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Case report

# An Alternative Route of Treatment in Transient Hypothyroxinemia of Prematurity: Rectal Administration of Levothyroxine

## Tunçel et al. Rectal Administration of Levothyroxine In Newborns

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**What is already known on this topic?**
When levothyroxine treatment is indicated in newborns enteral administration is the preferred route. Rectal administration of the drug has not been reported before in preterm infants although it has been used successfully in adult patients with poor oral absorbtion.

**What the study adds?**
In preterm babies with serious gastrointestinal problems rectal administration of levothyroxine tablet is effective in the treatment of thyroid disorders.

**Abstract**
Transient hypothyroxinaemia of prematurity (THOP) is a disorder encountered especially in extremely low birth weight and preterm newborns. In recent years, the survival rates of these babies have increased, owing to the advances in neonatal care, thereby increasing the incidence of THOP. Controversies about the management of this disorder still continues while accompanying morbidites may create difficulties in the treatment of these patients.
A preterm baby boy, born at $25^{6/7}$ gestational week with a birthweight of 665g who developed short bowel syndrome after necrotizing enterocolitis surgery and who was treated with rectal levothyroxine, is presented.
**Keywords:** levothyroxine, prematurity, short bowel, rectal

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**Introduction**
Transient hypothyroxinemia of prematurity is defined as thyroid dysfunction with low circulating free and total throxine(T4) without the expected increase of thyroid stimulating hormone (TSH). (1). It has been reported that THOP occurs in almost half of the babies born at or less than 30 weeks of gestation (2,3).
In preterm babies, the TSH surge is delayed and free T4 levels (fT4) remain low due to several factors including discontinuation of maternal and placental thyroid hormone support, immaturity of the hypothalamo-pituitary axis, limitation of iodine intake and retention, insufficient volume and capacity of the thyroid gland (1,4). It has been reported that THOP may increase the risk of perinatal mortality and morbidity, however the management of this thyroid dysfunction in premature infants is still controversial (2).
Parallel to the improved survival of more immature preterm babies, studies on THOP have also increased. Conflicting results have been reported considering neurodevelopmental, auditory and cognitive outcomes of very low birth weight babies with or without THOP, some showing no significant difference between the two groups (5). Reports on the effect of treatment of THOP on neurodevelopmental outcome in preterm babies are also controversial. Some studies have shown no significant effect of treatment, while others have found better language skills, motor and cognitive functions in the group given thyroxine treatment (6). Hence, studies comparing the long-term effects of treatment in preterm babies with a diagnosis of THOP are still needed (7,8,9). When a treatment decision is made, serious gastrointestinal problems in some very low birth weight babies may create difficulties in the administration of levothyroxine when oral formulation is the only option.

In this paper, a case of THOP in a preterm baby who was born at $25^{6/7}$ gestational week and treated with rectal levothyroxine is presented. The baby developed short bowel syndrome after necrotizing enterocolitis (NEC) surgery and did not respond to oral administration of the drug.

**Case**

A baby boy, was born by emergency cesarean section due to severe preeclampsia in the mother, at $25^{6/7}$ gestational week with a birthweight of 665 g. He was intubated in the delivery room and transferred to the neonatal intensive care unit. He was on mechanical ventilation; total parenteral nutrition (TPN) and minimal enteral nutrition with breast milk were started on the postnatal first day. The baby had delayed meconium passage and developed abdominal distension with increased gastric residuals. Laboratory and radiological findings were compatible with NEC. Minimal enteral feeding was discontinued, gastric free drainage and broad-spectrum antibiotic therapy were initiated. He was operated on the postnatal sixth day due to perforated NEC(Figure-1). As there were multiple areas of perforation and circulatory disturbances in the intestinal wall, a long segment including the jejunum and ileum was resected. A stoma was formed with the proximal end whereas the distal end was left closed in the abdomen. The baby was on TPN until postoperative seventh day when minimal enteral feeding was started and gradually increased. However TPN support could not be discontinued as enteral nutrition alone was insufficient due to short bowel syndrome.

