Original Article

Combined Effects of Thyroxine with Vitamin B_{12} on Electrophysiological Changes in motor functions of Median Nerve of Newly Diagnosed Hypothyroid Female Patients

Ahmed F[1], Sultana N[2], Rahman M[3], Chowdhury MA[4], Saha KC[5]

1. ***Dr. Farjana Ahmed, Assistant Professor, Department of Physiology, Dhaka National Medical College**
2. ***Dr. Nayma Sultana, Professor, Department of Physiology, Sir Salimullah Medical College***
3. ***Dr. Mahaboba Rahman, Assistant Professor, Department of Physiology & Biochemistry, University Dental college & Hospital***
4. ***Dr. Md. Arifuzzaman Chowdhury, Medical officer, Department of Orthopedics, Dhaka National Medical College***
5. ***Dr. Kartik Chandra Saha, Assistant Professor, Department of Pharmacology, Dhaka National Medical College***

Address of correspondence

Abstract

Background: *Peripheral neuropathy may remain latent in the early phase of Hypothyroidism. Combination of thyroxine with vitamin B_{12} can improve the electrophysiological status of motor function of median nerve in newly diagnosed hypothyroid patients.*

Objective : *To observe the combined effects of thyroxine with vitamin B_{12} on electrophysiological changes in motor function of median nerve in newly diagnosed hypothyroid female with abnormal neurological sign/symptom.*

Method: *This prospective interventional study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC) between July 2015 to June 2016 on 40 newly diagnosed hypothyroid female patients with abnormal motor nerve conduction parameters. Among them, 20 hypothyroid patients received only thyroxine (HT-T4) and another 20 hypothyroid patients received combined therapy of thyroxine with vitamin B_{12} (HT-C) for 90 consecutive days. All the patients were studied two times; on day 1(before starting their treatment and they were designated as HT-T4b and HT-Cb) and on day 90 (after treatment and they were designated as HT-T4a and HT-Ca). Furthermore, 20 euthyroid female subjects (ET) with normal electrophysiological status were taken for comparison and were studied only on day 1. The neurological examinations of all subjects were done to evaluate their motor functions under the guidance of expert neurologists of BSMMU. Their serum TSH, FT_4, FT_3 levels were estimated for assessment of thyroid function status by ELISA method. Nerve conduction parameters of motor functions of median nerve were studied to observe the electrophysiological status and vitamin B_{12} level was also estimated to observe its level by using standard method. The statistical analysis was done by ANOVA test, paired independent sample 't' test and Chi-square (χ^2) test as applicable.*

Results: *In this study, serum TSH was decreased and FT_4 and FT_3 levels were significantly increased in both groups after 90 days supplementation of thyroxine alone and combined therapy of thyroxine with vitamin B_{12}. Again, latency was significantly decreased, amplitude and NCV were significantly increased in motor functions of median nerve of hypothyroid patients after 90 days supplementation of combined therapy of thyroxine with vitamin B_{12} in comparison to those of their pre-supplemented state and also to those of patients with only thyroxine treatment. Moreover, vitamin B_{12} level was significantly increased after 90 days supplementation of combined therapy of thyroxine with vitamin B_{12} in HT-Ca in comparison to those of their pre supplemented state HT-Ca and also to that only thyroxine group (HT-T4a). Moreover, sign- symptoms were improved after 90 days supplementation of combined therapy of thyroxine with vitamin B_{12} in comparison to those of only thyroxine group.*

Conclusion: *The present study revealed that thyroxine alone can improve nerve conduction parameters to some extent but the combination of thyroxine with vitamin B_{12} can reduce the symptoms of hypothyroid induced peripheral neuropathy and accelerate the nerve conduction velocity of motor functions of median nerve more efficiently than the treatment with thyroxine alone.*

Key words: *Nerve conduction velocity, distal latency, amplitude, thyroxine, vitamin B_{12}.*

Received: *31.11.2021*

Accepted: *04.04.2022*

Introduction

Hypothyroidism is a clinical condition resulting from reduced circulating levels of free thyroxine (FT_4) and triiodothyronine (FT_3)[1]. However, the thyroid hormones increase the metabolic activities of almost all tissues of the body. The basal metabolic rate can increase 60 to 100 percent above normal when large amount of hormones are secrected[2]. The thyroid gland is not essential for life, but its absence or hypo function during fetal and neonatal life results in severe mental retardation and dwarfism[3].

