences between study groups. Because of the randomized nature of the study and our small sample size, we did not stratify treatment versus placebo groups in regard to the occurrence of seizures, although seizures were slightly more frequent in the treatment group; though the difference was not statistically significant.

The lack of response to treatment once dementia has been diagnosed in individuals with DS may be related to structural developmental abnormalities in the brains of those with this disorder. These abnormalities include fewer neurons, decreased neuronal densities, and abnormal neuronal distribution in cortical layers II and IV [Raz et al., 1995; Pinter et al., 2001]. These abnormalities appear to correlate with the baseline learning and memory deficits in DS and may be responsible for a lack of treatment-responsive brain reserve. Another potential reason for the lack of observed efficacy of antioxidant supplementation may relate to the combination of antioxidants used or the dosage of individual antioxidants. Combinatorial antioxidant supplementation has been useful in vitro to protect neuroblastoma cells from the toxic effects of beta-amyloid [Dhitavat et al., 2005]. Yet even combinatorial antioxidants may not attain sufficient concentration within the central nervous system in order to exert therapeutic efficacy in neuronal cytosol [Polidori et al., 2004]. The selection of antioxidants used in this study was determined, in part, from efficacy studies in a canine model for brain aging [Christie et al., 2009]. In the canine studies, treatment with an antioxidant enriched diet resulted in improved cognitive functioning within 2 weeks, an improvement that was sustained over the 2 years course of study [Milgram et al., 2005]. The antioxidant diet included 800 IU of alpha-tocopherol, 16 mg ascorbic acid, and 26 mg of alpha-lipoic acid daily with dogs averaging 10 kg in weight [Cotman and Head, 2008]. Compared to this current trial, dogs were receiving signifi-cantly higher doses by weight of the antioxidants. Thus, dose could be a critical factor in determining whether cognitive benefits were observed in our study population.

Compliance with the supplementation regimen is seen in the alpha-tocopherol levels which rose significantly reflecting compliance with the regimen by the treatment group. The approximate doubling of the alpha-tocopherol level with the dosage employed in this study (900 IU) is consistent with the plasma dose–response curve shown in other studies [Pappert et al., 1996].

The potency of the isomeric form of alpha-tocopherol may determine its antioxidant effectiveness [Gutierrez et al., 2009] and in this study the isomeric form used might not be the most potent. The gamma-form of the vitamin has been shown to have greater antioxidant effect than the alpha-form [Devaraj et al., 2008]. In fact, there is some evidence that the alpha-form of the vitamin may suppress the biological effect of the gamma form [Handelman et al., 1985; Huang and Appel, 2003]. The response to alpha-tocopherol is confounded further by observations suggesting that in non-responders, the vitamin may act as a pro-oxidant and worsen the effects of oxidative stress [Bowry et al., 1992, 1995; Abudu et al., 2004; Lloret et al., 2009].

Ascorbic acid functions as an antioxidant which protects lipids from oxidative damage induced by peroxyl radicals [Frei, 1991; Niki, 1991]. The combined administration of alpha-tocopherol and ascorbic acid is thought to induce an antioxidant effect by exporting an alpha-tocopherol radical away from lipid membranes [Suarna et al., 1995; Neuzil et al., 1997]. This function appears to stabilize the concentrations of alpha-tocopherol in plasma [Bruno et al., 2006].

Another mechanism for the lack of antioxidant effect in individuals with DS and dementia may relate to the age of onset of oxidative stress. In DS brain, “intact” appearing neurons within early senile plaque formation contain fodrin cleavage products, a manifestation of caspase activation and potential apoptosis [Cotman et al., 2002]. Apoptotic cell death has been reported in the hippocampus of fetuses with DS [Guidi et al., 2008] and there is an activation of caspase-induced mitochondrial dysfunction in cultured fetal cells in DS [Helguera et al., 2005]. These findings suggest that antioxidant intervention to preserve brain health in DS may need to start earlier in life, before the onset of dementia.

Comparison to Other Studies

We have been unable to find other published clinical trials of antioxidant treatment for dementia in adults with DS. Our results are similar to those reported in antioxidant trials for AD in the general population in which treatment with alpha-tocopherol showed no clear beneficial effects on cognition. In a literature review assessing the efficacy of alpha-tocopherol to either treat AD in the general population or to prevent the progression of mild cognitive impairment to AD, it was determined that those treated with alpha-tocopherol were less likely to reach endpoints of death, institutionalization, severe loss of daily skills, or a diagnosis of severe dementia than those receiving placebo [Isaac et al., 2008]. However, there was no recognizable benefit on cognition following these alpha-tocopherol trials. A small open-label study of alpha-lipoic acid in patients with AD showed some stabilization of cognitive decline suggesting that a phase 2 trial was indicated [Hager et al., 2007]. Oxidative stress and DNA damage were not diminished after a 6-month trial of ascorbic acid (1,000 mg) and alpha-tocopherol (400 IU) in healthy elderly adults [Retana-Ugalde et al., 2008]. Reducing oxidative stress and the complexity of the redox system may not be sufficient in overcoming the other contributing factors that foster the manifestations of AD [Lee et al., 2010].

