ORIGINAL ARTICLE

Thyroid Hormone Levels in Preterm Neonates with Birth Weight Less than 2500 g, Treated with Phenobarbital.

How to Cite This Article: Bidabadi E , Zarkesh M, Mirzaii Chaghakabudi1 M. Thyroid Hormone Levels in Preterm Neonates with Birth Weight Less than 2500 g, Treated with Phenobarbital. Iran J Child Neurol. Autumn2023; 17 (4): 155-162

Elham BIDABADI MD[1], Marjaneh ZARKESH MD[1], Maryam MIRZAII CHAGHAKABUDI MD [1],

1-Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran
Elham Bidabadi and Marjaneh Zarkesh are equal contributions to this work and designated as co-first authors

Corresponding Author
Bidabadi E. MD
Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.
Email: bidabadi@mail.com

Received:01- Jul - 2023
Accepted: 07-Aug-2023
Published: 26-Oct-2023

Abstract

Objectives

Indicatively, phenobarbital can impair thyroid function in adults and children. The present research aims to evaluate the thyroid hormone levels in preterm neonates who had received phenobarbital treatment.

Materials & Methods

This study was conducted on preterm neonates who weighed less or equal to 2500 g when phenobarbital was prescribed for treatment in the first 15 days of life. TSH and total T4 measurements were performed before and three months after initiation of phenobarbital.

Results

In this study, the sum of preterm neonates stood at 94, of which 53 were girls, with a mean birth weight of 2004.41 ± 315.41g. Weight of 8.5% were under 1500 g. The mean gestational age was estimated at 33.64 ± 2.01 weeks. Mean T4 levels were 12.24 ± 1.96 and 12.07 ± 1.95 (p=0.334), and mean TSH levels were 5.34 ± 2.14 and5.15 ± 2.15 (p=0.376) before and after prescribing phenobarbital, respectively. The same results were compared based on sex, gestational age, birth weight, and height for T4 and TSH and T4 based on head circumference. The only significant difference was TSH in preterm infants with head circumference <32 cm before and after prescribing phenobarbital (p=0.030).

Conclusion

In preterm newborns that had less than 2500 g birth weight, phenobarbital did not significantly alter the serum thyroid hormone levels.

Keywords: Preterm Infants, Phenobarbital, Thyroid, TSH, T4 Thyroid Hormone.
DOI: 10.22037/ijcn.v17i4.42583

Introduction

In preterm births, intraventricular hemorrhage (IVH) is a significant problem; extensive hemorrhages linked to parenchymal brain lesions have a high propensity for disabling effects and a high fatality rate (1). The postnatal phenobarbital administration for prevention of IVH in low birth weight infants is governed by suggestions and traces of evidence that in premature infants, phenobarbital treatment is capable of dampening fluctuations in systemic blood pressure and can further partially safeguard the brain from any kind of hypoxic-ischemic damage (2-6). However, recent evaluation and research established that phenobarbital treatment as prophylaxis to prevent IVH in preterm neonates is not recommended (7).

When comparing the risk of seizures in full-term infants and premature neonates, the severity is higher in premature neonates. This severity is characterized by its timing and a unique profile of etiologies. For newborns under32 weeks of gestational age, the common cause of the seizure is IVH, attributed to physiologic susceptibility (8, 9). Despite consolidated efforts to enhance neonatal care, seizures in preterm infants remain high. Consequently, these infants face an increased risk of abnormal neurodevelopment outcomes. Accordingly, newborns are more vulnerable to seizures compared to alternatives.

One of the critical challenges associated with using anti-seizure medications in premature neonates includes concerns over the drug's safety, effectiveness, and pharmacokinetics, all of which remain largely unexplored. . There is an urgent need to carefully plan clinical trials that investigate and validate the medications' safety, the drug's effectiveness, and the results of seizure therapy in premature neonates. Currently, no drug with a defined indication exists in preterm neonates, despite improvements in managing seizure in term neonates, except that phenobarbital treatment is the most common and widely acknowledged first-line intervention in full-term infants and is most commonly used in preterm neonates (10-12).

