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Effects of Short-term and Long-termUse of Lithium on Thyroid Hormones in Nepalese Patients with Bipolar Disorder

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Lithium has been used for decades as mood-stabilizing agents in the management of bipolar disorder and other condition with a manic component. However, some studies have also reported varying degrees of thyroid abnormalities associated with lithium therapy and effect of such therapy on thyroid function is unclear in this part of world. Therefore, we aimed to determine the effect of long term use of lithium on thyroidfunctionin the individual with bipolar disorder receiving lithium therapy.
Methods: A total of 75 bipolar disorder patients (24 males, 51 females) who are under lithium therapy and equal number of control were recruited for this study. Diagnosis of bipolar disorder was

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made by psychiatrist according to ICD-10-DCR guidelines and DSM-IV criteria. Serum fT3, fT4 and TSH were measured by enhanced chemiluminescence immunoassay. Statistical analysis was performed using SPSS 20.0 version.

Results: The prevalence of primary hypothyroidism and subclinical hypothyroidism were found significantly increased in lithium treated group (12% and 17%, respectively) which was further increased with duration of treatment. The mean fT3 and fT4 concentration is low in lithium treated group compared to control group.Butmean TSH level was found significantlyhigher in lithium treated group compared to control (9.67±12.47 vs. 3.41±3.69, p<0.005).

Conclusion: Our findings indicate that use of lithium therapy is associated with higher degree of primary hypothyroidism and subclinical hypothyroidism and female are more susceptible for the thyroid dysfunction associated with lithium therapy.

Keywords: Bipolar disorder; lithium; FT3; FT4; TSH; hypothyroidism.

1. INTRODUCTION

Bipolar disorder is a chronic psychiatric illness characterized by recurrent episodes of mania, hypomania, mixed states, and depression [1]. People with bipolar disorder experience unusually intense emotional states that occur in distinct periods called mood episodes. Each mood episode represents a drastic change from a person's usual mood and behavior**.** Data suggest that 25% and 60% of individuals with bipolar disorder will attempt suicide at least once in their lives and between 4% and 19% will complete suicide [2]. The National Comorbidity Survey suggested a lifetime prevalence of bipolar disorder to 1.6% [3]. Lithium has been used for decades as a mood-stabilizing agents in the management of bipolar disorder and other condition with a manic component. It is recommended by major international guidelines as first-line prophylactic treatment in bipolar disorder [4]. Lithium and the lamotrigine are the drugs approved by the US Food and Drug Administration for maintenance and long term treatment of bipolar disorder [6,7].

Lithium have a narrow therapeutic target range with blood level over 1.5 mmol/L shows acute toxicity which is characterized by lethargy, muscular weakness, and speech difficulties [8]. Concentration over 2.5 mmol/L can result life-threatening seizures. On the other hand, long-term use of lithium is associated with numerous of clinical shortcoming including nephrogenic diabetes insipidus, thyroid abnormalities, renal tubular dysfunction, transient hyperglycemia and hyperparathyroidism [8-11]. Lithium affects the synthesis, release, and metabolism of thyroid hormones (T3 and T4) and thyroid stimulating hormone (TSH) and the iodinization of tyrosine in various ways which results in inhibition of thyroid hormones release from the gland, causinghypothyroidism [12-14]. Thyroid function can be assess with radiological examination and laboratory investigation of hormone of pituitary-thyroid axis. For the radiological examination, Iodine-123 is the isotope of choice for medical imaging that concentrated in thyroid directly with a half-life to 13.22 hours and decays by emission of gamma radiation with an energy of 159 keV [15-27]. There is no report on the effect of short-term and long-term effect of lithium therapyon the hypothalamic-pituitary-thyroid axis in Nepalese population. Therefore, this study was conducted to understand the effect of lithium therapy on thyroid physiology in Nepalese individuals with bipolar disorder.