In a general population study of elderly individuals living in a rural southeastern US county, neither baseline use of ascorbic acid or alpha-tocopherol nor high dose regimens of these vitamins appeared to delay the incidence of dementia or AD [Fillenbaum et al., 2005]. In a study of 2,969 participants age 65 years or older, supplemental ascorbic acid or alpha-tocopherol either alone or in combination did not reduce the risk of dementia or AD [Gray et al., 2008]. In a large study of healthy women, addition of alpha-tocopherol (600 IU) did not provide significant cognitive benefits [Kang et al., 2006]. In a study of individuals with DS between 18 and 45 years, neither activities of superoxide dismutase or glutathione peroxidase were related neither to elevated markers of lipid peroxidation or to cognitive performance [Strydom et al., 2009]. Contrary to expectations low ratios of superoxide dismutase 1 to glutathione peroxidase were associated with worse memory ability suggesting that the relationship of oxidative stress to cognitive outcome in DS is complex.

STUDY LIMITATIONS

Given the paucity of clinical trials for dementia in DS, this pilot trial focused on feasibility as well as potential efficacy with respect to cognitive outcomes. While baseline intellectual disability is a potential confounder in the diagnosis of AD, our use of DSM-IV criteria proved to be accurate for determining dementia. All of the patients who were considered to be demented at baseline were scored as demented on the DMR, an informant measure of cognitive and social functioning. The attrition rate of 47% was higher than we expected but in keeping with trials for dementia in the general population with AD [Gutierrez et al., 2009]. Attrition rate in a 2-year study of cholinesterase inhibitors for AD in the general population was approximately 16%, a rate considerably lower than ours perhaps due to the fact that only mild to moderate cases were enrolled [Gardette et al., 2010]. Attrition rate in a

study of a national study of a secondary prevention trial for AD in the general population was 30% for NIH-funded research centers [Edland et al., 2010].

CONCLUSION AND IMPLICATIONS

Individuals with intellectual disability including those with DS are exposed to many forms of alternative therapies and often receive vitamins as well as other antioxidants [Brown and Patel, 2005]. The need to provide controlled clinical trials for individuals with intellectual disability have been recently emphasized [Anon, 2010]. Our study shows that clinical trials for dementia in DS, although challenging, are feasible. Future investigations may focus on the use of antioxidants at earlier age epochs in DS and/or the development of new methods to control oxidative stress in the disorder. We agree with the conclusions of Strydom et al. [2009] that, while oxidative stress is clearly implicated in the cognitive phenotype of DS, much more research needs to be done before it will be possible to select efficacious antioxidants.

