EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 4 Number 1 (January-2016) pp. 192-201

Journal home page: http://www.ijcrar.com

doi: http://dx.doi.org/10.20546/ijcrar.2016.401.019

Evaluation the Effects of Levothy Roxine on Patients with Chronic Pruritus and Anti-TPO+

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KEYWORDS

Urticaria,
Pruritus,
Levothyroxine

A B S T R A C T

Urticaria was a skin lesions of varying size that are characterized with erythematous plaque with regular or irregular margins in the red, sometimes with a red pressure go away. The aim of this study was evaluation the effects of Levothyroxine on patients with chronic pruritus and anti-TPO^{+}. In a clinical trial study that performed in department of endocrinology and metabolism of Tabriz University of Medical Sciences on patients with chronic pruritus, the effects of Levothyroxine on patients with chronic pruritus and anti-TPO^{+} evaluated. Mean age of case groups patients was 32.30±9.99 year and mean age of control groups patients was 36.83±11.92 (P=0.085). Two patients of case group and 3 patients of control group were male and 34 patients of case group and 33 patients of control group were female(P=0.500). Before of study; in case group, 12 of patients had mild pruritus, 18 of them had moderate pruritus and 6 of them had severe pruritus. In control group, 6 of patients had mild pruritus, 22 of them had moderate pruritus, 7 of them had severe pruritus and one of them had very sever pruritus. Significant difference was not found between pre-study pruritus severity of patients and two groups was matched in pre-study pruritus severity (P=0.142). At the end of study; in case group, 20 of patients had mild pruritus, 6 of them had moderate pruritus and 10 of tham had no pruritus. In control group, 16 of patients had mild pruritus, 11 of them had moderate pruritus and 9 of them had no pruritus. Significant difference was not found between post-study pruritus severity of patients of two groups (P=0.327). Mean TSH level of case group patients was 5.86±7.23 and mean TSH level of control group patients was 4.23±2.41 (P=0.210). Mean anti-TPO level of case group patients was 816.67±681.79 and mean anti-TPO level of control group patients was 920.43±1953.32(P=0.764). In patients of case and control groups, pruritus severity was significantly decrease at post-study than pre-study and results indicate that, both treatment was effective in decrease of pruritus severity of patient, but, treatment with Levothyroxine was more effects due to routine treatment.

Introduction

Urticaria is a kind of rash of different sizes, which manifests as erythematous plaques with regular or irregular margin in a red background. The redness of the manifestations sometimes disappears by applying pressure (1-2).

The rash is mainly reciprocating and does not last for more than 24 hours. The condition becomes chronic when the rash lasts more than 6 weeks or relapses (1-2).

Chronic urticaria is a clinical syndrome development of which involves various factors. Identification of these factors is highly important for the treatment of patients (3). However, the agent(s) causing this disease are only discovered in less than 30% of cases (3).

Studies in recent years have pointed to the role of autoimmune diseases in pathogenesis of this disease (4-5). The cause of urticaria or chronic angioedema is still not exactly known in autoimmune diseases. However, these are probably caused by the formation and storage of immunity complexes, and activation and release of pro-inflammatory mediators by activated cells. Moreover, autoantibodies probably increase the persistence of inflammatory changes in urticaria or chronic angioedema, and lead to the induction and release of histamine by basophiles and skin mast cells (6). Among the autoimmune diseases, thyroid autoimmune diseases are of significant importance (7).

The estimated prevalence of the effect of anti-thyroid antibodies in the general population is 3-6% (7), but a higher prevalence has been reported for people suffering from urticaria or chronic angioedema (7).

The prevalence of positive thyroid antibodies in urticaria cases has been reported to be 12-29% in different studies (8). In addition, numerous studies have been carried out on the treatment of these patients with thyroid drugs and the effect of this treatment on the improvement these skin lesions (9).

In view of the possibility of involvement of thyroid autoimmune diseases in the pathogenesis of chronic urticaria and considering the effect of the diagnosis and treatment of this disorder on the management of patients with chronic urticaria or angioedema, the present study aimed to examine the relationship between the aforementioned disorders in a sample of Iranian patients. In this research, it was tried to study the effect of treatment with Levothyroxine on these patients.