The prevalence of primary hypothyroidism is 10/1000 but increases to 50/1000 if patients with sub-clinical hypothyroidism (normal FT_4, raised TSH) are included and the female: male ratio is approximately 6:1[4].

However, Hypothyroidism might be reversible at early stages; on the other hand irreversible cases might have longer duration of diseases or might present etiologies other than hypothyroidism. Long term accumulation of mucinous tissue is the possible cause of irreversibility[5].

In hypothyroidism, delayed distal latencies with lower nerve conduction velocities were observed in median and ulnar nerves for both motor and sensory conduction, in peroneal nerves for motor conduction and in sural nerve for sensory conduction in nerve conduction study by using electromylogram machine[6]. Majority of the hypothyroid female patients with a diagnosis of polyneuropathy had electrophysiological evidence of prominent sensory neuropathy involving the median nerve[7].

Most of the hypothyroid patients complain some sensory symptoms like tingling sensation, numbness, paresthesia, burning pain and some motor symptoms like weakness, muscle fatigability, stiffness and cramp[8]. Again, decreased tendon reflexes, decreased muscle strength, Hypothyroidism is a clinical condition resulting from reduced circulating levels of free thyroxine (FT_4) and triiodothyronine (FT_3)[1]. However, the thyroid hormones increase the metabolic activities of almost all tissues of the body.

Again, decreased tendon reflexes& decreased muscle strength, positive Phalen's test and Tinel's sign at the

wrist (test for clinical diagnosis of carpal tunnel syndrome) were also found in some hypothyrpod female[9].

Some investigator revealed that, sensory and motor sign/symptoms such as tingling sensation, numbness, loss of vibration, pain, decreased muscle strength and delayed tendon reflexes were still persisted in hypothyroid patients even after 1 year of thyroxine replacement therapy[10].

However, For clinical diagnosis of peripheral neuropathy, elicitation of reflexes, assessment of strength of major muscle groups on both side to evaluating motor system and fine/crude touch, two point discrimination test, pin prick, vibration sense to evaluating sensory system were observed in some study and they found the significant alteration in maximum newly diagnosed hypothyroid patients[9].

After thyroxine therapy, the central and peripheral nerve conduction velocities returned to normal limits, whereas the abnormalities in amplitude were still persisted[11].

In a follow-up study, some researchers demonstrated that abnormalities related to entrapment neuropathy and polyneuropathy in hypothyroid patients can be reversed within 3 months of thyroid hormone replacement therapy. But the researchers also found that, 13.8% of the patients still had carpal tunnel syndrome after 3 months of thyroxine replacement therapy and were subjected to surgical decompression[7].

Methods

The present interventional study was carried out in the Department of Physiology, SSMC, Dhaka from 1st July 2015 to 30th June 2016. In this study, 40 newly diagnosed hypothyroid female patients with abnormal nerve conduction parameters (delayed distal latency, decreased amplitude and NCV) of motor functions of median nerve, age ranged from 20-45 years were selected.

All the study subjects were selected from out patients department of SSMC and BSMMU belonged to middle socioeconomic status. Subjects with hypertension, diabetic Mellitus, heart disease, kidney disease, hyperthyroidism, past history of neuropathy or neuromuscular diseases, use of drugs known to cause neuropathy or myopathy, malignancy or other serious diseases, pregnancy or lactation, history of gastric or ileal resection were excluded from the study.

Among them, 20 hypothyroid patients (HT-T4b) received only thyroxine at a dose of 50 µg per day for 3wks, 100 µg per day for the next 3 wks and finally to a maintenance dose of 150 µg per day for the remaining day of the study period (upto day-90).

Another, 20 hypothyroid patients (HT-Cb) received combined therapy of thyroxine (as above mentioned dose) with vitamin B_{12} (500µg 8 hourly orally) for 90 consecutive days.

All the patients were studied two times; on day 1 and on day 90. Furthermore, 20 euthyroid female subjects (ET) with normal electrophysiological status were taken for comparison and were studied only day 1.

