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Do Children With Falling Blood Lead Levels Have Improved Cognition?

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ABSTRACT. *Objective.* **Exposure to lead at levels encountered by urban children impairs cognitive development. An observational study suggested improvement in IQ when blood lead level fell, but the only randomized trial of chelation showed no benefit in IQ.**

Methods. **We did a new analysis of the data from the clinical trial using change in blood lead level as the independent variable. The 741 children began with blood lead levels between 20 and 44 μg/dL, and were 13 to 33 months old at randomization to chelation or placebo. Blood lead levels were measured repeatedly, and cognitive tests were given at baseline, 6 months, and 36 months follow-up.**

Results. **By 6 months after randomization, blood lead levels had fallen by similar amounts in both chelated and placebo children, despite the immediate drops in the chelated group; there was no association between change in blood lead level and change in cognitive test score. Blood lead levels continued to fall. At 36 months follow-up, in the placebo group only, cognitive test scores had increased 4.0 points per 10 μg/dL fall in blood lead level from baseline to 36 months follow-up and 5.1 points from 6 to 36 months.**

Conclusions. **The improvement in scores in the placebo group only implies that factors other than declining blood lead levels per se are responsible for cognitive improvement; it is possible but less likely that succimer, the active drug, impairs cognition.** ***Pediatrics*** **2002;110: 787–791;** ***child, preschool; environmental exposure; lead poisoning/blood/etiology; cognition/physiology; chelation therapy.***

ABBREVIATIONS. TLC, Treatment of Lead-Exposed Children; MDI, Mental Development Index; SD, standard deviation.

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Prospective data from multiple studies in several countries show that lead exposure insufficient to produce symptoms still results in cognitive deficits in young children. Peak blood lead level, which is usually achieved around 2 years of age, is associated with lower scores on IQ tests administered at 4 years old and later.[1] It is not known whether such effects can be reduced or prevented once exposure has taken place. In an observational study, New York children 13 to 87 months old with blood lead levels between 25 and 55 μg/dL were given chelation with EDTA and therapeutic iron when clinically indicated, then followed for 6 months. Those whose blood lead levels fell the most had improved cognitive test scores, independent of whether they had been given iron or chelation therapy.[2]

The optimism about reversibility of lead-induced cognitive impairment engendered by this study was tempered by an Australian study with longer follow-up. It found small and inconsistent improvement in the IQs of children whose blood lead level fell the most.[3] Most recently, a large formal trial of chelation therapy, the Treatment of Lead-exposed Children (TLC) Trial, showed no benefit on cognitive or neuropsychological testing despite an abrupt reduction in the treated children's blood lead levels.[4] The analysis on which that conclusion was based was an intent-to-treat analysis, which compared the cognitive and neuropsychological test scores in all children assigned to succimer (the oral chelating drug used in TLC) with all children assigned to placebo. The object of intent-to-treat analysis is to test the effect of deciding to treat with active drug, which includes the possibilities that the child cannot or will not take the drug and that it may be ineffective for lowering the blood lead level. Results from an intent-to-treat analysis permit the strongest inference, because with a large sample and randomization, all other differences between the placebo and active drug group except those attributable to the drug should even out.

The New York study, conducted by Ruff and colleagues,[2] was not a formal trial. Children could not be randomized to a greater drop in blood lead level and their cognitive test scores compared. Rather, the differences in children's cognitive test scores between baseline and 6-month follow-up were compared with the differences in their blood lead levels, adjusting statistically for other differences. This kind of study and analysis does not permit experimental inference the way a trial does. If replicated, however,

such observations can be persuasive. We thus attempted to replicate the observed relationship between falling blood lead levels and improved cognitive test scores in a new analysis of data from the TLC Trial. In the previously published intent-to-treat analysis, the independent variable was assigned treatment group: succimer or placebo. The analyses reported here use the observed change in blood lead level of an individual child as the independent variable, and the observed change in cognitive test score as the dependent variable. The analytical approach is modeled closely on the methods used in the New York study.[2] In addition, the TLC study followed children for 36 months rather than the 6 months in New York.

