ORIGINAL ARTICLE

EFFICACY OF DIFFERENT DOSAGE REGIMENS OF CARBIMAZOLE IN THE TREATMENT OF PRIMARY HYPERTHYROIDISM

Rashid Usman[1], Shafaq Ismail[1], Rimsha Tahir[1], Muhammad Jamil[2]

Department of Surgery, CMH Lahore Medical College and CMH Hospital Lahore, [2]CMH Rawalpindi-Pakistan

Objectives: To compare the efficacy of Single dose with Divided dose regimen of Carbimazole for the induction of Euthyroidism in hyperthyroid patients. **Methods:** All consecutive hyperthyroidism patients from December 2018 to December 2019 fulfilling the inclusion criteria were included. They were allocated randomly into 2 groups: Group A - single dose of Carbimazole (OD-CMZ) and Group B - divided dose of Carbimazole (DD-CMZ). The therapeutic efficacy was measured at regular intervals (every 4 weeks) for 6 months. Their demographics and therapeutic management were analysed. **Results:** Of a total of 69 (n=34 in Group A, n=35 in Group B) patients, there was no significant difference in baseline concentrations of TSH and T4 as well as their cumulative rate of reductions (*p*-value, 0.023). Furthermore, no difference in achieving euthyroidism was noted at follow-up visits between Group A and B respectively ([0:0%; *p*-value 1.00, month 1], [70.6:74.3%; *p* value 0.22, month 2], [85.3:85.7%; *p* value 0.39, month 3], 97.1:82.9%; *p*-value 0.23, month 4], [100:91.4%; *p*-value 0.29, month 5], [100:100%%; *p* value 1.00, month 6] at monthly intervals. Cases of Hypothyroidism were reported more in the DD-CMZ (14.3%) and the difference was statistically significant (*p*-value 0.003). **Conclusion:** Due to no significant difference in the efficacy and more chances of getting hypothyroid in divided dose regimen, we conclude that single dose regimen is more effective method for treating hyperthyroidism.

Keywords: Carbimazole; Hyperthyroidism; Single dose; Multidose; Drug therapy

Citation: Usman R, Ismail S, Tahir R, Jamil M. Efficacy of different dosage regimens of carbimazole in the treatment of primary hyperthyroidism. J Ayub Med Coll Abbottabad 2021;33(2):244–7.

INTRODUCTION

Carbimazole is a prodrug that is converted to methimazole as soon as it is taken orally (15–30 minutes required). The plasma half-life of carbimazole is 5.3–5.4 hours, while that of its active counterpart, methimazole, is 64 hours.[1,2] However, in the thyroid gland its half-life is up to 20 hours prompting to the sufficiency of a single dose of its pro drug carbimazole in hyperthyroid patients.[1,2] Worldwide including Pakistan, most of the centers follow the DD-CMZ regimen.[3,4] However considering the long half-life of its metabolite in the body, studies have been published shifting the focus to OD-CMZ regimen.[5–9] Since we have scarce data locally for OD-CMZ, we decided to do a comparative study to see the effectiveness of OD-CMZ to DD-CMZ regimen.

MATERIAL AND METHODS

This interventional comparative study was conducted at CMH Lahore Medical College and CMH Lahore Pakistan from December 2018 to December 2019. After approval from the Institutional Research Ethical Review Committee, the sample size (n) was calculated using the formula

$$\frac{\left(Z_{\beta}+Z_{1-\alpha/2}\right)^2\times 2SD^2}{\left(\mu_1-\mu_2\right)^2}$$

Where Z_{β} is the desired power (0.84 for 80% power), $Z_{1-\alpha/2}$ is standard normal variate of 1.96 at $p<0.05$, $(\mu_1-\mu_2)^2$ is the difference in means calculated as $(68.47-56.76)^2$ and the average Standard Deviation (SD) of the variable is taken from a previously done study [$SD^2=(23.94)^2$].[10] Sample size calculated as required for the study was 66.

All patients with age less than 16 or greater than 70 years, painful goitre, on immunosuppression, undergone ablative treatment and women who were pregnant; were excluded. Clinical effects were balanced by giving all patients in both groups a fixed dose of oral beta blocker (Propranolol 20 mg twice a day). Informed consent was taken. Patients were randomly divided into 2 groups using random draw number method. Group A included patients on a single dose of carbimazole (OD-CMZ), while group B included patients who were prescribed divided doses of carbimazole (DD-CMZ), adjusted according to the thyroid function test (TFTs) outcomes. The participants were briefed on the importance of drug compliance. Regular monthly follow-ups were performed for a total duration of 6 months. At each monthly visit, TFTs were repeated and the dose of carbimazole adjusted accordingly. The values were recorded in a printed datasheet.

Statistical analysis was performed using SPSS-24. *p*-value of <0.05 was considered as statistically significant. Shapiro-Wilk's Normality test was used to assess the normality of all the continuous variables of the study. The Means were compared using the

independent sample t test. The monthly values of TFTs were recorded using the cut off values of normal ranges (T4: 7–21 pmol/L, TSH: 0.4–4.5 mIU/L) provided by the Hormone Laboratory at the Pathology Department of Combined Military Hospital Lahore. Percentage Euthyroidism achieved at each visit was assessed based on these laboratory values.