Results

In this study, the mean (±SD) serum TSH level was significantly ($p<0.001$) higher and FT_4, FT_3 and vitamin B_{12} level were significantly (<0.001) lower in group HT-T4b and HT-Cb in comparison to those of group ET. Whereas, the levels were almost similar and differences were not statistically significant between group HT-T4b and HT-Cb.

Again, TSH level was significantly ($p<0.01$) decreased, whereas FT_4 and FT_3 levels were significantly ($p<0.01$, $p<0.001$) increased in group HT-T4a and HT-Ca in comparison to those of group HT-T4b and HT-Cb respectively and vitamin B_{12} level was significantly ($p<0.001$, $p<0.01$) increased only in group HT-Ca in comparison to that of group HT-Cb and HT-T4b respectively.

However, FT_4 level was almost similar and the difference was not statistically significant between groups HT-T4a vs HT-Ca, ET vs HT-T4a and ET vs HT-Ca. Again, TSH level was significantly ($p<0.01$) lower, whereas FT_3 level was significantly ($P<0.05$) higher in group HT- T4a and HT-Ca in comparison to those of group ET.

But, these levels were almost similar and the differences were not statistically significant between groups HT-T4a vs HT-Ca.

Again, Vitamin B_{12} level was reached towards the level of group ET, though this level still showed significant ($p<0.05$) difference between ET vs HT-Ca.

In this study, the M d latency was significantly ($p<0.01$) higher whereas, M amplitude and MNCV were significantly ($p<0.001$) lower in group HT-T4b and HT-Cb when compared to those of group ET. However, these levels were almost similar and the differences were not statistically significant between group HT-T4b and group HT-Cb.

Again, M d latency was significantly ($p<0.01$) decreased and M amplitude was significantly ($p<0.01$) increased in group HT-T4a and HT-Ca in comparison to those of HT-T4b and HT-Cb respectively. However, these levels in group HT-T4a and HT-Ca projected towards the levels of group ET, though the differences among them were still statistically significant ($p<0.05$, $p<0.01$). Whereas, these levels were almost similar and the differences were not statistically significant between HT-T4a and HT-Ca. Moreover, MNCV was significantly ($p<0.01$) increased in group HT-Ca when compared to that ofgroupsHT-CbandT4a.

However, this level in group HT-T4a projected towards the level of group ET, though the differences between ET vs HT-Ca was still statistically significant ($p<0.05$).

Table I: Serum Thyroid Stimulating Hormone (TSH), free Thyroxine (FT_4), free Triiodothyronin (FT_3), and Vitamin B_{12} levels in different groups (n=60)

Groups	n	TSH (µIU/l)	FT_4 (pmol/L)	FT_3 (pmol/L)	Vitamin B_{12} (pg/ml)
EC	20	1.28±0.8 (0.3-2.6)	13.87±1.53 (12.2-14.5)	3.2±0.44 (2.2-4.4)	275±4.2 (261-285)
HT-T_{4b}	20	8.99±1.74*** (5.9-11.4)	9.8±1.5*** (7.4-13.4)	1.4±0.4*** (1-1.9)	235±4.6*** (220-245)
HT-T_{4a}	20	4.06±0.5$^{\Delta\Delta\times}$ (3.3-4.9)	13.6±0.9$^{\Delta\Delta}$(12.4-14.5)	2.3±0.6$^{\Delta\Delta\times}$ (1.8-2.7)	235±3.7$^{\times}$ (230-240)
HT-C_b	20	9.56±2.1^{+++} (5.8-13.2)	10.67±3.05^{+++} (6.5-16.2)	1.5±0.4^{+++} (1.0-2.2)	234±5.2^{+++} (230-238)
HT-Ca	20 20	4.32±0.6$^{¥¥\&\&}$ (3.4-5.5)	12.92±0.53$^{¥¥}$ (11.52-13.8)	2.2±0.4$^{¥¥\&}$ (1.5-3.1)	250±5.400$^{¥¥¥\&\&\&}$ (244-256)

Data were expressed as mean ± SD. For statistical analysis, one way ANOVA, paired 't' test and independent sample 't' test were done. Figures in parentheses indicate ranges.