METHODS

Subjects

The data used in this analysis come from the TLC Trial, which was a 780-child, randomized, placebo-controlled, double-blind clinical trial that evaluated the use of the oral chelating drug, succimer, for reducing or preventing lead-associated deficits in cognitive, neuropsychological, and behavioral function. Eligible children were between 12 and 33 months old, had a blood lead level between 20 and 44 μg/dL, and had no more than 2 residences. Three hundred ninety-six were randomly assigned to succimer and 384 to placebo.[5] Iron deficiency, if present, was treated before the child was eligible to be randomized. Succimer or placebo was administered in courses, with each course of therapy lasting 26 days. An additional course of treatment was given to succimer-treated children if they had blood lead levels of 15 μg/dL or higher 2 weeks after the completion of a first or second course of succimer. Children given placebo were randomly assigned to 1, 2, or 3 courses in the same proportion as in the succimer group. All children had home clean-up and were given vitamin and mineral supplements.[6]

Measurements

Measurements of blood lead levels were scheduled twice before randomization, and then on days 7, 28, and 42 after the beginning of each course of treatment. After treatment was stopped, blood lead levels were measured every 3 to 4 months. We used the second of the prerandomization blood lead levels as the baseline. Before treatment began and at 6 months of follow-up, we administered the Bayley Scales of Infant Development II,[7] the current version of the most widely used scales of infant development. At 36 months of follow-up, we administered the Wechsler Preschool and Primary Scales of Intelligence–Revised.[8] The psychometricians did not know whether the children had been given succimer or placebo and did not know the children's blood lead levels. The IQ of the caregiver in attendance (the mother for 86% of the children, the father for 4%, and another caregiver for 10%) was assessed during one of the follow-up visits with a short form of the Wechsler Adult Intelligence Scale–Revised.[9] We excluded data from the 39 children tested in Spanish, because the instruments are not standardized in Spanish and, in our hands, the correlations over time in children tested in Spanish are lower.[10] This left 741 children for this analysis.

Statistical Analysis

In the TLC data, blood lead levels fell faster in the treated group, but blood lead levels fell in both groups, and the differences between blood lead levels in children given succimer and those given placebo are primarily confined to the first 6 months after treatment began.[6] In addition, in intent-to-treat analyses, there was no significant difference in any of the psychological test scores between children given succimer and those given placebo.[4] Thus, the scores on the cognitive tests from the 2 treatment groups can be analyzed either within the treatment groups or as a whole, and we present both analyses here.

We verified that blood lead level was related to cognitive test score in the TLC data. We then examined 1) the changes in blood lead levels versus changes in cognitive test scores between baseline and the first 6 months of follow-up, because the New York children whose blood lead levels fell the most showed cognitive improvement at 6 months;[2] 2) the change between baseline and 36 months follow-up, by which time there is no difference between blood lead levels of the children given succimer and those given placebo, although the trajectory over which their blood lead levels traveled are different; and 3) the changes between 6 and 36 months of follow-up, when there is no difference between the blood lead levels by treatment group and the trajectory of the levels in the 2 groups has been the same.

We used the Mental Developmental Index (MDI) score of the Bayley Scales of Infant Development II and Full Scale IQ of the Wechsler Preschool and Primary Scales of Intelligence—Revised, depending on the age of the child. Because both of these tests are scaled to means of 100 and standard deviations of 15, we estimated cognitive test score change by the simple difference in scores at any 2 time points. In the TLC data, the correlations between the MDI and full scale IQ are 0.56 between the baseline MDI and full scale IQ measured 36 months later and 0.64 between MDI measured 6 months after baseline and 36 month follow-up IQ. These high correlations imply that, at least over the relatively short time scale of TLC, the 2 instruments are measuring something stable, and make subtraction a plausible way to measure differences.

We did regression analyses of blood lead level and cognitive test score at baseline and at 6 and 36 months of follow-up. The terms in those models were cognitive test score as the dependent variable; closest blood lead as the independent variable; and age of the child, gender, parental education, marital status, employed/unemployed, parental IQ, and number of people in the household as covariables.

We used hierarchical multiple regression to model changes in cognitive test scores with declines in blood lead levels at the 3 different time periods. First, simple regression analysis was performed. Second, the child's age and sex were added to the model. Third, blood lead level at baseline or at 6 months, and MDI score at baseline or at 6 months were added to the second model. This adjusts for the fact that children with higher blood lead levels or higher cognitive test scores might fall farther than children with lower values. Finally, family covariates were added to the third model. The family covariates included parental education, 1 or 2 parents living in household, head of household employed or not, caregiver's IQ, and number of people in the household. This final model is closest to those used in the New York and Australian studies. To examine treatment effects, we performed separate analyses for succimer and placebo groups.

RESULTS

Overall, data from 741 children are included for this report: the mean age at randomization was 24 months (SD = 5.62), 56% were boys, 77% were black, 72% were in single-parent families, 40% of the parents had less than a high school education, 42% of the families had least 1 parent employed, and the mean IQ of the caregivers was 80.0 (SD = 10.9).

