Motor nerve conduction velocity and somatosensory evoked potentials in the newborn and young child in relation to thyroid function

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Somatosensory evoked potentials in very preterm infants in relation to L-thyroxine supplementation

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Abstract

Objective:
To study the effect of L-thyroxine supplementation on neurologic maturation in very preterm infants with transient hypothyroxinemia.

Design:
Randomized, double-blind, placebo controlled L-thyroxine supplementation trial.

Setting:
Level III neonatal intensive care unit.

Subjects:
200 Infants < 30 weeks’ gestational age.

Intervention:
Subjects were randomly assigned to receive L-thyroxine (8 μg/kg birthweight/d) or a placebo during the first six weeks of life.

Methods:
Median nerve somatosensory evoked potentials (SEPs) were recorded, measuring cortical N\textsubscript{1} peak latency at two weeks of age, at term and at six months (corrected) age.

Results:
Cortical N\textsubscript{1} peak latency was not significantly decreased in the L-thyroxine group compared to the placebo group throughout the study period.

Conclusion:
L-thyroxine supplementation during the first six weeks of life did not decrease cortical N\textsubscript{1} peak latency in infants of < 30 weeks’ gestational age.

Key words: electrophysiology, evoked potentials, hypothyroidism, hypothyroxinemia, preterm infant, somatosensory, thyroxine
Introduction

Thyroid hormones are essential for normal brain development.¹ Shortage of thyroid hormones during brain development, as in congenital hypothyroidism, can cause subsequent problems in motor and cognitive development.² ³ Transient hypothyroxinemia is common in preterm infants and has been associated with an increased risk of neurodevelopmental dysfunction.⁴-⁶ It is still unknown whether transient hypothyroxinemia in preterm infants causes a shortage of thyroid hormone at the cellular level in the nervous system as is the case in congenital hypothyroidism and thus requires L-thyroxine supplementation.⁷ ⁹ In patients with congenital hypothyroidism a delay in neurologic maturation is determined by measurement of prolonged latencies in SEPs.¹⁰-¹³ Likewise, in preterm infants with transient hypothyroxinemia recording SEPs could provide new insight into the effects of low plasma T₄ on neurologic maturation at an early stage. We were the first to record SEPs in a randomized, double-blind, placebo controlled trial of L-thyroxine supplementation in 200 infants of < 30 weeks' gestational age.¹⁴ We hypothesized that by L-thyroxine supplementation cortical N₁ peak latency in median nerve SEPs would decrease.

Patients and Methods

We enrolled 200 infants between January 1991 and July 1993. The study size of 200 infants was based on the primary end point of developmental outcome at 24 months.¹⁴ The study was approved by the Research and Ethics Committee of the Academic Medical Center in Amsterdam. Inclusion criteria were gestational age between 25 and 30 weeks and admission to our neonatal intensive care unit within the first 24 hours after birth. Exclusion criteria were severe congenital malformations, maternal endocrine disease and maternal illicit drug dependency. After informed consent of at least one parent, the infants were randomly and blindly assigned to receive either L-thyroxine (8 μg per kilogram birth weight) or a placebo. Trial medication commenced 12-24 hours after birth once daily during the first six weeks of life; initially by intravenous injection as long as parenteral nutrition was given and orally thereafter. In a preliminary study we found that with this dose a physiologic replacement therapy is achieved.¹⁵
Measurement of somatosensory evoked potentials

