CASE REPORT

DOI: 10.4274/jcrpe.galenos.2021.2021.0153

J Clin Res Pediatr Endocrinol 2023;15(2):220-224

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

Duygu Tunçel[1], Zeynep İnce[1], Erhan Aygün[2], Asuman Çoban[1]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Neonatology, İstanbul, Turkey
[2]University of Health Sciences Turkey Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İstanbul, Turkey

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 previously been reported in preterm infants although it has been used successfully in adult patients with poor oral absorbtion.

What this study adds?

In preterm babies with serious gastrointestinal problems rectal administration of levothyroxine tablet may be effective in the treatment of transient hypothyroxinaemia of prematurity.

Abstract

Transient hypothyroxinaemia of prematurity (THOP) is a disorder encountered particularly 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 weeks with a birthweight of 665 g who developed short bowel syndrome after necrotizing enterocolitis surgery and who was treated with rectal levothyroxine, is presented.
Keywords: Levothyroxine, prematurity, short bowel, rectal

Introduction

Transient hypothyroxinemia of prematurity (THOP) is defined as thyroid dysfunction with low circulating free and total throxine (T4) without an expected increase in 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-thyroid axis, limitation of iodine intake and retention, and 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 but the management of this thyroid dysfunction in premature infants is still controversial (2).

Parallel to the improved survival of more immature preterm babies, studies concerning 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

Address for Correspondence: Duygu Tunçel MD, İstanbul University, İstanbul Faculty of Medicine, Department of Neonatology, İstanbul, Turkey
Phone: +90 506 732 98 29 **E-mail:** tncldyg@yahoo.com **ORCID:** orcid.org/0000-0002-2130-6821

Conflict of interest: None declared
Received: 11.01.2021
Accepted: 22.09.2021

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 Report

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 the 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 fourteenth postnatal day, thyroid screening tests revealed serum levels of fT4: 0.87 ng/dL and TSH: 0.061 mIU/L, while cortisol was 5.75 µg/dL. Serum total bilirubin level was 12.12 mg/dL, predominant component being direct reacting bilirubin (DB: 11.48 mg/dL). One week later, as the fT4 level was 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 because the main site of oral thyroxine absorbtion is the duodenum, jejenum and ileum which were incomplete in this case. Since parenteral and suppository levothyroxine preparations were not available, the tablet form of the drug was ground and one tablet (25 µg) was diluted with 10 mL of saline to be administered rectally at a dose of 10 µg/kg/day (4 mL/kg) by a 6 Fr feeding tube. After nine days of rectal levothyroxine treatment fT4 levels increased and bilirubin levels decreased (Table 1, Figure 2).

Unfortunately the baby died on postnatal 77^{th} day, while still on rectal levothyroxine treatment; cause of death was a combination of severe bronchopulmonary dysplasia, surgical NEC, short bowel syndrome and sepsis. A written informed consent was obtained from the patient's 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 treatment of THOP, but issues such as the timing and duration of therapy are not yet clear (1,2,4). In the presented case, the gradual decrease in fT4 levels together