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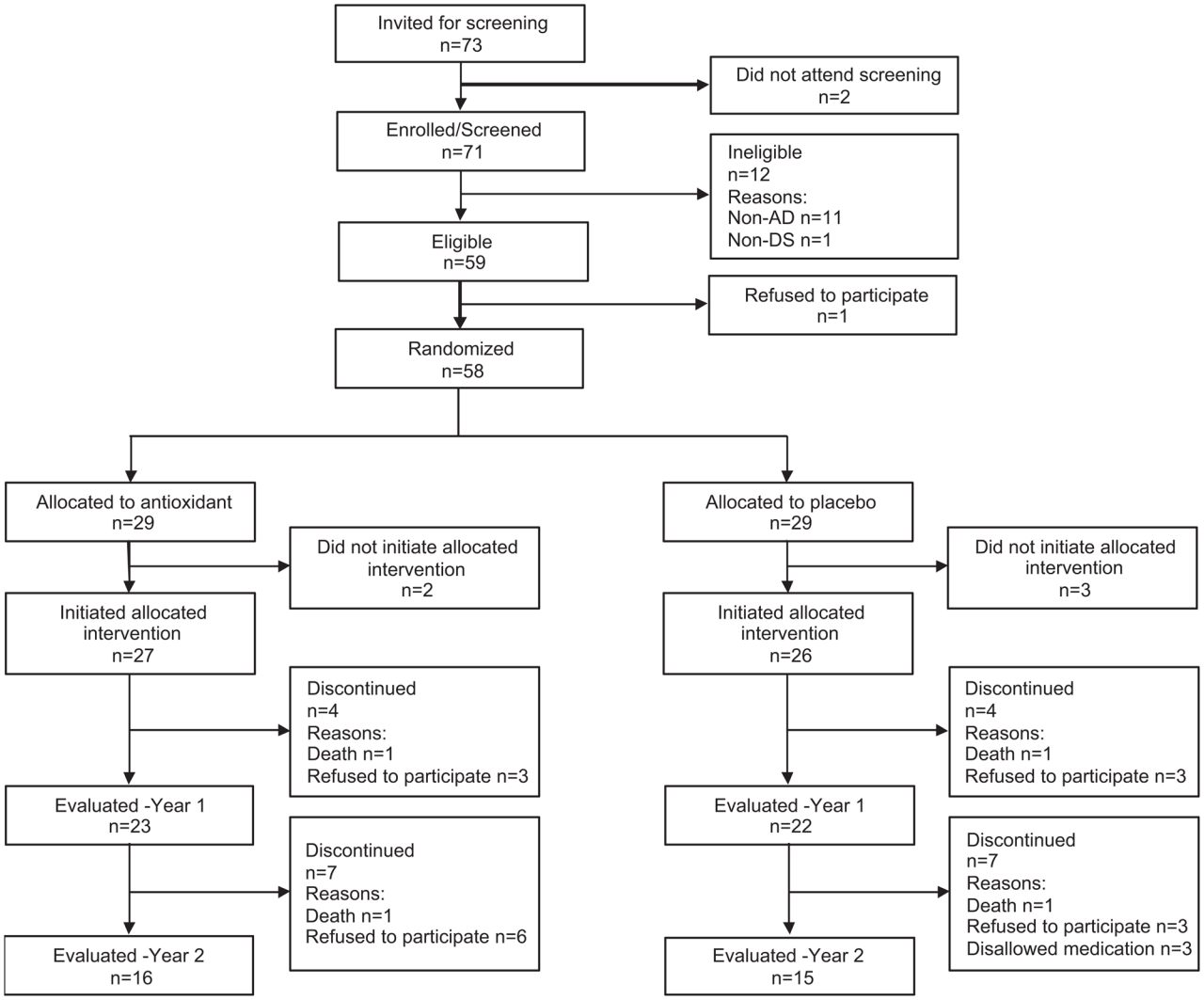

FIG. 1.
Trial profile.

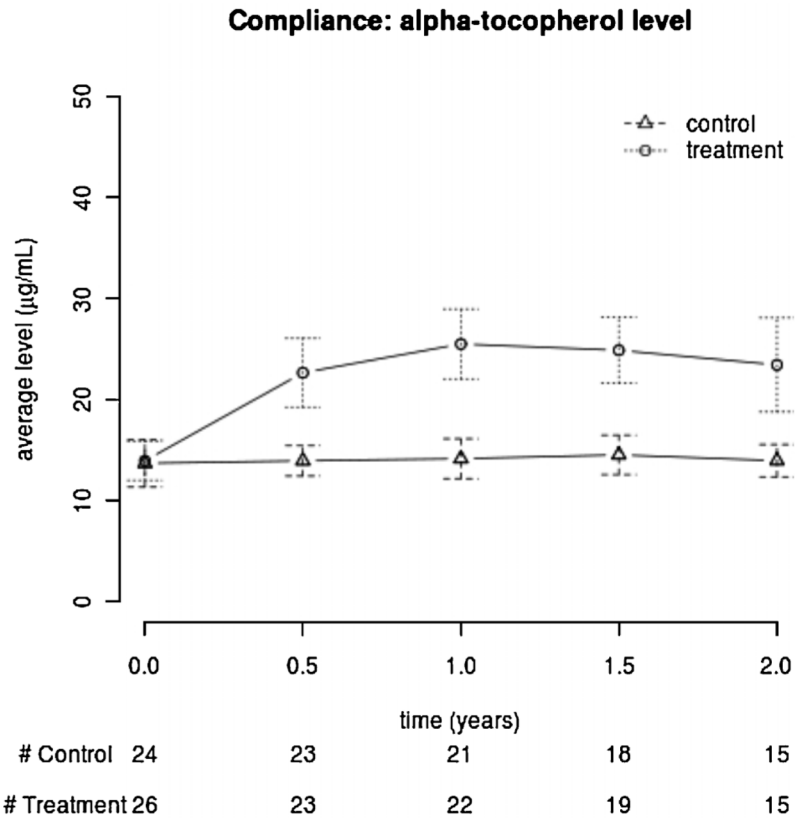

FIG. 2.
Elevated levels of the alpha-tocopherol in the treatment group indicate the compliance with the regimen.