The aim of this research was to determine the effect of Levothyroxine on the treatment of patients with chronic pruritus and positive anti-TPO (Thyroid Peroxidase Antibody).

In a clinical trial carried out in Tabriz on patients with chronic pruritus, the effect of Levothyroxine on the treatment of patients with chronic pruritus and positive anti-TPO was investigated.

Considering the 3-6% prevalence (5%) and 95% diagnostic precision of the ($n=z^2*p(1-p)/d^2$) formula, the sample size was calculated to be 72.

In this study, 72 patients with chronic pruritus and positive anti-TPO were selected and randomly classified into two groups. The patients that were diagnosed with chronic pruritus (over 3 months) in clinical examinations and assessments and demonstrated positive anti-TPO in

experimental examinations were selected and randomly divided into two groups.

The patients were randomly put in one of the experimental (intervention) or control groups in the order of inclusion using the www.random.org website.

At the beginning, the patients were classified randomly by a third person, and the patients and researcher were blind to the grouping.

Patients of the experimental group received Levothyroxine and antihistamines, whereas the control group only received antihistamines. The effect of treatment was studied after 3 months.

Inclusion Criteria

Aged between 20 and 60 years
Positive anti-TPO
Pruritus longer than 3 months

Exclusion Criteria

Diabetes
Intake of thyroid drugs
Pregnancy
Hyperthyroidism
Antihistamine intake

The severity of pruritus before and after treatment was measured using the VAS scale, which ranked pruritus severity from 0 to 10. The pruritus varied from mild pruritus to severe pruritus, and the scale revealed the severity of pruritus in such patients. The results were also examined.

Levothyroxine tablets (0.1 mg) made by Exir Pharmaceutical Company were used. The antihistamine tablets were also made by Exir Pharmaceutical Company.

The primary outcome was severity of pruritus before treatment and the second outcome was severity of pruritus after treatment in the patients. Both outcomes were ranked in the 0-10 range using the VAS scale and the results were analyzed.

Patients that used drugs that reduce pruritus (such as other antihistamines, etc.) in the course of treatment were excluded from the research and were replaced by other patients, who met the inclusion criteria.

The missed-to-follow-up cases included patients who did not visit the center regularly or did not cooperate adequately in the research and in terms of consumption of research drugs or other drugs during the study. To cope with these cases, the required training was provided to all patients at the beginning of the research, and the patients were exposed to regular follow-ups. The as-treated clinical trial strategy was employ. This clinical trial is listed on Irct.ir as IRCT2014112613612N3.

Ethical Considerations

No invasive action was taken on the study patients. Their treatment procedures were not changed and no additional cost was imposed on the patients for the consumption of Levothyroxine. At the beginning of the research, the researcher provided free Levothyroxine to the patients. All of the patients' information will also remain confidential.

Results and Discussion

In this research, 72 patients suffering from chronic pruritus were classified into the experimental and control groups and the following results were obtained.
The average age of patients in the experimental group and control group was

32.30 ± 9.99 years and 36.83 ± 11.92 years, respectively. There was no significant difference between the mean age of the two groups (P=0.085).

Two patients in the experimental group and 3 patients in the control group were male, while 34 patients in the experimental group and 33 patients in the control group were female (P=0.500).

Prior to the investigations, 12, 18, and 6 patients in the experimental group were suffering from mild pruritus, moderate pruritus and severe pruritus, respectively. Moreover, 6, 22, and 7 patients in the control group demonstrated mild pruritus, moderate pruritus and severe pruritus prior to the research. One patient in this group was also suffering from extremely severe pruritus.

No significant difference was observed between pre- and post-treatment severities of pruritus in patients of the two groups (P=0.142).

Following the investigation, 20, 6, and 10 patients in the experimental group demonstrated mild, moderate and no pruritus, respectively. In the control up, 16, 11, and 9 patients showed mild pruritus, moderate pruritus, and no pruritus, respectively. No significant difference was observed between pre- and post-treatment severities of pruritus in the two groups (P=0.327).

The experimental findings on the patients in the beginning of the research are presented in a table.

TSH Levels in Patients

The average TSH level in patients of the experimental and control groups was 5.68 ± 7.32 and 4.23 ± 2.41, respectively.