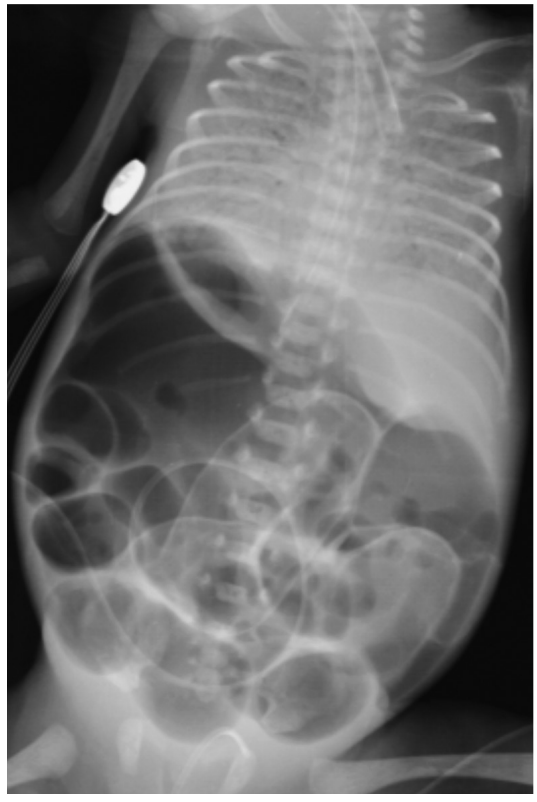

Figure 1. The abdomen X-ray of the baby with diffuse distention in necrotizing enterocolitis

with increasing TSH levels prompted us to initiate treatment. However the baby had short bowel syndrome after NEC surgery, when the main sites of absorbtion of oral thyroxine had been largely removed and fT4 levels did not respond to incremental doses of oral levothyroxine.

In a recently published article, alternative routes of levothyroxine administration were discussed (10). If refractory hypothyroidism persists despite oral therapy, it has been suggested to try different formulae. Among these, it was proposed 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 other forms that would prolong the stay of the drug in the gastrointestinal tract were not available, it was decided to give a diluted tablet form by the rectal route in this case.

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 fT4 after the administration of the

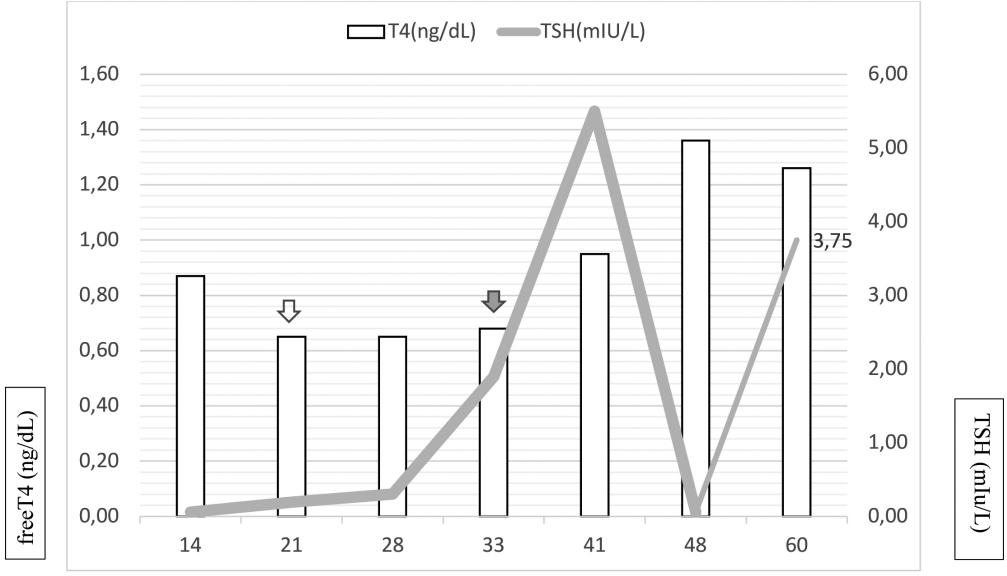

Figure 2. Thyroid hormone levels and treatment

TSH: thyroid stimulating hormone

Enteral levothyroxine

Rectal levothyroxine

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

drug in suppository form to thyroidectomized rats and subsequently to six adult patients with hypothyroidism. The results showed that the bioavailability of levothyroxine was lower after rectal administration than after receiving 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 (10 µg/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. Before each administration the drug was prepared freshly. Clinical and laboratory recovery was achieved at the end of four weeks of rectal treatment (12).

In another case report, a 58-year-old adult 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).

The presented case who had short bowel syndrome, was unresponsive to oral tablet formulation of levothyroxine very probably because of poor intestinal absorbtion. Due to the lack of intravenous and suppository forms of the drug as alternative formulations, the oral tablet form of levothyroxine was administered by the rectal route after being ground and diluted with saline. Laboratory recovery was determined after nine 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, to the best of our knowledge, this case is the first premature infant, or even newborn infant, who was treated with rectal levothyroxine to be published.

