COMPARATIVE STUDY OF CLINICAL EFFICACY OF DILTIAZEM AND PROPRANOLOL IN PATIENTS WITH HYPERTHYROIDISM

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ABSTRACT

Objectives: *To compare the efficacy of diltiazem and propranolol in controlling the adrenergic manifestations of hyperthyroidism.*

Material and Methods: *This prospective, interventional study included 44 newly diagnosed, untreated patients with hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine, Peshawar. Patients were randomized to two matched groups. Group I (n = 23, mean age 37.91 ± 10.48 years) took diltiazem 30 mg three times a day for 6 weeks. Group II (n = 21, mean age 37.57 ± 14.27 years) took propranolol 20 mg three times a day for a period of 6 weeks. Clinical assessment was done before starting therapy and then after 6 weeks (± 3 days) using standardized and modified hyperthyroid symptom score (HSS).*

Results: *HSS decreased from 16.35 ± 2.31 to 11.26 ± 2.56 in group I after 6 weeks of therapy with diltiazem (P < 0.001). HSS declined from 15.62 ± 2.25 to 11.38 ± 2.13 in group II after 6 weeks of therapy with propranolol (P < 0.001).*

Conclusion: *Diltiazem, like propranolol, effectively controls the clinical manifestations of hyperthyroidism.*

Key words: *Diltiazem, propranolol, hyperthyroidism,Hyperthyriod Symptom Score (HSS).*

INTRODUCTION

The elevated levels of thyroid hormones can result in clinical manifestations like tachycardia, enhanced thermogenesis, tremor, sweating, weight loss, diarrhoea, lid-lag and hyperkinetic behaviour, leading towards mortality and morbidity for the affected patients. Many of these thyrotoxic manifestations resemble those produced by excess catecholamines.[1,2] However, there is no evidence that patients with hyperthyroidism have increased catecholamine secretions; plasma concentrations of adrenaline and noradrenaline are normal or even decreased in hyperthyroidism.[3] Available evidence suggests that excess levels of thyroid hormones result in enhanced tissue responsiveness to endogenous catecholamines, an effect most reasonably explained by the increased densities of β-adrenergic receptors, or perhaps modulation of post-receptor cellular events in those target tissues.[4,5]

Drugs with sympatholytic activity have been successfully employed in the management of hyperthyroidism. Guanethidine and reserpine, which deplete tissue catecholamines, were used in the past in combination with antithyroid drugs. However, these drugs had troublesome side effects, and with the availability of β-adrenergic receptor blocking drugs, trend changed towards the latter drugs; propranolol, a non-selective β-blocker, is the drug now used almost exclusively as adjunct to antithyroid drugs in thyrotoxic patients. But there are clinical conditions in which these drugs are clearly contraindicated or hazardous, e.g. asthma and COPD,[6] atrioventricular conduction defects,[7]

diabetes,[8-10] hyperlipidaemia[11] and depression.[12]

In a search for an alternative form of therapy as an adjunct to antithyroid drugs, Clozel and his colleagues (1984) studied the effects of propranolol and verapamil on heart rate and blood pressure in hyperthyroid patients but reached the conclusion that verapamil is not a good alternative to propranolol in hyperthyroidism.[13] Roti et al (1988) suggested that diltiazem (a non-dihydropyridine calcium channel blocker) may be used as adjunctive therapy for thyrotoxicosis in the presence of angina and congestive cardiac failure.[14] Milner et al (1990) concluded that diltiazem may serve as an alternative therapy for β-blockers in controlling thyrotoxic symptoms in patients in whom β-blockers are contraindicated.[15] Kelestimur and his colleagues (1993) found that diltiazem can be used in hyperthyroidism in place of propranolol where β-blockade is contraindicated.[16] Kelestimur and Aksu (1996) suggested that diltiazem can be used safely in hyperthyroid patients to alleviate the adrenergic manifestations of the disease.[17] later on, Marwat and his colleagues (2006) concluded that diltazem is an effective drug for controlling thyrotoxic symptoms but awaits further elucidation in future studies to be used as a routine alternative drug to propranolol in the management of hyperthyrodism[18].

The present study was undertaken in local population to compare the ameliorating effects of diltiazem and propranolol on the adrenergic manifestations of hyperthyroidism on a more prolonged time scale than done during the previous studies.

MATERIAL AND METHODS

Sixty (60) newly diagnosed, untreated cases of hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine, Peshawar were registered in this prospective, interventional study using the following criteria:

Inclusion criteria:

- Patients of 20-55 years of age of either sex,
- Mild to moderate stable cases of hyperthyroidism with serum free thyroxin (FT_4) levels not more than 50 pmol/L (normal reference range for FT_4 is 11.5- 23 pmol/L with values of > 74 pmol/L in severe disease), and
- Patients who gave a written, well informed consent.

Exclusion criteria:

- Patients with serum FT4 > 50 pmol/L,
- Pregnant or lactating mothers, and
- Patients with evidence of cardiovascular, renal or any other chronic illness e.g diabetes.