In central nervous system development, thyroid hormones are considered to play a vast and significant role in normal physiological brain function and repair mechanisms. Furthermore, impairment in thyroid function is common in preterm neonates because of their unique thyroid and the hypothalamic-pituitary-thyroid axis immaturity (13). Even though it is well known that anti-epileptic drugs (AED) can cause impaired thyroid function in older people (14), there have been few studies about the role of phenobarbital on thyroid function among pediatric patients. Some authors emphasized that in contrast to the significant effects of valproate on the thyroid hormone levels, phenobarbital had minimal effect on it (15). Furthermore, it has minimal evidence of the challenging population of preterm neonates. In actuality, periventricular leukomalacia, low birth weight, and immature central nervous system development are significant characteristics of

preterm neonates, providing seizure risks (16). Nonetheless, due to age-specific pharmacokinetic and pharmacodynamic characteristics, preterm babies are more likely to experience severe problems and exhibit decreased receptivity to traditional pharmaceutical treatment (17). An increasing sense of urgency exists in recognizing the need for evidence-based, specialist care for preterm infants with seizures due to an increased understanding of this population's distinct neurologic and metabolic characteristics (10, 18).

The present study aimed to examine the changes in preterm infants' serum thyroid hormone levels caused by phenobarbital monotherapy. Through previews of various kinds of literature, this is the first study of its kind in this era that we are aware of that involved preterm children.

Materials & Methods

This study's inclusion criteria were all preterm neonates with birth weights equal to or less than 2500 g who need to be prescribe phenobarbital treatment around their 15th day of life (day 14, 15, or 16) at Rasht 17th Shahrivar Pediatric Hospital. This study excluded all patients with abnormal imaging, such as neurological, hepatic, renal, and thyroid diseases or other endocrinopathies, and uncontrolled seizures with several anti-epileptic drugs.

Collected data included demographic and clinical data comprised gestational age, birth weight, sex, head circumference, and body height on birth. Serum total T4 and TSH concentrations were measured by chemiluminescent immunoassay before and three months after initiation of phenobarbital (20 mg/kg intravenous loading dose, then 2.5 mg/kg/dose per 12 hours).

The normality of data distribution of quantitative variables was done using the Kolmogorov-Smirnov test. All data had a normal distribution; therefore, this study used a paired T-test to compare mean levels. Discrete variables were expressed as counts (%) and compared using the Chi-square tests. Continuous variables were expressed as mean ± standard deviation (SD). Computation was done using the SPSS program from Windows version 19.0. $P<0.05$ was considered statistically significant.

Moreover, the institutional research committee's ethical guidelines, the 1964 Helsinki Statement, and its later amendments, or a comparable ethical standard, were all followed in all data collection procedures. Human rights were adhered to by all participants involved in the study. Besides, each participant had their parents or other legal guardians involved in giving their informed consent.

Results

A sum of 94 preterm neonates were qualified to be part of the study. There were 53 (56.4%) females and 41 (43.6%) males, with a mean birth weight of 2004.41 ± 315.41 g (1235 – 2490 g). 91.5% of all neonates were in the 1500-2500 g range of weight, and only 8.5% were under 1500 g. In 48.9% of cases, gestational age was between 28-34 weeks, and 51.1% between 34-37 weeks (mean gestational age was 33.64 ± 2.01 weeks). Most cases (62.8%) had a head circumference less than 32 cm, and only 37.2% had more than 32 cm, with a mean of 32.08 ± 1.97 cm (28-39 cm). 51.1% of cases had more than 45 cm height and 48.9% less than 45 cm, with a mean height of 45.32 ± 2.03 cm (38 – 50 cm). The Kolmogorov-Smirnov test was also used to determine whether the data distribution proved normal. Evidently, all T4 and TSH data had normal distribution before and after

prescribing phenobarbital, so a paired T-test was performed (Table 1).

Discussion

Evidently, AEDs, through various mechanisms such as changes in the biosynthesis and secretion of hormones and their transport, the metabolism processes, and the excretion of thyroid hormones, significantly affect thyroid hormone levels. Most of these factors alter the clearance of thyroid hormones. This is achieved by increasing the induction of an enzyme referred to the hepatic microsomal system or via the hypothalamic-pituitary axis (19). However, the significant side effects of AEDs on the endocrinological systems are subclinical and clinical hypothyroidism. Phenobarbital can be described as an anti-epileptic drug with strong enzyme-inducing and weak protein-binding activity (20).