RESULTS

A total of 75 patients were included in the study. 8% (n=6) patients were lost to follow up. The data of hence 69 patients is analysed. There were 34 patients in Group A with mean age of 32.62±SD 4.55 years. There were 26 males with male to female ratio of 3.25:1. The mean age in Group B (n=35) was 31.34±SD 4.9 years. There were 13 males with male to female ratio was 1:1.7. The two groups were comparable with respect to age (p=0.267). However, there was a significantly greater portion of males in the once daily group and a significantly greater number of females in the divided daily treatment group.

As shown in table-1 intergroup comparisons for visit 1 TSH (p=0.199) and T4 (p=0.260) levels are comparable as there is no significant difference between the two treatment regimens at baseline levels. The results of the study showed a significant reduction in serum T4 and TSH levels of both treatment groups [Table 1 and Table 2]. Monthly differences in serum T4 levels were not significant between once daily and divided daily carbimazole groups at all visits respectively with a p-value of >0.05 (Visit 1: 32.53±5.75 versus 30.91±6.05, Visit 2: 24.12±5.38 versus 21.74±8.03, Visit 3: 18.74±4.20 versus 18.46±5.59, Visit 4: 17.62±3.15 versus 17.17±5.07, Visit 5: 16.29±2.78 versus 17.64±5.53, Visit 6: 16.18±1.70 versus 16.00±2.43).

Monthly differences in serum TSH levels were only found significant on visit 2 (1.14±0.87 for once daily carbimazole versus 1.75±1.37 of divided daily carbimazole (p=0.032). The rate at which Euthyroidism was achieved was cumulated and expressed as a percentage with no significant differences during all visits throughout the 6 months duration between once daily and divided daily carbimazole therapy administration (Visit 1: 0% versus 0%; p value 1.00, visit 2: 70.6% versus 74.3%; p-value 0.22, visit 3: 85.3% versus 85.7%; p value 0.39, visit 4: 97.1% versus 82.9% p value 0.23, visit 5: 100% versus 91.4%; p-value 0.29 and visit 6: 100% versus 100%; p value 1.00). No side effects were reported by any of the participants during the course of the study. Hypothyroidism was noted in 14.3% (n=5) participants in the DD-CMZ regimen. When compared to OD-CMZ group, only 2.9% (n=1) patients had hypothyroidism (p value 0.003).

Table-1: Comparative analysis of changes in Serum T4 and TSH levels during course of treatment between OD-CMZ and DD-CMZ groups.

Follow up (in months)	1	2	3	4	5	6
Serum T4 levels (pmol/L)						
OD-CMZ (Group A)	32.53±5.75	24.12±5.38	18.74±4.20	17.62±3.15	16.29±2.78	16.18±1.70
DD-CMZ (Group B)	30.91±6.05	21.74±8.03	18.46±5.59	17.17±5.07	17.64±5.53	16.00±2.43
***p* Value**	0.260	0.155	0.816	0.663	0.311	0.728
Serum TSH levels(MIU/L)						
OD-CMZ (Group A)	0.08±0.08	1.14±0.87	1.86±0.97	2.26±1.02	2.63±0.69	2.57±0.63
DD-CMZ (Group B)	0.11±0.11	1.75±1.37	2.13±1.23	2.42±1.53	2.41±1.24	2.29±0.76
***p*Value**	0.199	**0.032**	0.306	0.592	0.366	0.099

Table-2: Cumulative rate of achieving Hypothyroidism, Euthyroidism and Hyperthyroidism during treatment with OD-CMZ and DD-CMZ regimens

Follow-up (in months)	1	2	3	4	5	6
Hypothyroidism						
OD-CMZ [n (%)]	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)	0 (0)
DD-CMZ [n (%)]	0 (0)	1 (2.9)	1 (2.9)	5 (14.3)	1 (2.9)	0 (0)
Euthyroidism						
OD-CMZ [n (%)]	0 (0)	24 (70.6)	29 (85.3)	33 (97.1)	34 (100)	34 (100)
DD-CMZ [n (%)]	0 (0%)	26 (74.3)	30 (85.7)	29 (82.9)	32 (91.4)	35 (100)
Hyperthyroidism						
OD-CMZ [n (%)]	34 (100%)	10 (29.4)	5 (14.7)	0 (0)	0 (0)	0 (0)
DD-CMZ [n (%)]	35 (100)	8 (22.9)	4 (11.4)	1 (2.9)	2 (5.7)	0 (0)

DISCUSSION

In this interventional comparative study, it was found that there is no significant difference in the treatment efficacy of the two regimens of once daily carbimazole therapy and divided daily carbimazole therapy in the induction of euthyroid in hyperthyroid patients. The results of our study are consistent with those of previously conducted studies. Some studies administered only single dose regime while several

others focused on the comparison between the two groups.