Patients were randomized to two matched groups using random number table. Group I (initially n = 30 but after drop out n = 23, with 22 females and 1 male, having mean age of 37.91 ± 10.48 years) took diltiazem (Dilzem – Park-Davis) 30 mg three times a day for 6 weeks. Group II (initially n = 30 but after drop out n = 21, with 19 females and 2 males, having mean age of 37.57 ± 14.27 years) took propranolol (Inderal – ICI) 20 mg three times a day for 6 weeks. Clinical assessment was done on day 0 (baseline) and then after 6 weeks (± 3 days) of starting therapy with diltiazem (group I) and propranolol (group II), using standardized and modified hyperthyroid symptom score (HSS).

The HSS is a clinician-rated instrument for the assessment of symptoms associated with hypermetabolic thyroid hormone conditions and based on an evaluation of symptoms available in the endocrine literature. Patients were asked to what extent each symptom (excessive sweating,

BASELINE AND POST-INTERVENTION CHARACTERISTICS REGARDING HSS

Category of patients	Baseline HSS	Post-intervention HSS	*P* value*
Group I (diltiazem therapy) n = 23	16.35 ± 2.31	11.26 ± 2.56	< 0.001
Group II (propranolol therapy) n = 21	15.62 ± 2.25	11.38 ± 2.13	< 0.001

* P values between means of baseline HSS and post-intervention HSS (6 weeks after starting therapy).

Table 1

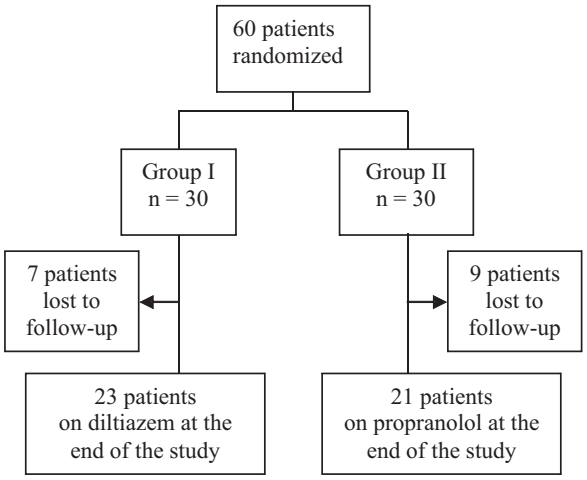

Figure 1. Trial profile.

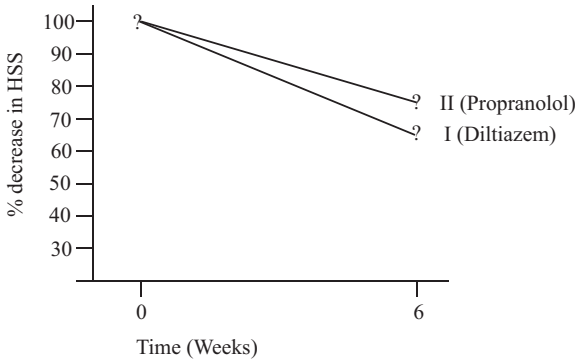

Figure 2 Percentage decrease in post - intervention HSS.

trembling hands, heat intolerance, easy fatigability, nervousness, diarrhoea, increased appetite, palpitation, dyspnoea on exertion) was present during the week before the interview. Answers were scored from 0 (not present) to 3 (severe).[19,20]

Data collected were analyzed statistically using SPSS. The mean HSS of two groups were compared by applying 'unpaired' (independent) t-test while mean baseline HSS in each group was compared with the post-interventional mean HSS after 6 weeks of therapy using 'paired' t-test. Values of '*P*' less than 0.05 were considered significant while those less than 0.001 were taken as highly significant.

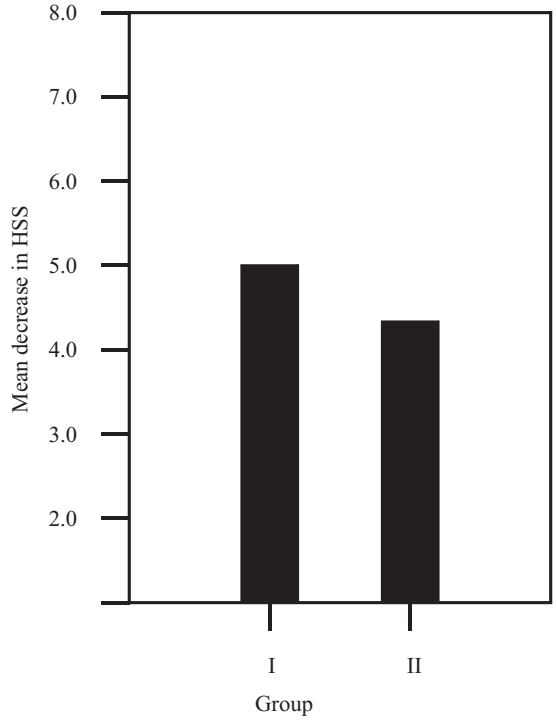

Figure 3. Mean decline in post-intervention HSS — Group I versus GroupII.