According to a systematic review conducted by Rochtus et al. on the articles published between January 1990 and early 2021 about thyroid hormone function and AEDs (20), only four studies were cross-examined to provide information on the effect of phenobarbital on thyroid function among children (20-24). In a network meta-analysis, Han et al. (25) reviewed 35 studies, including 4135 participants, revealed that 25 studies concentrated on children and adolescents and only five on phenobarbital (20, 23, 26-28). No study was available study on the effect of phenobarbital on thyroid function tests in preterm infants.

Research conducted by Castro-Gago et al. on five epileptic children who were receiving phenobarbital treatment and had a mean age of 9.1 ±2.5 years and therapy lasting 6.8 ± 3.1 years, elaborated that TSH levels remained stable, but free T4 levels considerably decreased (20). In addition, Tanaka et al. demonstrated the same outcomes on 63 kids whose T4 was reduced after receiving phenobarbital treatment for more than six years (29). A significant decrease in T4 ($p<0.01$) and free T4 ($p<0.05$) was established by Yüksel et al. in research on ten kids with a mean age of 4 years and ten months and a mean length of therapy with phenobarbital of 20 months (30).

The thyroid hormone levels are significantly influenced by enzyme induction of cytochrome P450. On the other hand, phenobarbital treatment usually causes only minimal induction of T4 and has fragile protein-binding properties (19). Generally, the impact of phenobarbital treatment on thyroid hormone metabolism can be described as mild.

On the other hand, in different research on 17 kids who had a mean age of 3.7 years, no discernible difference was found in serum-free T4 and TSH levels between the phenobarbital-treated patients and the control group in the third, sixth, and ninth months of treatment (22).

Furthermore, in another case study that involved 69 children who also had a mean age of 17.1 ± 3.7 months, undergoing phenobarbital treatment, it was evaluated that serum-free T4 levels in patients receiving phenobarbital treatment were not found to be significantly reduced in the 12th month. Still, a significant increase was detected in TSH levels ($p < 0.001$) (26).

Therefore, this study concluded some controversy regarding how phenobarbital treatment affects children's thyroid function.

The results of the current research could not be compared with those from other studies since, as previously stated, no published research on the effects of phenobarbital medication on the thyroid function of preterm infants is currently available,

Table 1. Comparison of mean of T4 and TSH levels before and after phenobarbital prescription.

		No. of patients	Total T4			TSH		
			before	after	P-value	before	after	P-value
Total		94	12.24 ± 1.96	12.07 ± 1.95	0.334	5.34 ± 2.14	5.15 ± 2.15	0.376
Sex	**Male**	41	12.39 ± 1.88	12.02 ± 2.12	0.212	5.20 ± 2.07	5.28 ± 2.23	0.817
	Female	53	12.13 ± 2.02	12.11 ± 1.81	0.936	5.45 ± 2.21	5.04 ± 2.08	0.147
Gestational age	**28-34 weeks**	46	11.89 ± 1.75	11.96 ± 1.81	0.845	4.89 ± 2.01	4.66 ± 1.94	0.443
	34-37 weeks	48	12.59 ± 2.09	12.07 ± 2.08	0.112	5.77 ± 2.19	5.61 ± 2.24	0.621
Birth weight	**<1500g**	8	12.14 ± 2.55	11.68 ± 1.51	0.562	5.15 ± 2.59	5.25 ± 2.91	0.839
	1500-2500g	86	12.26 ± 1.91	12.05 ± 1.98	0.407	5.36 ± 2.11	5.14 ± 2.08	0.349
Head circumference	**<32cm**	59	12.30 ± 2.02	11.74 ± 1.77	0.060	5.37 ± 2.06	4.83 ± 2.00	**0.030**
	>32cm	35	12.16 ± 1.86	12.49 ± 2.14	0.393	5.29 ± 2.30	5.68 ± 2.29	0.333
Height	**<45cm**	46	11.89 ± 1.79	11.91 ± 1.95	0.950	5.06 ± 2.11	4.89 ± 2.03	0.586
	>45cm	48	12.59 ± 2.06	12.12 ± 1.94	0.131	5.61 ± 2.16	5.39 ± 2.23	0.489

and we must emphasize the paucity of literature in this era. This study's mean was T4 (p=0.334), and the mean TSH levels were (p=0.376). Therefore, there were no significant differences before and after the phenobarbital prescription. In addition, the same results were compared based on sex, gestational age, birth weight, and height for T4 and TSH and for T4 based on head circumference. The only statistically significant variation was the TSH level in preterm infants with a head circumference smaller than 32 cm before and after the prescribed phenobarbital (p=0.030). Possibly, confounding factors can play a role in this result because it is the only statistically significant result in this study. Further studies with bigger sample sizes, multivariate analyses, and backward stepwise logistic regression analysis are recommended.