On the postnatal 14th day, thyroid screening tests revealed serum levels of fT4:0.87 ng/dL, TSH: 0.061 mIU/L, cortisol: 5,75µg/dL. Serum total bilirubin (STB) level was 12.12 mg/dL, predominant component being direct reacting bilirubin (DB,11.48 mg/dL). One week later, as fT4 level was found to be decreasing and close to the lower limit of normal, enteral levothyroxine 5 µg/kg/day was started. There was no response to treatment during follow-up and the enteral dose of levothyroxine was increased to 10 µg/kg/day (Table 1, Figure 2). However there was still no increase in fT4 levels which was thought to be the result of poor absorption of the drug due to short bowel syndrome. Since parenteral and suppository levothyroxine preparations were not available, the tablet form of the drug was ground and one tablet (25µg) was diluted with 10 mL of saline to be administered rectally at a dose of 10µg/kg/day (4mL/kg) by a 6 Fr feeding tube. After 9 days of rectal levothyroxine treatment fT4 levels increased and bilirubin levels decreased (Table 1, Figure 2).

Unfortunately the baby died on postnatal 77th day, while still on rectal levothyroxine treatment, with the diagnoses of severe bronchopulmonary dysplasia, surgical NEC, short bowel syndrome and sepsis. A written informed consent was obteined from the patients family for publication.

**Discussion**

Transient hypothyroxinemia is the most common thyroid dysfunction in preterm infants. Although it is controversial, it has been reported that some preterm babies can benefit from the treatment of THOP, but issues such as the time and duration are not yet clear (1,2,4). In our patient, the gradual decrease in fT4 levels together with TSH levels led us to make the decision for treatment. However the baby had developed short bowel syndrome after NEC surgery and fT4 levels did not respond to incremental doses of oral levothyroxine.

In a recently published article alternative routes of levothyroxine administration has been discussed (10). If refractory hypothyroidism persists despite oral therapy, it has been suggested to try different formulas. Among these, it has been stated that since the gastrointestinal transit time is longer, gel and capsules or in cases where absorption is not possible, intravenous and rectal forms could be tried. Since we could not reach other forms that would prolong the stay of the drug in the gastrointestinal tract, we preferred to give our patient the diluted tablet form by the rectal route.

There are a few publications reporting on the use of levothyroxine rectally. The efficacy of rectal levothyroxine treatment in suppository form was investigated in a study which reported both animal and human data. The authors examined the levels of free T4 (FT4) after the administration of the drug in suppository form to thyroidectomized rats and afterwards to 6 adult patients with hypothyroidism. The results showed that the bioavailability of levothyroxin was lower after rectal administration than after the oral medication. However it was suggested that T4 levels can be maintained if the suppository formulation was used at a dose 1.8 times higher than that of the oral dose and can be an alternative route in clinical practice (11).

In another study a 4-month-old baby who developed short bowel syndrome after multiple surgical operations due to gastroschisis was diagnosed with hypothyroidism while being investigated for direct hyperbilirubinemia and reduced intestinal motility. Since oral absorption was insufficient in this baby, the levothyroxine tablet was administered rectally. The initial dose was 12.5 µg/day (5 µg/kg/day) and increased to 25 µg/day (10µg/kg/day) after one week. The tablet was diluted in 3 mL of saline and administered in bolus, with a size 8 rectal probe, which was flushed with 5 mL of water. Clinical and laboratory recovery was achieved at the end of 4 weeks of rectal treatment (12).

In a case report a 58-year-old adult patient who had poor oral intake due to gastrointestinal system malignancy and who had impaired thyroid function was unresponsive to oral treatment. Due to the lack of parenteral preparations and rectal suppositories of levothyroxine, high doses of tablet formulation were ground and dissolved in 500 mL of normal saline and administered as a rectal enema for 21 days after which thyroid function tests returned to normal (13).