Conclusion

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

Ethics

Informed Consent: A written informed consent was obtained from the patient's family for publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zeynep İnce, Erhan Aygün, Asuman Çoban, Concept: Duygu Tunçel, Asuman Çoban, Design: Duygu Tunçel, Asuman Çoban, Data Collection or Processing: Duygu Tunçel, Zeynep İnce, Erhan Aygün, Asuman Çoban, Analysis or Interpretation: Duygu Tunçel, Asuman Çoban, Literature Search: Duygu Tunçel, Zeynep İnce, Erhan Aygün, Asuman Çoban, Writing: Duygu Tunçel, Zeynep İnce, Erhan Aygün, Asuman Çoban.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Eerdekens A, Langouche L, Van den Berghe G, Verhaeghe J, Naulaers G, Vanhole C. Review shows that thyroid hormone substitution could benefit transient hypothyroxinaemia of prematurity but treatment strategies need to be clarified. Acta Paediatr 2019;108:792-805. Epub 2019 Jan 4
2. Yoon SA, Chang YS, Ahn SY, Sung SI, Park WS. Incidence and severity of transient hypothyroxinaemia of prematurity associated with survival without composite morbidities in extremely low birth weight infants. Sci Rep 2019;9:9628.
3. Williams FL, Simpson J, Delahunty C, Ogston SA, Bongers-Schokking JJ, Murphy N, van Toor H, Wu SY, Visser TJ, Hume R; Collaboration from the Scottish Preterm Thyroid Group. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. J Clin Endocrinol Metab 2004;89:5314-5320.
4. Iijima S. Current knowledge of transient hypothyroxinemia of prematurity: to treat or not to treat? J Matern Fetal Neonatal Med 2019;32:2591-2597. Epub 2018 Feb 22
5. Tan LO, Tan MG, Poon WB. Lack of association between hypothyroxinemia of prematurity and transient thyroid abnormalities with adverse long term neurodevelopmental outcome in very low birth weight infants. PLoS One 2019;14:e0222018.
6. van Wassenaer AG, Kok JH, de Vijlder JJ, Briët JM, Smit BJ, Tamminga P, van Baar A, Dekker FW, Vulsma T. Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. N Engl J Med 1997;336:21-26.
7. Ng SM, Turner MA, Weindling AM. Neurodevelopmental Outcomes at 42 Months After Thyroxine Supplementation in Infants Below 28 Weeks' Gestation: A Randomized Controlled Trial. Thyroid 2020;30:948-954. Epub 2020 Mar 17
8. van Wassenaer AG, Kok JH. Trials with thyroid hormone in preterm infants: clinical and neurodevelopmental effects. Semin Perinatol 2008;32:423-430.

9. Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC. Reference ranges for newer thyroid function tests in premature infants. J Pediatr 1995;126:122-127.
10. Ritter MJ, Gupta S, Hennessey JV. Alternative routes of levothyroxine administration for hypothyroidism. Curr Opin Endocrinol Diabetes Obes 2020;27:318-322.
11. Kashiwagura Y, Uchida S, Tanaka S, Watanabe H, Masuzawa M, Sasaki T, Namiki N. Clinical efficacy and pharmacokinetics of levothyroxine suppository in patients with hypothyroidism. Biol Pharm Bull 2014;37:666-670.
12. Ybarra M, Dos Santos TJ, Pinheiro CTC, Dichtchekenian V, Damiani D. Rectal Levothyroxine for the Treatment of Hypothyroidism: A Case Study. Pediatrics 2018;142:20173317. Epub 2018 Jul 12
13. Obeidat KA, Saadeh NA, As'ad A, Bakkar S. Successful management of hypothyroidism in gastric outlet obstruction using levothyroxine rectal enemas: a case report. Am J Case Rep 2018;19:903-905.