This study had some limitations: The main drawback of this study was that it only looked at a small number of patients and did not examine whether different patient populations varied in terms of epilepsy syndrome or severity. Phenobarbital's long-term consequences were not also examined. Another limitation of the current study was the absence of a control group and the assessment of free T4 measurements.

In conclusion, phenobarbital did not majorly alter the serum thyroid hormone levels in preterm infants with birth weights less than 2500 g.

Acknowledgment

The authors thank all the parents and children who coordinated this research. (IR.GUMS.REC.1394.743)

Authors' contribution

Conceptualization: Elham Bidabadi

Methodology: Elham Bidabadi, Maryam Mirzaii Chaghakabudi

Software: Maryam Mirzaii Chaghakabudi

Validation: Elham Bidabadi, Maryam Mirzaii Chaghakabudi, Marjaneh Zarkesh

Formal analysis: Elham Bidabadi, Maryam Mirzaii Chaghakabudi

Investigation: Elham Bidabadi, Maryam Mirzaii Chaghakabudi

Data curation: Maryam Mirzaii Chaghakabudi, Marjaneh Zarkesh

Original draft preparation: Elham Bidabadi, Maryam Mirzaii Chaghakabudi

Review: Elham Bidabadi, Maryam Mirzaii Chaghakabudi

Editing: Elham Bidabadi

Conflict of interest

The authors declare that they have no conflict of interest.

Reference

1. Vohr BR, Garcia-Coll C, Mayfield S, Brann B, Shaul P, Oh W. Neurologic and developmental status related to the evolution of visual-motor abnormalities from birth to 2 years of age in preterm infants with intraventricular hemorrhage. The Journal of pediatrics. 1989 Aug 1;115(2):296-302.
2. Wimberley PD, Lou HC, Pedersen H, Hejl M, Lassen NA, Friis-Hansen BE. Hypertensive peaks in the pathogenesis of intraventricular hemorrhage in the newborn. Abolition by phenobarbitone sedation. Acta Pædiatrica. 1982 Jul;71(4):537-42.
3. Goddard-Finegold J, Armstrong DL. Reduction in incidence of periventricular, intraventricular hemorrhages in hypertensive newborn beagles pretreated with phenobarbital. Pediatrics. 1987 Jun;79(6):901-6.
4. Steen PA, Michenfelder JD. Barbiturate protection in tolerant and nontolerant hypoxic mice: comparison with hypothermic protection. Anesthesiology. 1979 May 1;50(5):404-8.
5. Ment LR, Stewart WB, Duncan CC. Beagle puppy model of intraventricular hemorrhage: effect of superoxide dismutase on cerebral blood flow and prostaglandins. Journal of neurosurgery. 1985 Apr 1;62(4):563-9.
6. Farrokhi M, Rigi A, Mangouri A, Fadaei M, Shabani E, Mashouf P, Shahraki T, Gharei F, Mehran M, Dehghani S, Nazarimanesh M. Role of Antioxidants in Autoimmune Diseases. Kindle. 2021 Oct 21;1(1):1-07.
7. Smit E, Odd D, Whitelaw A. Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants. Cochrane Database of Systematic Reviews. 2013(8).
8. Glass HC, Shellhaas RA, Tsuchida TN, Chang T, Wusthoff CJ, Chu CJ, Cilio MR, Bonifacio SL, Massey SL, Abend NS, Soul JS. Seizures in preterm neonates: a multicenter observational cohort study. Pediatric neurology. 2017 Jul 1;72:19-24.
9. Twanow JD. Diagnosis and Management of Seizures in the Preterm Infant. In Seminars in Pediatric Neurology 2022 Apr 12 (p. 100971). WB Saunders.