In each patient SEPs were obtained at two weeks of age (14-17 days), at term age (37-43 weeks PMA) and at six months (corrected) age (63-69 weeks PMA). Postmenstrual age is defined as gestational age at birth plus postnatal age. Corrected age is defined as age corrected for preterm birth, i.e. age from the expected date of birth. SEPs were recorded with a mobile SEP recording machine (Neuropack Four Mini, model MEB-5304K - Nihon Kohden, Tokyo, Japan). Electrical pulses of 0.1 ms duration were delivered at a rate of 1 per 2 seconds. A hand-held device was placed on the ventral wrist overlying the median nerve. The intensity of stimulation used was that which was necessary to produce a minimal thumb twitch. The skin temperature was guaranteed to be above 36°C. Recordings were obtained from the left somatosensory cortex, following stimulation of the right median nerve. In case of an infusion line in the right arm or unilateral brain lesions on the left side, recordings were obtained from the right somatosensory cortex, following stimulation of the left median nerve. Recording was done with silver-silverchloride disk electrodes (diameter 10 mm). The negative electrode was placed over the primary somatosensory area for the upper extremities (C3'/C4', i.e. two cm posterior to C3/C4, according to the international 10 - 20 electrode system). The reference electrode was placed in the midfrontal position (Fz) and one electrode was placed on the lower arm as ground. The skin-electrode resistance was usually kept under 2 and never over 5 kΩ. The analysis time was 200 ms. Thirty to fifty responses were averaged through a bandpass of 2-100 Hz. Each recording was duplicated to show reproducibility. After stimulation of the median nerve, the latency to the peak of the first negative wave (which signals the arrival of the afferent impulse at the cerebral cortex), recorded as cortical N1 peak latency was measured according to the criteria of Desmedt et al.\(^\text{16}\) If a bilobed N1-wave was present the latency to the first prominent peak was determined. All infants were tested without sedation. At two weeks of age, the infant’s behavioral state during recording was noted according to Prechtl.\(^\text{17}\) At term and at six months (corrected) age, the behavioural state was classified as awake or asleep. Furthermore, actual medication was recorded. Each SEP recording took about three-quarters of an hour to complete. All potentials were stored on a disk. Later on they were reassessed and classified for quality according to predefined criteria regarding configuration and reproducibility. If both configuration and reproducibility were good, the quality was considered good. If the configuration was good, but lacked good reproducibility, i.e. two cortical N1 peak latencies with a difference > 10 % of the largest value, the quality was considered moderate. In cases of good or moderate quality the mean
value of the two cortical N\textsubscript{1} peak latencies was used for the analysis. If neither configuration nor reproducibility were good, the quality of the potentials was considered poor. Potentials of poor quality were excluded from statistical analysis.

**Cranial ultrasound**

We did sequential cranial ultrasound examinations of all infants using a mechanical sector scanner (ATL Ultramark 4) with a 7.5 MHz transducer. Ultrasound scans were done before trial medication commenced and on days 5, 14, 28 and 42 or more often if clinically indicated. We classified hemorrhage according to Volpe,\textsuperscript{18} and periventricular leucomalacia according to De Vries et al.\textsuperscript{19} Unilateral hemorrhagic parenchymal involvement evolving in porencephalic cysts were classified as parenchymal hemorrhages. For the classification of ventriculomegaly we followed Levene.\textsuperscript{20}

**Statistical analysis**

Categorical data were analyzed using the Chi-square test for two and multiway tables (BMDP 4F). Continuous data were analyzed using the Student t-test (BMDP 3D). Linear regression analysis (BMDP 1R) was used to study the relationship between L-thyroxine supplementation and cortical N\textsubscript{1} peak latency at three points in time. Possible confounding factors included in the linear regression analysis were infants’ sex, weight class for gestational age,\textsuperscript{21} ethnic origin of the mother, antenatal steroids, asphyxia, cranial ultrasound findings (before trial medication), behavioral state, and PMA. Interaction analysis was done on every confounding factor with L-thyroxine supplementation. The distribution of residuals was checked for skewness. If appropriately, logarithmic transformation was applied.