Group EC: euthyroid subjects

Group HT: hypothyroid patient (**HT-T4b:** before treatment with thyroxine, **HT-T4a:** after treatment with thyroxine, **HT-Cb:** before treatment with thyroxine and vitamin B_{12}, **HT- Ca:** after treatment with thyroxine and vitamin B_{12}

[*= EC vs HT-T_{4b}, += EC vs HT-C_b, - = HT-T_{4a}vs HT-C_b, 0 =HT- T_{4a}vs HT-Ca, Δ =HT- T_{4b}vs HT- T_{4a}, ¥ =HT-$C_b$vs HT-C_a, & =EC vs HT-C_a, × = EC vs HT-T_{4a}]

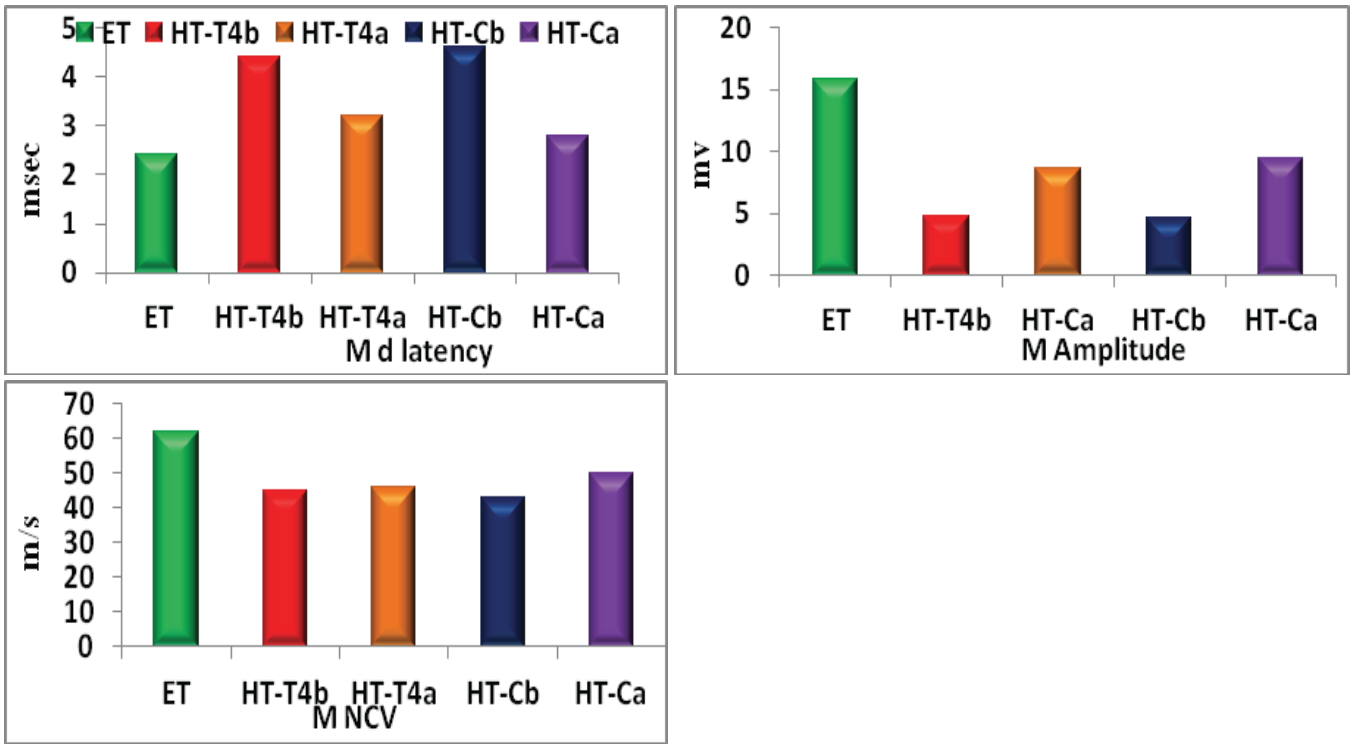

Figure 1: Mean nerve conduction parameters for motor functions of median nerve

Discussion

In the present study, the mean (±SD) serum TSH level was significantly ($p<0.001$) higher and FT_4 and FT_3 levels were significantly (<0.001) lower in both groups of hypothyroid female in the comparison to those of ET group. However, after supplementation, TSH level was significantly ($p<0.01$) decreased, whereas FT_4 and FT_3 levels were significantly ($p<0.01$, $p<0.001$) increased in both groups of HT female patients on day 90 in comparison to those of their pre-supplemented states on day 1. However, these levels were almost similar and the differences were not statistically significant between these two groups on day 90. Again, FT_4 level reached to the level of ET group after 90 days supplementation with combined therapy of thyroxine along with vitamin B_{12}.

Electrophysiological Status:

Motor function of median nerve:

In this study, the mean distal latency of median nerves (M d latency) was significantly decreased ($p<0.001$) and median amplitude (M amplitude) and nerve conduction velocity (MNCV) were significantly ($p<0.01$) increased in newly diagnosed HT female patients after supplementation with combined therapy of thyroxine along with vitamin B_{12} in comparison to

those of their pre- supplemented state (HT-Cb) and also of only thyroxine group (HT-T4b). Again, significant decreased value of M d latency and significant increased value of M amplitude with no significant change of MNCV were observed in only thyroxine group (HT-T4a) in comparison to those of their presupplemented state (HT-T4b). Almost similar type of findings were observed by some other researchers in pateints who suffered from uremic neuropathy and supplemented with only vitamin B_{12} for 6 months[19].

Different investigators have suggested some mechanism responsible for defective motor nerve conduction in HT patients. The mechanism involved in the development of neuropathy in hypothyroidism still remains unclear. Some investigator suggested that the weight gain in HT may be the contributory factors for the nerve conduction abnormalities[12]. The increased body weight and BMI in HT might be due to accumulation of mucopolysaccharides, hyaluronic acid and chondroitin sulphate in the interstitial spaces which because of their hydrophilic nature retain water along with them resulting in weight gain[4]. In addition, decreased rate of basal metabolism also causes increased body weight in HT[2].