10. Ramantani G, Schmitt B, Plecko B, Pressler RM, Wohlrab G, Klebermass-Schrehof K, Hagmann C, Pisani F, Boylan GB. Neonatal seizures—are we there yet?. Neuropediatrics. 2019 Oct;50(05):280-93.
11. Keene JC, Morgan LA, Abend NS, Bates SV, Huang SL, Chang T, Chu CJ, Glass HC, Massey SL, Ostrander B, Pardo AC. Treatment of neonatal seizures: comparison of treatment pathways from 11 neonatal intensive care units. Pediatric neurology. 2022 Mar 1;128:67-74.
12. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, Kuperman R, Harbert MJ, Michelson D, Joe P, Wang S. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics. 2020 Jun 1;145(6).
13. Surks MI, Sievert R. Drugs and thyroid function. New England Journal of Medicine. 1995 Dec 21;333(25):1688-94.
14. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. InSeminars in Fetal and Neonatal Medicine 2013 Aug 1 (Vol. 18, No. 4, pp. 185-191). WB Saunders.
15. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. Drugs. 2016 Apr;76(6):647-61.
16. Soul JS, Pressler R, Allen M, Boylan G, Rabe H, Portman R, Hardy P, Zohar S, Romero K, Tseng B, Bhatt-Mehta V. Recommendations for the design of therapeutic trials for neonatal seizures. Pediatric research. 2019 Jun;85(7):943-54.
17. Benedetti MS, Whomsley R, Baltes E, Tonner F. Alteration of thyroid hormone homeostasis by antiepileptic drugs in humans: involvement of glucuronosyltransferase induction. European journal of clinical pharmacology. 2005 Dec;61(12):863-72.
18. Castro-Gago M, Novo-Rodríguez MI, Gómez-Lado C, Rodríguez-García J, Rodríguez-Segade S, Eirís-Puñal J. Evolution of subclinical hypothyroidism in children treated with antiepileptic drugs. Pediatric neurology. 2007 Dec 1;37(6):426-30.
19. Rochtus AM, Herijgers D, Jansen K, Decallonne B. Antiseizure medications and thyroid hormone homeostasis: Literature review and practical recommendations. Epilepsia. 2022 Feb;63(2):259-70.
20. Aygün F, Ekici B, Aydınlı N, Aydın BK, Baş F, Tatlı B. Thyroid hormones in children on antiepileptic therapy. International Journal of Neuroscience. 2012 Jan 1;122(2):69-73.
21. Turan MI, Cayir A, Ozden O, Tan H. An examination of the mutual effects of valproic acid, carbamazepine, and phenobarbital on 25-hydroxyvitamin D levels and thyroid function tests. Neuropediatrics. 2014 Feb;45(01):016-21.
22. Yılmaz Ü, Yılmaz TS, Akıncı G, Korkmaz HA, Tekgül H. The effect of antiepileptic drugs on thyroid function in children. Seizure. 2014 Jan 1;23(1):29-35.
23. Han Y, Yang J, Zhong R, Guo X, Cai M, Lin W. Side effects of long-term oral anti-seizure drugs on thyroid hormones in patients with epilepsy: a systematic review and network meta-analysis. Neurological Sciences. 2022 May 30:1-1.
24. Güngör O, Özkaya AK, Temiz F. The effect of antiepileptic drugs on thyroid hormonal function: valproic acid and phenobarbital. Acta Neurologica Belgica. 2020 Jun;120(3):615-9.
25. Momen AA, Kajbaf TZ, Sepehran A, Aminzadeh M, Malamiri RA. Subclinical hypothyroidism in children with well-controlled epilepsy.

Pediatria Polska-Polish Journal of Paediatrics. 2018;93(6):438-43.

26. Cayir A, Turan MI, Esin IS. An Examination of the Effects of Phenobarbital on Thyroid Function Tests in Childhood Epilepsy. HK J Paediatr (new series). 2014;19(2):71-4.
27. Tanaka K, Kodama S, Yokoyama S, Komatsu M, Konishi H, Momota K, Matsuo T. Thyroid function in children with long-term anticonvulsant treatment. Pediatric Neurosurgery. 1987;13(2):90-4.
28. Yüksel A, Kartal A, Cenani A, Yalçin E. Serum thyroid hormones and pituitary response to thyrotropin-releasing hormone in epileptic children receiving anti-epileptic medication. Pediatrics International. 1993 Apr;35(2):108-12