Our case who had short bowel syndrome, was unresponsive to oral tablet formulation of levothyroxine because of poor intestinal absorbtion. Due to the lack of intravenous and suppository forms of the drug as alternative routes, the oral tablet form of levothyroxine was administered by the rectal route after being ground and diluted with saline. Laboratory recovery was determined after 9 days of rectal treatment with increasing fT4 levels and decreasing direct bilirubin levels.

However, the fact that our patient did not survive for a long time limits our long-term follow-up and interpretation of THOP and treatment. Nevertheless, in our best knowledge, our patient is the first premature infant even newborn infant who was treated with rectal levothyroxine in the literature.

In conclusion, rectal administration of the diluted oral form of levothyroxine can be used as an alternative route of drug administration in the absence of other forms of the drug in preterm neonates with impaired oral intake or absorption.

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Table 1: Thyroid functions, bilirubin values and treatment

| Postnatal age, day | Postmenstrual age, week | fT4, ng/dL (N)* | TSH, mIU/L (N)* | Cortisol µg/dL | TSB/DB/IB**, mg/dL | Treatment |
|---|---|---|---|---|---|---|
| 14 | 27 6/7 | 0.87 **(0.6-2.2)** | 0.061 **(0.2-30.3)** | 5.75 | 12.12/11.48/0.64 | No treatment |
| 21 | 28 6/7 | 0.65 **(0.6-3.4)** | 0.191 **(0.2-20.6)** | | 18.9/4.4/4.7 | 5 µg/kg/day levothyroxine, enteral |
| 28 | 29 6/7 | 0.65 **(0.6-3.4)** | 0.301 (0.2-20.6) | | 9.05 /8.24 /0.81 | 10 µg/kg/day levothyroxine, enteral |
| 33 | 30 4/7 | 0.68 **(0.6-3.4)** | 1.9 (0.2-20.6) | | 6.46/6.17/0.29 | 10 µg/kg/day levothyroxine, rectal |
| 41 | 31 6/7 | 0.95 **(1.0-3.8)** | 5.5 (0.7-27.9) | | 8.7/7.89 /0.81 | 10 µg/kg/day levothyroxine, rectal |
| 48 | 33 0/7 | 1.36 **(1.0-3.8)** | 0.06 (0.7-27.9) | 0.51 | - | 10 µg/kg/day levothyroxine, rectal |
| 60 | 34 3/7 | 1.26 **(1.2-4.4)** | 3.73 (1.2-21.6) | 0.96 | 8.8/7.4/1.4 | 10 µg/kg/day levothyroxine, rectal |

*Normal values for postmenstrual age (9)
** TSB: Total Serum Bilirubin DB: Direct Bilirubin IB: Indirect Bilirubin

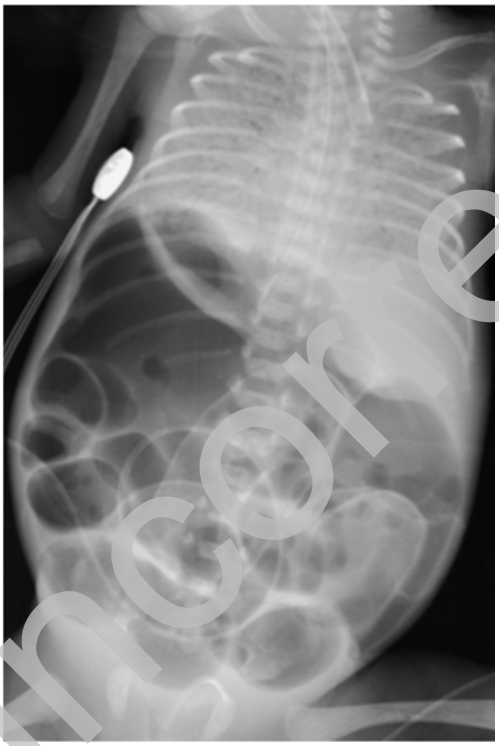

Figure-1: The abdomen X-Ray of the baby with diffuse distention in necrotizing enterocolitis