RESULTS

Out of 60 registered patients, 16 were lost to follow-up (7 in group I and 9 in group II). So 44 patients remained in the study and were finally available for analysis (Figure 1). Results are described as mean ± SD.

Group I (diltiazem group) included 23 patients (22 females and 01 male with mean age of 37.91± 10.48 years) and group II (propranolol group) included 21 patients (19 females and 02 males with mean age of 37.57 ± 14.27 years).

HSS decreased from 16.35 ± 2.31 to 11.26 ± 2.56 after 6 weeks of therapy with diltiazem in group I. This decline is highly significant ($P < 0.001$). HSS decreased from 15.62 ± 2.25 to 11.38 ± 2.13 after 6 weeks of therapy with propranolol in group II. This decline is also highly significant ($P < 0.001$) (Table 1). The mean decline in HSS in group I (5.09 ± 2.13) when compared with that in group II (4.24 ± 1.81), the difference was non-significant ($P > 0.05$) (Figures 2& 3).

DISCUSSION

The antithyroid drugs (carbimazole and propylthiouracil) used in the management of hyperthyroidism act primarily to prevent the biosynthesis of thyroid hormones. They have no effect on the release of thyroid hormones previously stored in the gland, which take several weeks to be depleted.[21] So sympatholytic drugs (which deplete tissue catecholamines or block their peripheral effects) are used in conjunction with antithyroid drugs to ameliorate the clinical manifestations of the disease. Propranolol, a non-selective β-adrenergic receptor blocking drug with

no intrinsic sympathomimetic activity, is now the drug used almost exclusively as adjuvant therapy to antithyroid drugs.[14]

No doubt, propranolol works very well in almost any set up of thyrotoxicosis, e.g. in Graves' disease (including that occurring in newborns), in the preparation of patients undergoing thyroidectomy, before and following treatment with radioactive iodine, in thyrotoxicosis due to some self-limited causes such as silent or painless sporadic or postpartum thyroiditis,[14] but there are clinical situations which limit the use of propranolol (and also other β-blockers, including cardioselective ones).[22] Diltiazem, a calcium channel blocker with non-specific antiadrenergic activity more than any other member of this family, has been suggested as an adjunct to antithyroid drugs in patients in whom β-blockade is contraindicated. But this drug is underused, rather not used at all, in the set up of hyperthyroidism.

The present study was conducted on local population to compare the clinical efficacy of diltiazem and propranolol in alleviating the adrenergic manifestations of hyperthyroidism on a more prolonged time scale.

Our data have clearly shown that diltiazem is an effective drug for controlling the thyrotoxic symptoms. The mean decline in HSS in group I is highly significant after 6 weeks of therapy with diltiazem ($P < 0.001$). The mean decline in HSS in group II is also highly significant ($P < 0.001$) (Figure 3). The difference in clinical response (decrease in mean HSS) between the two groups (diltiazem versus propranolol) is non-significant ($P > 0.05$) (Figures 2 & 3). These findings are in agreement with the results of the studies done by Milner et al,[15] Kelestimur et al,[16] and Kelestimur and Aksu.[17]

Milner et al compared the efficacy of diltiazem and propranolol in a randomized, prospective, double-blind, crossover study in six patients with untreated thyrotoxicosis and observed that all subjects felt better with drug therapy, with three preferring diltiazem to propranolol. No significant difference in clinical response or in haemodynamic effects was noted between the agents.[15] Kelestimur et al did a randomized study comparing the effects of diltiazem on cardiac and thryroid function with propranolol therapy in a larger group (20 hyperthyroid patients) and demonstrated that diltiazem was effective as well as propranolol for the treatment of sympathomimetic manifestations caused by hyperthyroidism.[16] Kelestimur and Aksu did a prospective, randomized and placebo controlled study on 22 newly diagnosed hyperthyroid patients and demonstrated that diltiazem is an effective and safe drug and may be used as an adjunctive therapy in patients with hyperthyroidism.[17]

The clinical efficacy of diltiazem in alleviating the adrenergic manifestations of hyperthyroidism may be due to the following facts: (i) diltiazem has nonspecific antiadrenergic activity (this adrenolytic activity is more than any other calcium antagonist used clinically);[23] (ii) raised thyroid hormone levels are associated with increased number of slow Ca^{2+} channels, resulting in increased Ca^{2+} influx in some tissues of thyrotoxic chicks. Diltiazem may interfere with these and other similar phenomena in hyperthyroid patients;[24] and (iii) diltiazem administration may possibly interfere with noradrenaline release from the sympathetic nerve endings. Indeed, diltiazem administration has been shown to diminish the release of noradrenaline in rabbit arteries.[25]

CONCLUSION

Diltiazem, like propranolol, has worked very well in controlling the adrenergic manifestations of hyperthyroidism. In view of the present findings, it is reasonable to suggest that diltiazem may be used in the set up of hyperthyroidism where β-blockade is contraindicated or hazardous, such as in patients with asthma or COPD, diabetes, hyperlipidaemia and depression.

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