2. METHODS

Thisstudy consisting of 75 bipolar disorder patients (24 males, 51 females) who were under lithium therapy.Diagnosis of bipolar disorder was made by psychiatristaccording to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria [28] and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [29]. The patients were recruited in department of psychiatric of Tribhuvan University Teaching Hospital, Kathmandu Nepal with informed written consent. This study was approved by the Institutional Review Board (IRB) of Institute of Medicine, Kathmandu. Equal number of age and sex matched bipolar disorder patients without lithium treatment was chosen as control. Individuals with preexisting history of thyroid dysfunction, dyslipidemia,diabetes and other chronic diseases were excluded.

5 mL of blood were collected from each study participants. FT3, FT4 and TSH wereestimated by the enhanced chemiluminescence immunoassay by an automated analyzer

(VITROS ECi Immunodiagnostic System, Ortho Clinical Diagnostics, NJ, USA). Data were analyzed using SPSS 20.0 version (Statistical Package for Social Science for Window version; SPSS, Inc., Chicago, IL, USA). The means of the 2 groups were compared using the ANOVA test, and the results were considered significant when $p<0.05$.

3. RESULTS AND DISCUSSION

23 out of 75 lithium treated bipolar disorder patients have thyroid dysfunction. There were 9 cases (12.0%) of primary hypothyroidism and 13 cases (17.3%) of subclinical hypothyroidism. Among 13 cases of subclinical hypothyroidism 4 (16.6%) cases were seen in male and 9 (17.64%) cases in female whereas all 9 cases of primary hypothyroidism were seen only in female population as shown in Table 1. Only one case (1.3%) of hyperthyroidism was also observed in treated group.

The mean value of fT3 (5.61±1.35) and fT4 (17.57±6.35) of Li treated group were found to be lower than that of control. But mean TSH level treated group was found to be significantly ($p<0.001$) higher than that of control and this was also correlated as shown in Table 2.

Lithium treated patients were divided into three groups based on the duration of lithium therapy (<2 years, 2-8 years and >8 years). Mean values of fT3, fT4and TSH were compared between patients in these groups and ANOVA chi square test was carried out. Mean value offT3 and fT4 were found to be lowest in the patient with treatment for >8 years and the difference seen was statistically significant ($p=0.007$) in fT4, whereas insignificant ($P=0.38$) in case of fT3. Similarly, the mean value of TSH was found to be highest in more than 8 years treated patients and the difference seen was statistically significant ($p=0.011$) as shown in table 3.Only one case of subclinical hypothyroidism but no any cases of primary hypothyroidism were observed in less than 2 years treatment. However the prevalence of primary and subclinical hypothyroidism were increased with increased duration of therapy as shown in table 4. A single case of hyperthyroidism was also observed in this study.

This is the first case-control study in Nepal aiming at identifying the thyroid dysfunction in lithium treated bipolar disorder patients. Clinically, lithium has a relatively narrow therapeutic index that requires finding a suitable Balance between achieving effectiveness and producing adverse effects. The major finding of

Table 1. Frequency of clinical and subclinical hypothyroidism in bipolar disorder treated with lithium

Parameters	Male (n=24)	Female (n=51)	Total (n=75)
Euthyroid (Normal)	20 (83.33%)	32 (62.74%)	52(69.33%)
Primary hypothyroidism	0 (0%)	9 (17.64 %)	9 (12.0%)
Subclinical hypothyroidism	4(16.6%)	9(17.64%)	13(17.33%)
Hyperthyroidism	0 (0%)	1(1.9%)	1(1.33%)

Table 2. Mean comparison of fT3, fT4 and TSH between Li treated and control group

Parameters	Case Group Mean±S.D.[Range]	Control Group Mean±S.D.[Range]	P Value
fT3(pmol/L)	5.61±1.35[1.9-9.1]	6.02±1.1[2.5-8.1]	0.051
fT4(pmol/L)	17.57±6.35[4.5-40.0]	19.71±4.56[6.3-28.0]	0.019
TSH(µIU/ml)	9.67±12.47[0.15-60.0]	3.41±3.69[0.9-24.0]	<0.001