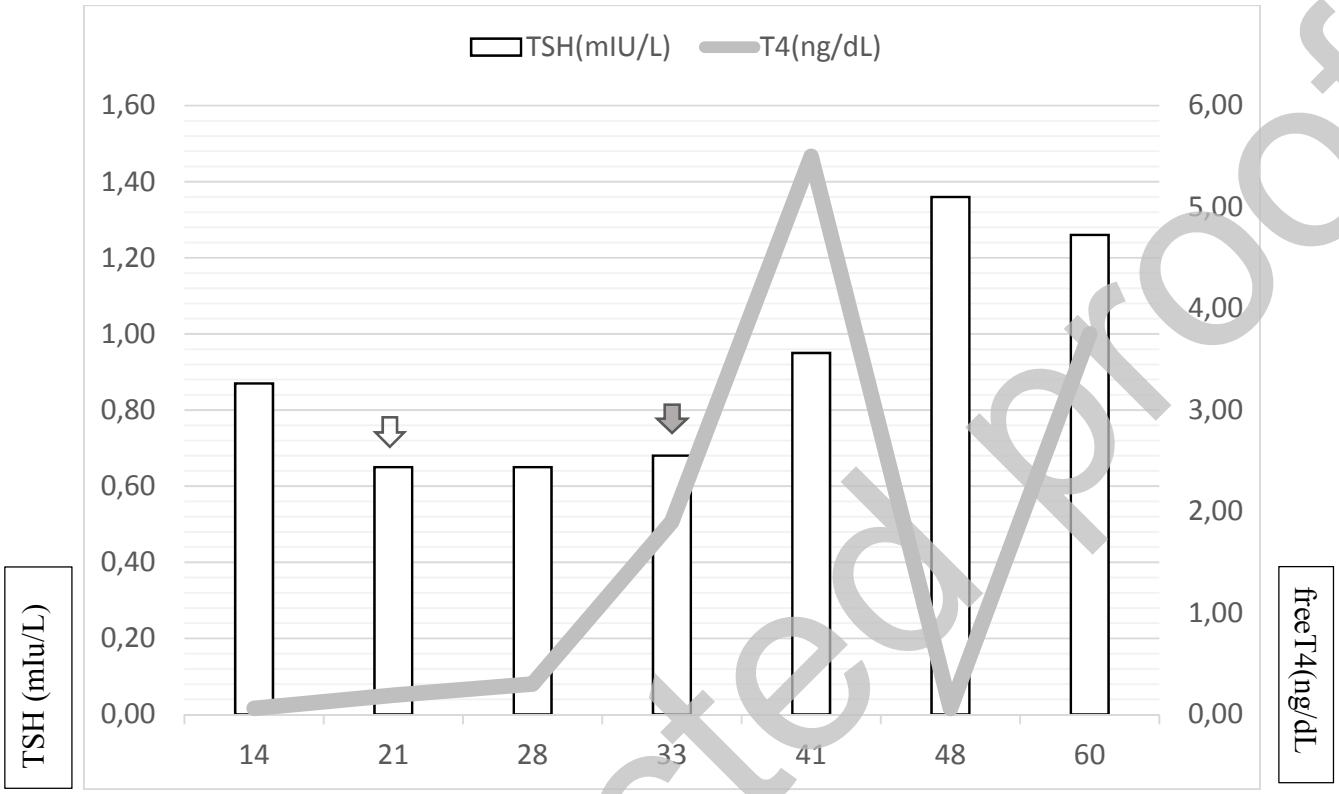


Figure-2: Thyroid hormone levels and treatment

Enteral levothyroxine
Rectal levothyroxine