On the other hand, an overall slowness in all metabolic pathways is seen in HT. Due to the reduction of the carbohydrate metabolism, glycosaminoglycans cannot be broken down; instead accumulate in the entrapment regions leading to entrapment neuropathy[13].

HT produces alteration of fluid balance and peripheral tissue edema, which may lead to carpal tunnel syndrome (CTS) development[14].

It has been suggested that CTS in hypothyroidism develops as a result of the mucinous infiltration in the perineurium and endoneurium of median nerve. The increased pressure as results of this infiltration is transferred to the median nerve and causes focal demyelination[15].

However, long term accumulation of mucinous tissue is a possible cause of irreversibility of CTS to replacement therapy[5]. Again, the cause of irreversibility to replacement therapy in hypothyroid patients may be related to duration and severity of illness and also to treatment regimens[5].

Moreover, some researchers also explained that, deposition of glycosaminoglycans in nerves and soft tissues surrounding them with resultant axonal degeneration and segmental demyelination forms the pathological basis of alteration in peripheral nerve function in thyroid hormone deficiency[16]. HT may affect the multiple peripheral nerves of our body. Depresses the gene activation for synthesis of myelin basic protein, required for myelination thereby causes impairment of nerve conduction velocities as well as loss of tendon reflexes[17]. In HT, most frequent cause of peripheral nerve damage is median nerve entrapment at wrist but sensory-motor polyneuropathy such as ulnar, common peroneal and sural neuropathy can also be seen[18]. However, the mononeuropathy i.e. involvement of single nerve may be secondary to compression due to deposition of myxedematous tissue and the polyneuropathy i.e. involvement of more than one nerve may be due to either a demyelinating process or the axonal degeneration. The combination of both this two factors results in the development of the peripheral neuropathy[19].

Conclusion

From the result of the study, it can be concluded that, peripheral neuropathy along with deficiency of vitamin B_{12} was observed in newly diagnosed hypothyroid female before starting their treatment.

However, after treatment with T_4 alone can improve peripheral nerve conduction parameters to some extent in newly diagnosed hypothyroid.