Means and Changes of Cognitive Test Score and Blood Lead Levels

Table 1 shows means of cognitive test scores and blood lead levels at baseline and at 6 and 36 months of follow-up for all children and then separately by treatment group. Changes in cognitive test scores were –1.4 from baseline to the 6-month follow-up, –1.5 from baseline to the 36-month follow-up, and 0.1 between 6 and 36 months of follow-up for all children. There were no significant differences between the scores at the different times of follow-up nor were there significant differences by treatment group. Mean blood lead levels were 26.2 μg/dL at baseline, 20.2 μg/dL at 6 months of follow-up, and 12.2 μg/dL at 36-month follow-up. Mean declines in

TABLE 1. Means (SD) of Cognitive Test Scores and Blood Lead Levels at Baseline and Follow-up by Treatment Group, TLC Trial

	Overall			Succimer Group			Placebo Group		
	n	M	SD	*n*	M	SD	*n*	M	SD
Cognitive test score									
Baseline (MDI)	727	82.3	13.8	371	82.9	13.7	356	81.6	13.9
6-mo (MDI)	693	80.7	13.2	352	81.1	13.1	341	80.2	13.2
Δ from baseline	681	−1.4	11.6	347	−1.6	11.6	334	−1.2	11.6
36-mo (IQ)	690	80.7	13.3	352	80.6	13.5	338	80.7	13.1
Δ from baseline	677	−1.5	12.7	347	−2.3	12.6	330	−0.7	12.8
Δ from 6 mo	659	0.1	11.3	336	−0.2	11.5	323	0.5	11.0
Blood lead level (μg/dL)									
Baseline	741	26.2	5.1	377	26.5	5.4	364	26.0	4.8
At 6 mo	667	20.2	7.6	344	19.7	8.7	323	20.8	6.3
Δ from baseline	667	−6.0	7.1	344	−6.8	8.0	323	−5.1**	5.8
At 36 mo	685	12.2	5.2	347	12.3	5.5	338	12.1	4.9
Δ from baseline	685	−14.1	5.7	347	−14.3	6.2	338	−13.9	5.1
Δ from 6 mo	631	−8.0	7.1	323	−7.4	8.3	308	−8.6*	5.7

Δ from baseline indicates change from the beginning of treatment to the specified months of follow-up; Δ from 6 months, indicates change in score from 6 months after the beginning of treatment to the specified months of follow-up.
Note that mean differences may be based on different children than means.
Placebo and succimer group means differ: * $P < .05$, ** $P < .01$, Student *t*-test.

blood lead levels were 6.0 μg/dL from baseline to 6-month follow-up, 14.1 μg/dL from baseline to 36-month follow-up, and 8.0 μg/dL from 6- to 36-month follow-ups. Blood lead levels declined more quickly in the first 6 months in the succimer group than in the placebo group ($P < .01$), but the mean blood lead levels were very similar at baseline and at 36-month follow-ups.

Cognitive Test Scores by Current Blood Lead Level

After adjustment for the terms given in the Methods section, the coefficients for the current blood lead level at baseline and 36 months of follow-up were very close to each other and to the value predicted from the literature: for each 10 μg/dL increase in blood lead level, cognitive test score decreased by 3.2 points (standard error 0.1; $P < .001$) at baseline and 3.3 points (standard error 0.1; $P < .001$) at the 36-month follow-up. At the 6-month follow-up visit, however, using the same model, the coefficient was much smaller (0.4 points per 10 μg/dL blood lead level) and not significant.

Change in Cognitive Test Scores by Change in Blood Lead Level

Table 2 shows regression coefficients and standard errors for the effects of a change in blood lead level (in μg/dL) on changes in cognitive test scores for the 3 different periods of follow-up, the associated *P* values, and the R^2 (ie, percentage of the variance explained by the model). The simpler models explained little of the variance, and *P* values for all of the hypothesized contrasts were large. The full model, which adjusted for the terms given in the "Methods" section, explains substantial variance and is the closest possible to the model used in the New York study,[2] so we present only results for it. The slope estimates from this model, however, are similar to those from the simpler models. From baseline to 6 months, we found no effect overall of changing

TABLE 2. Regression Coefficients* for Increase in Cognitive Test Score by Decrease in Blood Lead Level From Baseline to 6-Month Follow-up, Baseline to 36-Month Follow-up, and 6-Month to 36-Month Follow-up