Table 3. Comparison of fT3, fT4 and TSH according to duration of lithium treatment

Duration of Li Use (Years)	fT3(pmol/L) Mean ± S.D. [Range]	fT4(pmol/L) Mean ± S.D. [Range]	TSH(µIU/ml) Mean ± S.D. [Range]
<2 Years	5.84±0.99[4.7-8.0]	19.3±4.3[12.4-27.0]	4.0±4.63[1.3-18.5]
2-8 Years	5.6±1.50[1.9-9.1]	18.3±6.8[4.5-40.0]	8.9±13.00[15-60]
>8 Years	5.1±0.91[3.9-6.7]	12.4±2.1[9.0-15.6]	18.5±11.4[1.5-40.0]
P value	0.38	0.007	0.011

Table 4. Thyroid statuses according to duration of lithium treatment

Duration of Li therapy	Thyroid status			
	Euthyroid	Primary hypothyroidism	Subclinical hypothyroidism	Hyperthyroidism
<2 Years	11(91.7%)	0(0%)	1(8.3%)	0(0%)
2-8 Years	39(76.5%)	6(11.8%)	5(9.8%)	1(2.0%)
>8 Years	2(16.7%)	3(25.0%)	7(58.3%)	0(0%)

our study is that lithium therapy increased the risk of clinical and subclinical hypothyroidism (Table 1). We found that females are susceptibility to develop subclinical hypothyroidism during lithium therapy. Similar observations were made in previous studies. Johnston A et al reported the prevalence of clinical hypothyroidism during lithium treatment as 10.4% having higher rates in female gender (women 14% vs. men 4.5%) [14]. Similar prevalence of hypothyroidism (10.3%) in lithium treated patients was found in another cross sectional study by Kirov G et al. [30]. Kraszewska A et al. [31] in a cross sectional study of 66 bipolar disorder patients receiving therapy for 10-44 years showing 22% hypothyroidism in female with normal male patients. Henry C, et al. reported slightly different result from our study; prevalence of hypothyroidism 27%with significantly higher rates in female (37% female vs. 9% male) population [32].

In our study, we were interested to compare short term and long term effect of lithium therapy on thyroid function tests (fT3, fT4 and TSH) in bipolar disorder and we found that mean value of fT3 and fT4 were decreased with duration of lithium therapy whereas mean value of TSH was increased significantly with the duration. In the group who received lithium for less than 2 years, we observed only one case of subclinical hypothyroidism but no case of primary hypothyroidism. But the prevalence of primary and subclinical hypothyroidism were increased significantly in those who received long term lithium therapy. The exact mechanism by which lithium induces hypothyroidism is still not clear. Lithium can inhibit the cyclic AMP-mediated cellular events and also exerts inhibitory effect on the phosphatidylinositol pathway. It is reported that thyroid can concentrate lithium by 3-4 times that it plasma [33]. Increase accumulation of lithium on the thyroid gland can result the cellular disturbance leading to reduce function of thyroid. Lithium is also known to get concentrated in pituitary and hypothalamus leading disturbance of cellular functions [34]. Furthermore, it has been shown that lithium treatment is associated with increase prevalence of thyroid antibodies [35]. Thus the pathogenesis of lithium-induced hypothyroidism can be explained by either increase cellular concentration of lithium in thyroid leading to decrease synthesis and secretion of thyroid hormone and presence of antithyroid antibody.

4. CONCLUSION

Lithium therapy is one of the risk factors of primary and sub clinical hypothyroidism. Our findings also point out the greater susceptibility of female subjects for primary hypothyroidism which is being increased with duration of lithium therapy. Therefore, it is recommended that individuals with lithium therapy should be receive close monitoring of thyroid functions.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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