Original Article

Combined Effects of Thyroxine with Vitamin B12 on Electrophysiological Changes in Sensory Functions of Sural Nerve of Newly Diagnosed Hypothyroid Female Patients

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Abstract

Background: *Combination of thyroxine with vitamin B12 can improve the electrophysiological status of sensory function of sural nerve in newly diagnosed hypothyroid patients.* ***Objectives:*** *To observe the combined effects of thyroxine with vitamin B12 on electrophysiological changes in sensory function of sural nerve of newly diagnosed hypothyroid female.* ***Materials and Methods:*** *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. Among them, 20 hypothyroid patients received only thyroxine (HT-T4) and another 20 hypothyroid patients received combined therapy of thyroxine with vitamin B12 (HT-C) for 90 consecutive days. Nerve conduction parameters of sensory functions of sural nerve were studied to observe the electrophysiological status and vitamin B12 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 ($\chi 2$) test.* ***Results:*** *In this study, latency was significantly decreased, amplitude and NCV were significantly increased in sensory functions of sural nerve of hypothyroid patients after 90 days supplementation of combined therapy of thyroxine with vitamin B12 in comparison to those of their pre-supplemented state and also to those of patients with only thyroxine treatment.* ***Conclusion:*** *The present study revealed the combination of thyroxine with vitamin B12 can reduce the symptoms of hypothyroid and accelerate the nerve conduction velocity of sensory functions of sural nerve more efficiently than the treatment with thyroxine alone.*

Key words: *Nerve conduction velocity, distal latency, amplitude, thyroxine, vitamin B12.*

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Introduction

Hypothyroidism is a clinical condition resulting from reduced circulating levels of free thyroxine (FT4) and triiodothyronine (FT3).[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 FT4, 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

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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, paraesthesia, burning pain and some motor symptoms like weakness, muscle fatigability, stiffness and cramp.[8] 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 hypothyroid 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]

Metherials and 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 sensory nerve conduction parameters (delayed distal latency, decreased amplitude and NCV) of sensory functions of sural 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 B12 (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 on day 1

Results

In this study, the mean (±SD) serum TSH level was significantly ($p<0.001$) higher and FT4, FT3 and vitamin B12 level were significantly (<0.001) lower in group HT-T4band HT-Cbin comparison to those of group ET. Whereas, the levels were almost similar and differences were not statistically significant between group HT-T4band HT-Cb.

Again, TSH level was significantly ($p<0.01$) decreased, whereas FT4 and FT3 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 B12 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-T4brespectively.

However, FT4 level was almost similar and the difference was not statistically significant between groups HT-T4avsHT-Ca, ETvsHT-T4a and ET vs HT-Ca. Again, TSH level was significantly ($p<0.01$) lower, whereas FT3 level was significantly ($P<0.05$) higher in group HT-T4aand HT-Ca in comparison to those of group ET. But, these levels were almost similar and the differences werenot statistically significant between groups HT-T4a vs HT-Ca. Again, Vitamin B12 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 S d latency was significantly ($p<0.01$) higher whereas, S amplitude and SNCV were significantly ($p<0.001$) lower in group HT-T4band 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-T4band group HT-Cb.. Again, S d latency was significantly ($p<0.01$) decreased and S amplitude was significantly ($p<0.01$) increased in group HT-T4aand 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-T4aand HT-Ca.

Moreover, SNCV was significantly ($p<0.01$) increased in group HT-Cawhen compared to that of groupsHT-CbanT4a. However, this level in group HT-T4a projected towards the level of group ET, though the differences between ETvsHT-Ca was still statistically significant ($p<0.01$)

Table I: Serum Thyroid Stimulating Hormone (TSH), free Thyroxine (FT4), free Triiodothyronin (FT3), and Vitamin B12 levels in different groups (n=60)

Groups	n	TSH (µIU/ml)	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 ΔΔ× (3.3 -4.9)	13.6±0.9 ΔΔ (12.4 -14.5)	2.3±0.6 ΔΔ× (1.8 -2.7)	235 ± 3.7 × (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 -C a	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 ±5.4 00 ¥¥¥ &&& (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 B12 , HT- Ca: after treatment with thyroxine and vitamin B12) [*= EC vs HT-T4b , += EC vs HT-Cb , - = HT-T4a vs HT-Cb, 0 =HT- T4a vs HT-Ca, Δ =HT- T4b vs HT- T4a ,¥ =HT-Cbvs HT-Ca,& =EC vs HT-Ca, × = EC vs HT-T4a]