	Overall	Succimer Group	Placebo Group
Baseline to 6-mo follow-up			
No. of children	613	315	298
β for Δ BPb (SE)	0.00 (0.06)	0.05 (0.07)	−0.08 (0.10)
P value	0.951	0.431	0.397
R^2	0.335	0.337	0.364
6-mo to 36-mo follow-up			
No. of children	590	299	291
β for Δ BPb (SE)	0.28 (0.09)	0.18 (0.12)	0.51 (0.13)
P value	0.001	0.122	<0.001
R^2	0.274	0.244	0.342
Baseline to 36-mo follow-up			
No. of children	638	322	316
β for Δ BPb (SE)	0.22 (0.09)	0.08 (0.12)	0.40 (0.14)
P value	0.015	0.495	0.003
R^2	0.338	0.318	0.393

SE indicates standard error.
* The model has change in cognitive test score as the dependent variable, and includes terms for decline in blood lead level, gender and age of the child, blood lead level at baseline or 6 months of follow-up, MDI at baseline or 6 months follow-up, caregiver's IQ, parent's employment (employed 1, unemployed 0), parent's education (less than college 0, college and over 1), parent's marital status (unmarried 0, married 1), and number of people in the household.

blood lead level on change in cognitive test score—the slope is estimated to be 0.0 points per 10 μg/dL change in blood lead level ($P = .95$).

For follow-up from baseline to 36 months and from 6 months to 36 months, however, falling blood lead level was associated with increased cognitive test scores, but only because of an association in the placebo group. Cognitive test scores increased by 2 points overall and 4 points in the placebo group when blood lead levels declined by 10 μg/dL from baseline to 36 months. From 6 to 36 months, cognitive test scores increased by 3 and 5 points overall and in the placebo groups, respectively. The overall and placebo group slopes were all significant at $P = .02$ or less. The slopes in the succimer group were small and not significant (Table 2). We also tried a nonlinear approach and found similar results (Fig 1). We also did all analyses including the 39 children tested in Spanish and got essentially identical results (data not shown).

DISCUSSION

This analysis of the TLC trial data using techniques for observational studies failed to replicate the finding of Ruff et al[2] that a fall in blood lead level over the first 6 months of follow-up was associated with improved cognitive test scores. The children studied are similar: mean baseline MDI was 77 in New York and 82 in TLC, and IQ was 84 in New York and 81 in TLC. Mean maternal IQ in New York was 89, and 80 in TLC. The families in New York had low socioeconomic status and a high prevalence of prenatal or perinatal complications and were considered "disadvantaged and at risk for developmental delays" by the authors.[2] The children in TLC were similarly disadvantaged: 97% were receiving public assistance, and 72% lived in single parent households.[4] The New York children were older, up to 87 months at baseline; the TLC children were ≤68 months old even after 36 months of follow-up. Although the New York families were more often Hispanic than those in TLC (57% vs 5%), the findings from this analysis were unchanged by the inclusion of the children tested in Spanish. It is not clear how the inclusion of the Hispanic families in the New York study could have produced the effects seen.

Higher blood lead levels were associated with lower IQs in the TLC data at baseline, when the children were ~2 years old, and at 36 months of follow-up, when they were ~5 years old. The size of this association, 3 IQ points per 10 μg/dL blood lead, is what is commonly found in the literature.[1] There is not a relationship at 6 months of follow-up, when blood leads have been changing relatively rapidly,