TABLE I

Demographic Characteristics of Study Population by Group At Baseline

Variable	Control (n = 26)	Treatment (n = 27)
Age (years)	50.65 ± 4.50	50.63 ± 4.88
Gender		
Female	11 (42%)	17 (63%)
Male	15 (58%)	10 (37%)
Race or ethnicity		
White or Caucasian	21 (81%)	25 (93%)
Hispanic or Latino	3 (12%)	2 (7%)
American Indian or Alaska Native	1 (4%)	0 (0%)
Asian	1 (4%)	0 (0%)
Premorbid level of cognitive impairment		
Mild	4 (15%)	10 (37%)
Moderate	13 (50%)	10 (37%)
Profound	2 (8%)	0 (0%)
Severe	7 (27%)	6 (22%)
Unknown	0 (0%)	1 (4%)
ApoE		
2/2	1 (4%)	0 (0%)
2/3	4 (15%)	3 (11%)
2/4	0 (0%)	2 (7%)
3/3	11 (42%)	16 (59%)
3/4	9 (35%)	5 (19%)
4/4	1 (4%)	1 (4%)

Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as counts and proportions.

TABLE II

Rates of Change in Primary Efficacy Outcome Measures

Assessment	Time trend	*P*-Value	1-year diff.	*P*-Value	2-year diff.	*P*-Value
DMR SOC	0.34 (−1.39, 2.07)	0.70	1.69 (−2.92, 6.31)	0.47	3.71 (−4.81, 12.22)	0.39
SIB	1.10 (−3.40, 5.59)	0.63	−9.08 (−23.86, 5.70)	0.23	−1.51 (−13.65, 10.63)	0.81

Total score for SIB (performance measure) and DMR SOC (informant measure) were considered as co-primary endpoints. No significant differences were determined between the treatment and control groups. Point estimates, 95% confidence intervals, and *P*-values for each test corresponding to longitudinal time trend (1/2-year), 1-year difference, and 2-year difference interaction comparing the antioxidant treatment to control.

TABLE III

Rates of Change in Secondary Efficacy Outcome Measures

Assessment	Time trend	*P*-Value	1-year diff.	*P*-Value	2-year diff.	*P*-Value
DMR SOS	0.45 (−1.67, 2.56)	0.68	4.24 (−2.10, 10.58)	0.19	4.03 (−5.10, 13.16)	0.39
BPT	−1.96 (−4.97, 1.05)	0.20	−7.97 (−20.21, 4.28)	0.20	−5.59 (−18.89, 7.71)	0.41
BADLS	0.46 (−1.87, 2.80)	0.70	3.14 (−6.26, 12.54)	0.51	4.82 (−4.55, 14.18)	0.31
VABS communication	−3.42 (−6.91, 0.06)	0.05	−0.07 (−9.33, 9.18)	0.99	−14.15 (−28.34, 0.04)	0.05
VABS daily living	−1.93 (−7.31, 3.44)	0.48	0.20 (−14.01, 14.40)	0.98	−13.22 (−32.17, 5.72)	0.17
VABS socialization	−2.75 (−7.37, 1.87)	0.24	−4.22 (−16.76, 8.31)	0.51	−9.94 (−28.67, 8.80)	0.30
VABS motor skills	−2.04 (−4.51, 0.42)	0.10	−1.39 (−9.88, 7.10)	0.75	−12.35 (−23.81, −0.89)	0.03

DMR SOS, BPT, BADLS, and subdomains of VABS were considered as secondary endpoints. No significant differences were determined between the treatment and control groups with the exception of the 2-year difference in VABS motor skills. Point estimates, 95% confidence intervals, and *P*-values for each test corresponding to longitudinal time trend (1/2-year), 1-year difference, and 2-year difference interaction comparing the antioxidant treatment to control.

TABLE IV

Serious Adverse Events Reported in Treatment and Control Groups Over the Study Course

Serious adverse events (# of subjects; %)	Control	Treatment
Any serious adverse event	11 (41%)	14 (52%)
Pneumonia	3 (11%)	7 (26%)
Deep vein thrombosis	2 (7%)	0 (0%)
Pulmonary embolism	1 (4%)	0 (0%)
Seizure	7 (26%)	12 (44%)
Bradycardia	1 (4%)	0 (0%)
Choking	1 (4%)	1 (4%)
Fracture	0 (0%)	1 (4%)
Death	2 (7%)	3 (11%)

The incidence of serious adverse events in both groups is nearly equal and is not attributable to the treatment. The number of participants and proportion in each treatment arm that experienced at least one serious adverse event are reported from the date of randomization until 30 days post-end of study visit. Serious adverse events are also broken down by type.