There was no significant difference between average TSH levels in patients of the two groups, and the groups were homogeneous in terms of TSH levels (P=0.210).

Anti-TPO Levels in Patients

The average anti-TPO level in patients of the experimental and control groups was 816.67 ± 681.79 and 920.43 ± 1953.32, respectively.

There was no significant difference between average anti-TPO levels in patients of the two groups, and the groups were homogeneous in terms of anti-TPO levels (P=0.764).

Table (4-1) presents the results of assessing the relationship of experimental parameters with gender and severity of pruritus in patients of the experimental group.

Results of the examination of the relationship of experimental parameters with the gender and severity of pruritus in patients of the control group are shown in Table (4-2).

In patients of the experimental group, the severity of pruritus following treatment was significantly lower than the pre-treatment pruritus severity (P<0.001).

In patients of the control group, the severity of pruritus after treatment was significantly lower than the pretreatment pruritus severity (P<0.001). Variations in severity of pruritus in patients of the two groups after treatment are presented in Figure (4-2) as compared to the pretreatment values.

Preliminary studies referred to the relationship between chronic urticaria and Hashimoto's thyroiditis (5). Later on, numerous studies were carried out and

published to examine the relationship of thyroid antibodies with chronic urticaria (10-15).

One of the reasons reflecting this relationship is the recovery of a considerable percentage of patients with Levothyroxine in spite of the normal performance of thyroid in such patients (16). It shall be mentioned that some studies have not had satisfactory results. For example, in the research by Levy et al. no improvement was observed in patients (17). Moreover, in the study by Feibelmann et al. no relationship was found (18). The relationship between chronic urticaria and thyroid disorders is debatable and contradictory findings are still reported.

In a study by Leznoff et al., the frequency of thyroid autoimmune disorders was investigated and a prevalence of 12.1% was reported (19).

Table.1 Evaluation of Laboratory Finding in Case Group Patients

		Anti_TPO	P	TSH	P
Sex	Male	854.50 ± 260.92	0.937	4.53 ± 4.99	0.795
	Female	814.45 ± 700.62		5.95 ± 7.48	
Primary Pruritus	Mild	903.79 ± 744.00		6.97 ± 11.18	
	Moderate	841.46 ± 644.40	0.615	6.11 ± 4.91	0.549
	Sever	568.12 ± 727.84		2.94 ± 2.21	
Secondary Pruritus	No	970.74 ± 706.72		4.50 ± 5.44	
	Mild	747.88 ± 606.69	0.708	6.62 ± 8.59	0.764
	Moderate	789.25 ± 942.85		5.66 ± 5.95	

Table.2 Evaluation of Laboratory Finding in Control Group Patients

		Anti_TPO	P	TSH	P
Sex	Male	769.00 ± 431.28	0.891	3.93 ± 1.24	0.826
	Female	934.21 ± 2039.41		4.26 ± 2.50	
Primary Pruritus	Mild	391.58 ± 190.84		4.38 ± 0.95	
	Moderate	1263.66 ± 2443.81	0.638	4.36 ± 2.91	0.950
	Sever	419.00 ± 439.65		3.76 ± 1.81	
	Very Sever	52.72		3.84	
Secondary Pruritus	No	1700.41 ± 3740.30		3.12 ± 1.57	
	Mild	631.28 ± 624.31	0.394	4.49 ± 3.07	0.274
	Moderate	702.88 ± 918.82		4.77 ± 1.65	

Chart.1 Distribution of Age

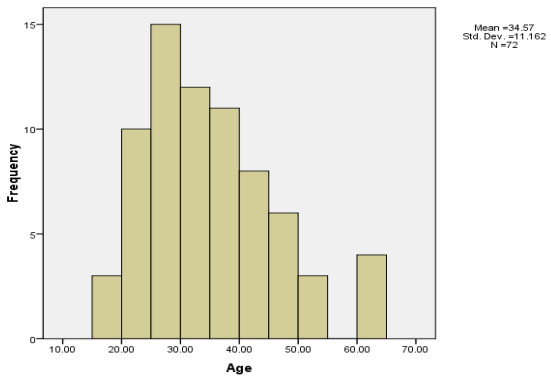


Chart.2 The Pruritus Changes in Patients After Treatment than Before Treatment in Both Gruoups