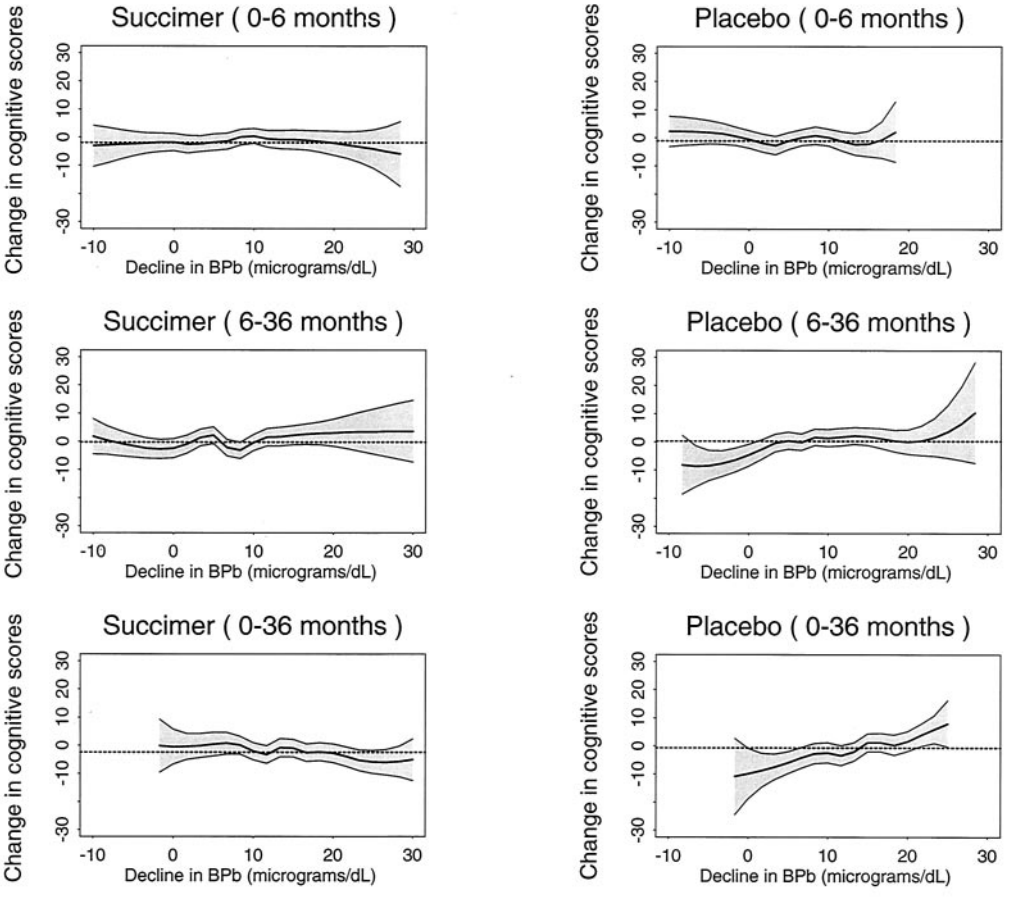

Fig 1. Increase in cognitive test score by decline in blood lead level using a moving average smooth, with estimated 95% confidence band.[12] The dotted line's *x*-intercept is at the mean cognitive test score change. It has a slope of 0, and therefore represents the null hypothesis of no relationship between change in cognitive test score and change in blood lead level. Based on 741 total children from the TLC Trial, 1994–2000.

perhaps because it takes longer than 6 months for the relationship to reemerge.

The results from following the children for 36 months, when they are ~5 years old, showed improved test scores with greater falls in blood lead level in the placebo group. This finding was absent in the succimer-treated children, raising the possibility that the drug regimen blunted the beneficial effect. The most likely mechanism, however, by which succimer would exert such toxicity would be to increase brain lead by making it easier to transport lead across the blood-brain barrier. Thus far, however, the experimental evidence shows lower brain lead levels in succimer-treated rodents and no change in brain lead in primates.[11] It could also be that eliminating exposure removes lead from the brain, while succimer removes lead from a different compartment such as soft tissue. It could be that eliminating exposure affects plasma lead differently from chelation, but we did not measure plasma lead. For whatever reason, these findings reinforce the result from TLC that chelation therapy is of no proven benefit for children with blood leads levels in the 20 to 44 μg/dL range.

We can speculate on how this result may have arisen. Some families might respond to the diagnosis of excess lead exposure in their children by effective cleaning and also with intellectual stimulation of their child, now identified as at-risk for cognitive impairment. If these 2 things commonly go together, reflecting some general ability for effective parental response to problems, they would produce an artifactual relationship between falling blood lead and increased test scores. Such an effect might not be seen at 6-month follow-up because that is not a sufficient period for increased stimulation to produce better cognitive scores. It would not be seen in the active drug group because the changes in blood lead there have more to do with the drug. However, at 36-month follow-up, those families who are able to effect greater reduction in exposure and provide more stimulating environments for their children now have children with improvement in cognitive performance.

CONCLUSION

This observational analysis of data collected in a large, randomized study of chelation therapy for lead exposure in young children showed no benefit of reduction in blood lead level on cognitive test score over the first 6 months. The study is large enough that, despite a narrow range of blood lead and age, the cross-sectional associations are present between blood lead level and cognitive test scores for 2 of the 3 time points analyzed. At 36-month follow-up, children whose blood lead levels fell the most showed improvement in test scores, but this association may not be attributable to the reversal of the effects of lead, because it was not seen in children whose blood lead level was lowered by chelation. We believe that, because of that inconsistency, the data do not indicate that lead-induced cognitive defects are reversible. Primary prevention and preventing additional increases in blood lead levels among children whose blood lead levels are high remain the only effective means of dealing with lead poisoning.

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