But, combined therapies of T_4 with vitamin B_{12} have synergistic effects on motor functions of peripheral nerve by improving all the parameters of electrophysiological study.

Acknowledgement

Authors of this study acknowledge the huge support from Neurology department of BSMMU for conducing

nerve conduction study. The authors are also thankful to the study subjects for their active and enthusiastic participation.

References

1. Keele CA, Neil E and Joels. Samsung Wright's Applied Physiology. 13th ed. Oxford University Press, New York. 1982; 542-545.

2. Hall JE. Textbook of Medical Physiology. 12th ed. Elseveir India Private limited. 2011; 550-552.

3. Barman SM, Boitano S and Brooks HL. Review of Medical Physiology. 24th ed. New York The McGraw-Hill Companies.2010; 587-588.

4. Edwards CRW, Toft AD and Walker BR. Endocrine Disease in Haslett C, Chilvers ER, Hunter JAA and Boon NA. Davidson's principle & practice of Medicine. 22nd ed. Churchillivingstone. India. 2014; 568-571.

5. Kecei H and Degirmenci. Hormone replacement theraphy in hypothyroidism and nerve conduction study. Neurophysiolclin. 2006; 35(2): 79-83.

6. Yeasmin S, Begum N, Begum S and Rahman SMH. Sensory neuropathy in Hypothyroidism: Electrophysiological and clinical findings. J Bangladesh Soc. Physiol. Dec 2007; (2): 1-6.

7. Kasem AA, Fathy SM, Shahin DA and Fikrt AA. Carpal tunnel syndrome in hypothyroid patients: The effect of hormone replacement therapy. American Journal of Internal Medicine. 2014; 2(3): 54-58.

8. Garg R, Bansal N, Singh N, Maria AK and Arora KS. Nerve conduction studies in newly diagnosed cases of Hypothyroidism' Sch. Acad . J. Biosci. 2015; 3(5): 479-488.

9. Mahadule AA, Jadhao PS and Phatak MS. Motor conduction parameters in recently diagnosed and untreated hypothyroidism. Annals of Neurosciences. 2015; 22(1).

10. Duyff RF, Bosch JVD, Laman DM, Loon BJPV and Linssen WHJP. Neuromuscular findings of thyroid dysdysfunction: prospective clinical electrodiagnistic study. J NeurolNeurosurg Psychiatry. 2000; 68: 750-755.

11. Lai CL, Liu CK, Tai CT, Lin RT and Howng SL. A Study of central and peripheral nerve conduction in patients with primary hypothyroidism: The effects of Thyroxine Replacement. Kaohsiung J Med Sci. 1988; 14(5) :294-302.

12. Preston DC and Shapiro BE. Electromyography and Neuromuscular Disorder, Clinical–Electrophysiologic correlation. 3rd ed. Elsevier Saundrs, Chaina. 1988: 115- 124.

13. Pollard JD. Neurology in diseases of the thyroid and pituitary glands. 3rd ed, Philedelphia: W.B. Sounders co. 1993.

14. Beghi E, Deledovici M, Boglium G, Crespi V, Paleari F, Gamba P et al. Hypothyroidism and polyneuropathy. J NeurolNeuroscience, psychiatry. 1989; 52: 1420-1423.

15. Dyck PJ, Lambert EH. Polyneuropathy associated with Hypothyroid. J NeuropatholExp Neurol. 1970; 29:631-58.

16. Misinumas A, Niepomniszeze H, Ravera B, Faraj G and Faure E. Peripheral neuropathy in subclinical hypothyroidism. Thyroid J.1995; 5: 283-6.

17. Barnal, J. Thyroid hormone and Brain development. Vitam. Horm. 2005; 71: 95-122.

18. Palumbo CF, Szabo RM and Olmsted SL. The effects of hypothyroidism and thyroid replacement on the development of carpal tunnel syndrome. J Hand Surg Am. 2000; 25: 734-739.

19. Madhavi LV, Rao DS, Ushasree T and Ramesh S. Efficacy of IV methylcobalamin and oral folic acid in the treatment of uremic neuropathy in chronic haemodialysis. Int J Pharm Biomed. 2013; 4: 65-68.