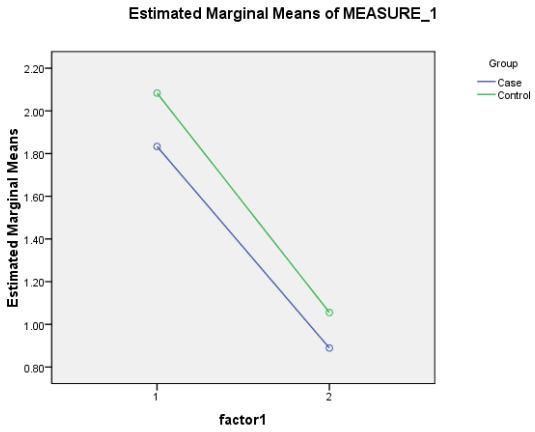


Chart.3 Tsh Level Distribution Based on Primary Pruritus in Case Group

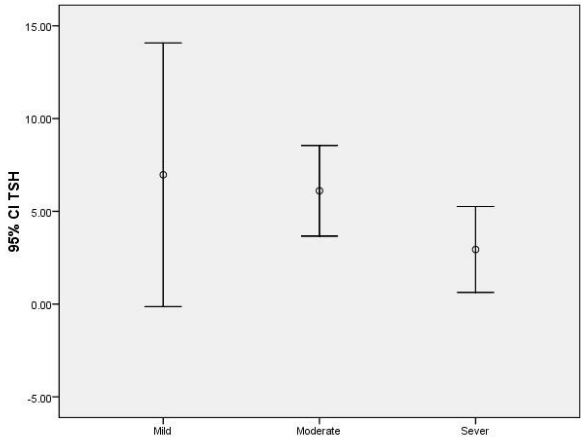


Chart.4 Anti-Tpo Level Distribution Based on Primary Pruritus in Case Group

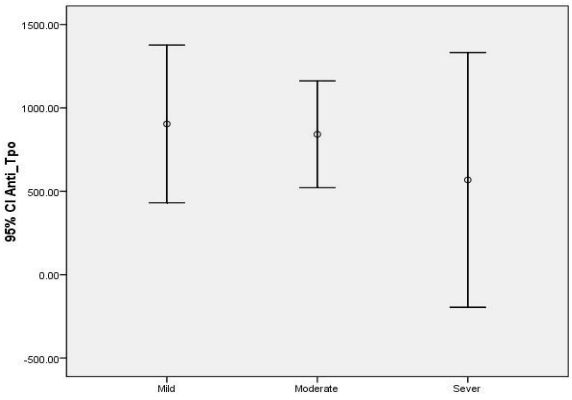


Chart.5 TSH Level Distribution Based on Primary Pruritus in Contrrol Group

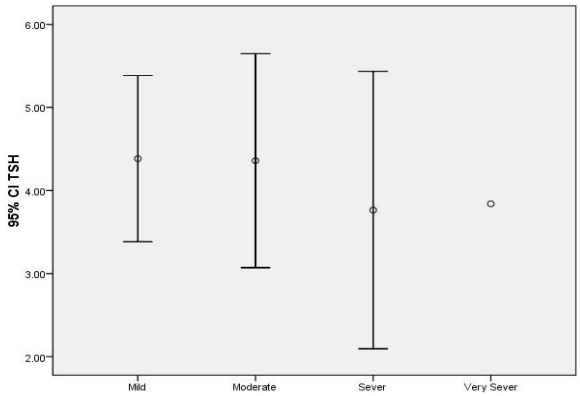
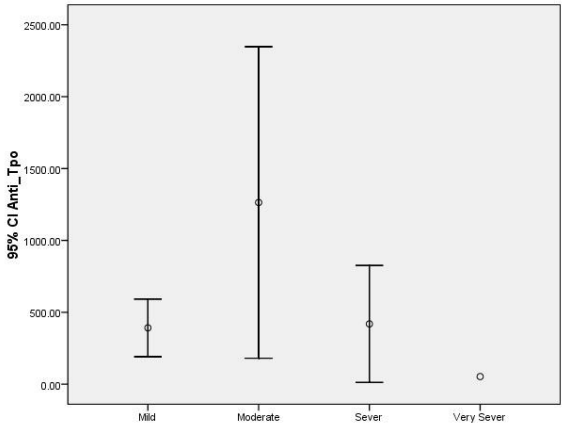


Chart.6 Anti-Tpo Level Distribution Based on Primary Pruritus in Contrrol Group



In an investigation by Sussman et al. the frequency of chronic urticaria in patients with thyroid disorders was examined and it was reported that frequency of chronic urticaria in such patients was 14.4% (20).