**Results**

**Patient population**

We enrolled 100 infants in both the L-thyroxine group and the placebo group. Seven infants were withdrawn from the study; four because of severe congenital malformations diagnosed after study entry and three because of parental discomfort about the study.\textsuperscript{14} The data collected from these patients were not excluded from the statistical analysis. On the three consecutive SEP recordings (14-17 days after birth,
37-43 weeks PMA and 63-69 weeks PMA) the initial group of 200 infants was reduced by mortalities (n = 29, 33, 35, respectively), poor clinical condition (n = 8, 4, 2, respectively), or for practical reasons (n = 13, 29, 56, respectively). The main practical reason at 37-43 and 63-69 weeks PMA was parental discomfort with the time-consuming aspect of the SEP recording. We could only obtain recordable SEPs from a few infants of less than 30 weeks PMA. Therefore, at two weeks of age, data of infants less than 30 weeks PMA (n = 67) were excluded. At the first SEP recording (14-17 days after birth), the L-thyroxine group and the placebo group were comparable with respect to baseline characteristics (Table 1). This was the case for all three points in time.

**Somatosensory evoked potentials**

Only SEP recordings of good or moderate quality were analyzed. Causes for a poor quality included unstable clinical condition and local factors as edema, especially during intensive care. Data reduction amounted to 40% (n = 33) at two weeks of age.

**Table 1. Baseline characteristics at first SEP measurement 14-17 days after birth**

<table>
<thead>
<tr>
<th></th>
<th>Thyroxine group (n=43)</th>
<th>Placebo group (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (♂)</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>gestational age (days)</td>
<td>203 ± 5</td>
<td>203 ± 6</td>
</tr>
<tr>
<td>birthweight (g)</td>
<td>1172 ± 190</td>
<td>1240 ± 208</td>
</tr>
<tr>
<td>SGA (&lt;P₁₀)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>maternal ethnic origin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>caucasian</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>antenatal steroids*</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>asphyxia†</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>serum peak concentration of bilirubin &gt; 250 mol/l</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>cerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>grade 3 or 4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>cerebral ischaemia: flaring</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>ventriculomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventricular index &gt; P₉₇</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>ventricular index &gt; P₉₇ + 4 mm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>normal cranial ultrasound</td>
<td>28</td>
<td>21</td>
</tr>
</tbody>
</table>

Values either number or mean ± SD; * two doses of 12 mg betamethasone; † APGAR score < 7 at 5'
7% (n=9) at term age, and 5% (n=5) at six months (corrected) age. After this data reduction, the number of SEP recordings and the baseline characteristics of corresponding patients remained comparable in the L-thyroxine group and the placebo group at the three points in time.

**Cortical N\textsubscript{1} peak latency in relation to L-thyroxine supplementation**

For N\textsubscript{1}-latency at two weeks of age (14-17 days; 30-32 weeks PMA), at term age (37-43 weeks PMA) and at six months (corrected) age (63-69 weeks PMA), we found no statistically significant difference between the L-thyroxine group and the placebo group (Table 2).

**Table 2. Cortical N\textsubscript{1} peak latency (ms) in median nerve SEP in relation to L-thyroxine supplementation**

<table>
<thead>
<tr>
<th></th>
<th>L-thyroxine group</th>
<th>Placebo group</th>
<th>D</th>
<th>D</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-17 days after birth*</td>
<td>68.3 ± 7.8 (n=27)</td>
<td>66.1 ± 8.5 (n=23)</td>
<td>+2.2</td>
<td>+1.0</td>
<td>-3.9 - 5.8</td>
</tr>
<tr>
<td>37-43 weeks PMA</td>
<td>37.5 ± 6.4 (n=67)</td>
<td>38.8 ± 9.7 (n=58)</td>
<td>-1.3</td>
<td>-1.0</td>
<td>-3.6 - 1.7</td>
</tr>
<tr>
<td>63-69 weeks PMA</td>
<td>20.1 ± 1.5 (n=52)</td>
<td>20.1 ± 1.1 (n=50)</td>
<td>0</td>
<td>-0.1</td>
<td>-0.6 - 0.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD; L-thyroxine - placebo; * 30-32 weeks PMA

**Cortical N\textsubscript{1} peak latency in relation to L-thyroxine supplementation and PMA**

Figure 1 shows N\textsubscript{1}-latency in relation to PMA at time of SEP recording in both the L-thyroxine and placebo groups at three points in time. N\textsubscript{1}-latency decreased with the increment of PMA from a mean value of 67 ms at two weeks of age to 38 ms at term age and 20 ms at six months (corrected) age. No significant effect of L-thyroxine supplementation was found at any of the three points in time (Fig. 1).

