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Combination of Thyroxine with Vitamin B_{12} on Motor Nerve Conduction Study of Ulanr Nerve in Newly Diagnosed Hypothyroid Female

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Abstract

Introduction: *Combination of thyroxine with vitamin B_{12} can improve the motor nerve conduction study of ulnar nerve in newly diagnosed hypothyroid female.* ***Objectives:*** *To observe the combined effects of thyroxine with vitamin B_{12} on motor nerve conduction study of ulnar 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. Among them, 20 hypothyroid patients received only thyroxine (HT-T_4) and another 20 hypothyroid patients received combined therapy of thyroxine with vitamin B_{12} (HT-C) for 90 consecutive days. Motor 2 nerve conduction study of ulnar nerve was 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, latency was significantly decreased, amplitude and NCV were significantly increased in motor functions of ulnar 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.* ***Conclusion:*** *The combination of thyroxine with vitamin B_{12} can reduce the symptoms of hypothyroid neuropathy and accelerate the nerve conduction velocity of motor functions of ulnar nerve more efficiently than the treatment with thyroxine alone.*

Key words: *Nerve conduction velocity, Distal latency, Amplitude,Thyroxine, Vitamin B_{12} .*

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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, paraesthesia, burning pain and some

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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 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].

Materials 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 nerve conduction parameters (delayed distal latency, decreased amplitude and NCV) of motor functions of ulnar 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-T_{4b}) received only thyroxine at a dose of 50 µg per day for 3 wks, 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-C_b) 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 on day 1.

Results:

In this study, the mean (±SD) serum TSH level was higher and FT_4, FT_3 and vitamin B_{12} levels were significantly lower in group HT-T4b and HT-Cb in the comparison to those of group ET. Whereas, the levels were almost similar and differences were not significant between group HT-T_{4b} and HT-Cb (Table-I). Again, TSH level was decreased, whereas FT_4 and FT_3 levels were increased in group HT-T_{4a} and HT-Ca in comparison to those of group HT-T_{4b} and HT-C_b respectively and vitamin B_{12} level was increased only in group HT-Ca in comparison to that of group HT-C_b and HT-T_{4b} respectively(Table-I). However, FT_4 level was almost similar and the difference was not significant between groups HT-T_{4a} vs HT-C_a, ET vs HT-T_{4a} and ET vs HT-C_a. Again, TSH level was lower, whereas FT_3 level was significantly ($P<0.05$) higher in group HT-$T4_a$ and HT-C_a in comparison to those of group ET (Table-I).But, these levels were almost similar and the differences were not significant between groups HT-T_{4a} vs HT-C_a. Again, Vitamin B_{12} level was reached towards the level of group ET, though this level still showed difference between ET vs HT-C_a (Table-I). In this study, the U d latency was significantly ($p<0.01$) higher whereas, U amplitude and UNCV were significantly ($p<0.001$) lower in group HT-T_{4b} and HT-C_b when compared to those of group ET. However, these levels were almost similar and the differences were not statistically significant between group HT-T_{4b} and group HT-C_b (Table-II). Again, U d latency was significantly ($p<0.01$) decreased and U amplitude was significantly ($p<0.01$) increased in group HT-T_{4a} and HT-C_a in comparison to those of HT-T_{4b} and HT-C_b respectively. However, these levels in group HT-T_{4a} and HT-C_a 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-T_{4a} and HT-C_a (Table-II). Moreover, UNCV was significantly ($p<0.01$) increased in group HT-C_a when compared to that of groups HT-C_b and T_{4a}. However, this level in group HT-T_{4a} projected towards the level of group ET, though the differences between ET vs HT-Ca was still statistically significant ($p<0.05$)(Table-II).

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/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 (3.3-4.9)	13.6±0.9 (12.4-14.5)	2.3±0.6 (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 (244-256)

Data were expressed as mean ± SD. Figures in parentheses indicate ranges.

Group ET: euthyroid subjects

Group HT: hypothyroid patient (HT-T_{4b}: before treatment with thyroxine , HT-T_{4a}: after treatment with thyroxine , HT-C_b: before treatment with thyroxine and vitamin B_{12} , HT- C_a: after treatment with thyroxine and vitamin B_{12}).

Table II: Nerve conduction parameters for motor function of ulnar nerve in different groups (n=60)

Groups	n	U d latency (msec)	U amplitude (mv)	U NCV (m/sec)
A	20	2.04±0.6 (1.2-3.1)	23.37±2.8 (20.2-27.5)	59±3.8 (55-65)
B_{1b}	20	3.1±1.1 (2.1-4.2)	10.6±5.7 (8-13.4)	47±3.5 (44-49)
B_{1a}	20	2.4±1.2 (1.7-3.0)	16.9±4.2 (13-19.5)	47.5±3.8 (45-51)
B_{2b}	20	3.3±0.8 (2.1-4.8)	9.5±4.6 (7.5-11.2)	48±4.3 (44-52)
B_{2a}	20	2.5±0.7 (1.8-3.8)	16.89±4.2 (12.6-20.5)	55±2.8 (48-61)

Statistical analysis

Groups	U d latency (p value)	U amplitude (p value)	U NCV (p value)
A vs B_{1b} vs B_{2b}	0.001**	0.000***	0.000***
A vs B_{1b}	0.021*	0.000***	0.000***
A vs B_{2b}	0.042*	0.000***	0.000***
B_{1b} vs B_{2b}	0.201^{ns}	0.101^{ns}	0.105^{ns}
B_{1a} vs B_{2a}	0.522^{ns}	0.416^{ns}	0.001**
B_{1b} vs B_{1a}	0.011*	0.007**	0.242^{ns}
B_{2b} vs B_{2a}	0.031*	0.001**	0.001**
A vs B_{1a}	0.714^{ns}	0.003**	0.001**
A vs B_{2a}	0.613^{ns}	0.005**	0.016*

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 A: euthyroid subjects

Group B: hypothyroid patients

B_{1b}: before treatment with thyroxine

B_{1a}: after treatment with thyroxine

B_{2b}: before treatment with thyroxine and vitamin B_{12}

B_{2a}: after treatment with thyroxine and vitamin B_{12}

***= Significant at P<0.00 **= Significant at P<0.01 *= Significant at P<0.05

ns = not significant n= total number of subjects

U d latency=Ulnar Distal Latency, **U Amplitude**=Ulnar Amplitude, **UNCV**=Ulnar Nerve Conduction Velocity

Discussion:

In the present study, the mean (±SD) serum TSH level was higher and FT_4 and FT_3 levels were lower in both groups of hypothyroid female in the comparison to those of ET group. However, after supplementation, TSH level was decreased, whereas FT_4 and FT_3 levels were 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 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 ulnar nerve:

In this study, the mean distal latency of ulnar nerves (U d latency) was significantly decreased (p<0.001) and ulnar amplitude (U amplitude) and nerve conduction velocity (UNCV) 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-C_b) and also of only thyroxine group (HT-T_{4b}). Again, significant decreased value of U d latency and significant increased value of U amplitude with no significant change of UNCV were observed in only thyroxine group (HT-T_{4a}) in comparison to those of their presupplemented state (HT-T_{4b}). Almost similar type of findings was observed by some others 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 mucopolysaccharide, 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, glycosaminoglycan 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, 20]. However, long term accumulation of mucinous tissue is a possible cause of irreversibility of CTS to replacement theraphy[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 glycosaminoglycan 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 conduc-

tion 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, 21].

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 ulnar nerve by improving all the parameters of electrophysiological study.

Conflict of Interest: None.

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