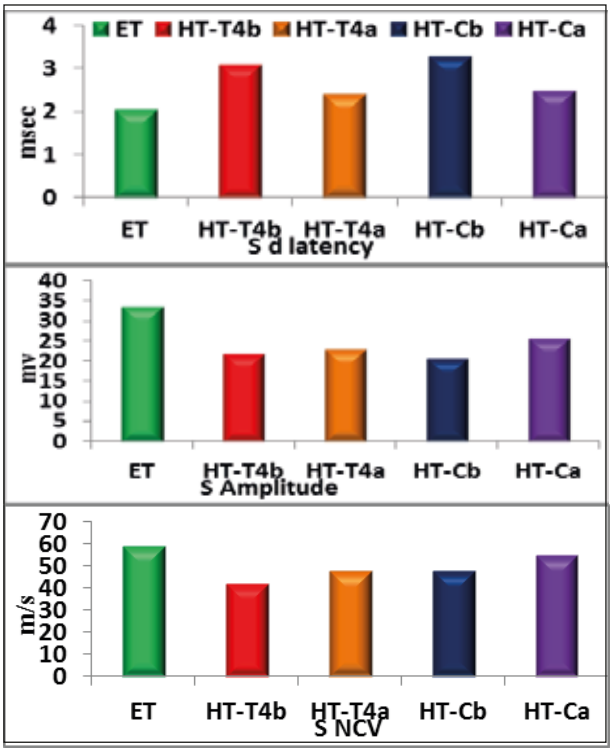

Figure I: Mean nerve conduction parameters for Sensory functions of Sural nerve

Discussion

In the present study, the mean (±SD) serum TSH level was significantly ($p<0.001$) higher and FT4 and FT3 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 FT4 and FT3 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, FT4 level reached to the level of ET group after 90 days supplementation with combined therapy of thyroxine along with vitamin B12.

Electrophysiological Status

Sensory function of sural nerve:

In this study, the mean distal latency of sural nerves (S d latency) was significantly decreased ($p<0.001$) and sural amplitude (S amplitude) and nerve conduction velocity (SNCV) were significantly ($p<0.01$) increased in newly diagnosed HT female patients after supplementation with combined therapy of thyroxine along with vitamin B12 in comparison to those of their pre-supplemented state(HT-Cb) and also of only thyroxine group(HT-T4b). Almost similar type of findings was observed by some others researchers in patients who suffered from uremic neuropathy and supplemented with only vitamin B12

for 6 months.[19] Different investigators have suggested some mechanism responsible for defective sural nerve conduction in HT patients. The mechanism involved in the development of neuropathy in hypothyroidism still remains unclear. Some investigators suggested that the weight gain in HT may be the contributory factors for the nerve conduction abnormalities in sural nerve.[12] The increased body weight and BMI in HT might be due to accumulation of mucopolysaccharide, hyaluronic acid and chondroitin sulphate in the interstitial spaces which, because of their hydrophilic nature retain water along with them resulting in weight gain4. In addition, decreased rate of basal metabolism also causes increased body weight in HT2.

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

HT produces alteration of fluid balance and peripheral tissue edema, which may lead to sural neuropathy.[14] It has been suggested that neuropathy in hypothyroidism develops as a result of the mucinous infiltration in the perineurium and endoneurium of sensory nerve. The increased pressure as results of this infiltration is transferred to the sensory nerve and causes focal demyelination.[15]

Moreover, some researchers also explained that, deposition of glycosaminoglycan in nerves and soft tissues surrounding them with resultant axonal degeneration and segmental demyelination forms the pathological basis of alteration in peripheral sensory 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 as sural 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 could be concluded that, sural neuropathy along with deficiency of vitamin B12 was observed in newly diagnosed hypothyroid female before starting their treatment. However, after treatment with T4 alone can improve peripheral nerve conduction parameters to some extent in newly diagnosed hypothyroid. But, combined therapies of T4 with vitamin B12 have synergistic effects on sensory functions of sural nerve by improving all the parameters of electrophysiological study.

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