**Cortical N\textsubscript{1} peak latency in relation to L-thyroxine supplementation, PMA, and possible confounding factors**

After adjusting for possible confounding factors, linear regression analysis gave no additional support for an effect of L-thyroxine supplementation on N\textsubscript{1}-latency at any of the three points in time (Table 2). We found no significant interactions between possible confounding factors and L-thyroxine supplementation. We discarded hyperbilirubinemia as confounding factor. There was no correlation between the serum peak concentration of bilirubin and N\textsubscript{1}-latency at two weeks of age, nor did inclusion or exclusion of the patients with a serum peak concentrations above 250 µmol/l (n=2, both in the placebo
group) change the results of the analyses. Actual medication was also discarded as confounding factor, because in this respect the L-thyroxine and placebo groups were completely similar. We treated all patients with caffeine at the age of two weeks. Throughout the study, no SEP recordings were made during anticonvulsive therapy. Cranial ultrasound findings (before trial medication) were used as confounding factors. However, we did diagnose more hemorrhages (grade 3 or 4: n=9), periventricular leucomalacia (grade 2 or 3: n=3), and ventriculomegaly (ventricular index > P_{97}: n=3) later on in the neonatal period. If ultrasound findings present at two weeks of age or the final summary of ultrasound findings on day 42 were used in the respective analyses, the results remained unchanged. Also, including or excluding behavioral state as a confounding factor, which could be related to L-thyroxine supplementation, had no effect on the results. Finally, logarithmic transformation was applied because of a moderate skewness and different variances of N\textsubscript{1}-latency at the three points in time. This had no effect on the results.

**Subgroup analysis in SEP recordings with good quality**

If we also excluded SEP recordings of moderate quality, a subgroup analysis of the remaining good quality SEPs revealed a prolonged N\textsubscript{1}-latency in the L-thyroxine group (69.3 ± 5.0 ms; n=12) at two weeks of age, as compared to the placebo group (63.2 ± 5.0 ms; n=9). Difference between means, adjusted for covariates: 4.6 ms; 95% CI: 0.1-9.2). At term age, N\textsubscript{1}-latency was similar in the L-thyroxine group (37.8 ± 6.6 ms; n=56) and the placebo group (37.6 ± 8.4 ms; n=44). This was also the case at six months (corrected) age (20.0 ± 1.3 ms; n=49 versus 20.0 ± 1.1 ms; n= 48).
Discussion

This study demonstrated that L-thyroxine supplementation during the first six weeks of life did not decrease cortical N1 peak latency in infants of < 30 weeks' gestational age. This finding can be explained by the transient and for some infants mild character of the hypothyroxinemia. Moreover, transient hypothyroxinemia does not necessarily cause hypothyroidism at the cellular level of the nervous system. Intracellular mechanisms like elevated type II deiodinase activity and increased binding capacity of T3 receptors, may protect the cell from hypothyroidism.22 23 Our finding can be regarded as being in agreement with the finding of Van Wassenaer et al, that L-thyroxine supplementation does not improve neurologic development at the age of two years.14

If, at two weeks of age, only SEPs with good configuration and reproducibility were analyzed, we found a prolonged N1-latency in the L-thyroxine group as compared to the placebo group. At two weeks of age only data of infants of > 30 weeks PMA were used for the analysis. Consequently, these infants were > 28 weeks' gestational age. This is of special interest in relation to the finding of Van Wassenaer et al: in infants of > 27 weeks' gestation the mental-developmental score of the L-thyroxine group is lower than that of the placebo group.14 If the result of our subgroup analysis (only good quality SEPs) is regarded as more reliable than that of the general analysis, then this could support the hypothesis that L-thyroxine supplementation in infants of > 27 weeks’ gestation may be harmful.