In a study by Callet et al., the frequency of chronic urticaria in patients with thyroid disorders was examined. According to the results, the frequency of chronic urticaria in such patients was 17.7%. However, the frequency of autoimmune thyroid disorders in the control group was 6% (21).

In similar studies, the frequency of autoimmune thyroid disorders in patients with chronic urticaria or angioedema in Turkey (13) and Italy (22) was 17.57% and 25%, respectively.

In a study that was recently carried out in France to examine the relationship between chronic urticaria and thyroid autoimmunity in patients with chronic urticaria and healthy people, the frequency of autoantibodies in patients with chronic urticaria was significantly higher than the healthy group (26.7% versus 3.3%). Based on the results, measurement of the level of autoantibodies

in patients is emphasized as a necessary assessment (23).

Similar to previous studies, in another research the frequency of thyroid autoantibodies in patients with chronic urticaria was higher than healthy people (27% versus 9%) (24).

In view of their similar findings, Zauli et al. recommended measurement of autoantibodies and thyroid performance tests in patients with chronic urticaria (8).

In a study by Kiyici et al. (2010) in the Endocrinology and Metabolism Department of Uludag University in Bursa (Turkey) it was reported that consumption of Levothyroxine did not significantly influence euthyroid patients with CIU (25).

Monge et al. studied the effect of Levothyroxine on the improvement of chronic pruritus symptoms in patients with thyroid autoimmune diseases. They stated that Levothyroxine was effective for the treatment of symptoms of the patients (26).

Dreskin et al. examined the relationship of chronic pruritus with thyroid involvement in patients and reported that use of Levothyroxine caused no side effects in the patients (27).

Similar to the results of the above study, in our research no side effect was observed in patients.

Palma-Carlos et al. (2005) conducted a study in the Endocrinology and Metabolism Department of Libson (Portugal) to examine the frequency of chronic pruritus in patients with thyroid autoimmune involvement. They stated that frequency of chronic pruritus in the patients was high (28).

In an investigation by Bagnasco et al. in Genoa (Italy) the relationship between chronic pruritus and thyroid autoimmune involvement was studied and it was concluded that screening is necessary for thyroid autoimmune involvement (29).

Gulee et al. (2011) conducted a study in the Internal Diseases Department of Ankara University of Turkey to examine the prevalence of chronic pruritus in patients with thyroid autoimmune diseases. They stated that in patients with chronic pruritus and thyroid autoimmune diseases, treatment with Levothyroxine reduced the severity of pruritus and inflammation of thyroid gland (30).

Similar to the results of the above research, in our study Levothyroxine consumption reduced severity of pruritus in these patients.

Magen et al. studied chronic pruritus in patients with autoimmune diseases and concluded that treatment with Levothyroxine reduced pruritus in such patients. The reduction was not statistically insignificant as compared to the control group patients (31).

In our study, consumption of Levothyroxine reduced severity of pruritus in patients. However, unlike the above research no significant difference was observed between the control and experimental groups.

Conclusion

In the experimental and control groups, the severity of pruritus following treatment was significantly lower than the pruritus before treatment. Research results suggest that both treatments were effective for reducing pruritus in patients. Moreover, treatment with Levothyroxine was not more effective than typical treatments.

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How to cite this article:

Farzad Najafipour, Mahnaz Sadeghi Shabestari, Behnam Nasiri Motlagh, Mostafa Najafipour, Behzad Nazari and Mohammad Khanmohammadi. 2016. Evaluation the Effects of Levothy Roxine on Patients with Chronic Pruritus and Anti-TPO+. *Int.J.Curr.Res.Aca.Rev.* 4(1): 192-201. doi: http://dx.doi.org/10.20546/ijcrar.2016.401.019