First, the dose of L-thyroxine could have been too high for some infants, resulting in intracellular hyperthyroidism. Second, L-thyroxine supplementation may lead to elevated type III deiodinase activity24 and subsequent conversion of T4 to reverse T3 (a not active metabolite of T4) instead of T3, which results in an inadvertent decrease of intracellular T3. Both hyperthyroidism and hypothyroidism may interfere with synaptogenesis.25

It is important to note that abnormal latencies in median nerve SEPs, established in patients with congenital hypothyroidism,10-13 are much more striking than our current findings in very preterm infants with transient hypothyroxinemia. In congenital hypothyroidism, especially in patients with a total deficient thyroxine production despite early initiation of L-thyroxine therapy, the extent and duration of decreased thyroxine levels is generally more serious than in transient hypothyroxinemia in preterm infants. In this study at two weeks after birth plasma thyroxine levels in the placebo group and L-thyroxine group were 89.8 ± 32.3 pmol/l and 121.5 ± 29.3 pmol/l, respectively.14 Furthermore, synaptogenesis and myelinisation within the
central nervous system progress most rapidly near term and after term age, respectively.\textsuperscript{26} This could explain the difference in impact of decreased plasma (free) thyroxine levels between term and preterm infants. It is of interest that also in patients with primary congenital hypothyroidism, overtreatment, like initial undertreatment, may lead to delayed maturation of the SEP and seems to be harmful.\textsuperscript{13} Median nerve SEPs have been studied extensively during the neonatal period.\textsuperscript{27-38} The short latency 'N\textsubscript{1}' component, regarded to reflect the maturation of the nervous system can be affected by many factors. As described in the literature these include behavioral state,\textsuperscript{30} medication,\textsuperscript{31} cranial ultrasound abnormalities,\textsuperscript{32-34} hyperbilirubinemia,\textsuperscript{35} low birth weight,\textsuperscript{36} adaptation to extrauterine life,\textsuperscript{37} and prenatal exposure to betamethasone / thyrotropin releasing hormone.\textsuperscript{38} Our study is the first randomized controlled trial in which cortical N\textsubscript{1} peak latency of median nerve SEP was measured in a large group of very preterm infants and analyzed all these factors as well. N\textsubscript{1}-latency values at two weeks of age (30-32 weeks PMA) and at term age were in agreement with those given in the literature.\textsuperscript{27,28} At six months (corrected) age, N\textsubscript{1}-latency reached a mean value of 20.1 ms. The slight variance and stability of N\textsubscript{1}-latency with increasing age, suggest full maturation of the somatosensory nervous pathway by the age of six months.

We considered the effect of methodological errors or selection bias. Measuring N\textsubscript{1}-latency of median nerve SEP in very preterm infants has its limitations owing to unstable clinical condition and adverse circumstances. Therefore, we excluded SEP recordings of poor quality. Data reduction was the same in both study groups. A larger study group would have decreased the width of confidence intervals, resulting in a more precise estimation of latencies. However, this would not have lead to other conclusions.

Recently, we reported that L-thyroxine supplementation during the first six weeks of life does not increase motor nerve conduction velocity in the ulnar and posterior tibial nerve in infants of < 30 weeks' gestational age.\textsuperscript{39} In the present study, we demonstrated that L-thyroxine supplementation did not cause cortical N\textsubscript{1} peak latency of median nerve SEP to decrease. In both studies, maturational processes as myelinisation and synaptogenesis are not accelerated by L-thyroxine supplementation. Both neurophysiological studies gave us the opportunity to assess the functional impact of L-thyroxine supplementation on the developing nervous system of very preterm infants with transient hypothyroxinemia. More studies are needed to unravel 'the missing link' between transient hypothyroxinemia and subsequent neurodevelopmental dysfunction.
Conclusion

L-thyroxine supplementation during the first six weeks of life did not decrease cortical N1 peak latency in infants of < 30 weeks’ gestational age.

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SEPs in relation to L-thyroxine supplementation