Twenty-one patients participated in one particular research that were prescribed once daily dose of carbimazole. All achieved normal serum T4 levels within 1–3 months.[10] Sriussadaporn *et al* conducted a trial in which 50 patients were recruited and divided into the two groups.[11] They were regularly followed up for 12 weeks. At the end of the trial, it was established that both regimens induced euthyroid levels of thyroxine levels. The T4 levels were 16.35±5.92 pmol/L versus 18.66±11.46 pmol/L (at 12 weeks), as in our study, i.e., 16.18±1.70 pmol/L versus 16.00±2.43 pmol/L (at 6 months).

In another instance, the study population was divided into three groups, including once daily, twice daily and thrice daily groups. Patients in all these three groups had no significant difference in the serum T3 and T4 levels while, as compared to the start of the treatment, there was a significant decrease in the levels of serum T3 and T4 levels.[12] Likewise in another longitudinal study in which both groups were assessed for up to 6 weeks, euthyroidism was achieved in almost the same period of time. Moreover, no statistically significant difference in T4 and T3 levels was noted between both groups.[13]

One notable finding in our study was that euthyroidism was achieved a visit earlier for OD dosage regimen (visit 2) as compared to the DD dosage regimen (visit 3).

The investigation to find out the effectiveness of either dosage regimes is of utmost importance as it determines the patient's ease and compliance to drugs. Factors that contribute to drug compliance can be grouped. The causes are identified as patient-centered including demographic factors (age, ethnicity, gender, education, marriage status), psychosocial factors (beliefs, motivation, attitude) forgetfulness, health literacy, patient knowledge, physical difficulties, tobacco smoking, patient-prescriber relationship; therapy-related comprising of side effects and taste of medication, route of administration, complexity of treatment, duration of treatment, requirements for drug storage and change in lifestyle; healthcare system consisting of long waiting hours, accessibility, unhappy clinical visits; as well as socioeconomic, i.e., lack of affordability and disease factors.[14] However, due to drug non-compliance there is a deficient result of the therapy. Drug compliance is, thus, necessary and has been taken up as a challenge by many. There are several ways to increase drug compliance, including: monitoring on drug reactions, counselling about the importance of adherence, follow up visits, responding to all queries of the patient, as well as by simplifying dosage regimens.[15]

Luckily in our study none of the patients reported any side effects of the drugs. However, the generally side effects of carbimazole therapy include headache, rash, fever, joint and muscle pain and urticaria while rarely gastrointestinal problems and agranulocytosis.[16]

In our study, there were some study limitations. We were not able to control for environmental factors such as the level of iodine intake. Furthermore, the dose of carbimazole varied among patients placed on the divided dose regimen in accordance to their TSH and T4 levels at each monthly visit thereby lacking standardization of the doses administered. However, the study gives us ample evidence about the usefulness of single dosage regimen.

CONCLUSION

Carbimazole is equally effective in treatment of hyperthyroidism when used in a single daily dosage regimen. Furthermore, it also increases the compliance of the patients when used as a single daily dose.

AUTHORS' CONTRIBUTION

RU: Study conception. RU, SI, RT: Data collection. SI, RT, MJ: Analysis. RU, SI, RT: Investigation. RU, SI, RT: Writing. RU, SI, RT, MJ: Critical review and revision, final approval of the article. RU, SI, RT, MJ: Accountability for all aspects of the work.

REFERENCES

1. Liu J, Fu J, Xu Y, Wang G. Antithyroid Drug Therapy for Graves' Disease and Implications for Recurrence. Int J Endocrinol 2017;2017:3813540.
2. Sjölin G, Holmberg M, Törring O, Byström K, Khamisi S, de Laval D, *et al*. The Long-Term Outcome of Treatment for Graves' Hyperthyroidism. Thyroid 2019;29(11):1545–57.
3. Iqbal MA, Naseem Z, Qureshy A, Shahid A, Roohi N. Prevalence and manifestations of thyroidal dysfunction in central Punjab Pakistan (A Case Study). Sci Int 2016;28(4):3959–63.
4. Attaullah S, Haq BS, Muska M. Thyroid dysfunction in Khyber Pakhtunkhwa, Pakistan. Pak J Med Sci 2016;32(1):111–5.
5. Messina M, Milani P, Gentile L, Monaco A, Brossa C, Porta M, *et al*. Initial treatment of thyrotoxic Graves' disease with methimazole: A randomized trial comparing different dosages. J Endocrinol Invest 1987;10(3):291–5.
6. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2007;92(6):2157–62.
7. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 2018;7(4):167–86.
8. Benker G, Reinwein D, Creutzig H, Hirche H, Alexander WD, McCruden D, *et al*. Effects of high and low doses of methimazole in patients with Graves' thyrotoxicosis. Acta Endocrinol Suppl (Copenh) 1987;281:312–7.

9. Mashio Y, Beniko M, Ikota A, Mizumoto H, Kunita H. Treatment of hyperthyroidism with a small single daily dose of methimazole. Acta Endocrinol (Copenh) 1988;119(1):139–44.
10. MacFarlane IA, Davies D, Longson D, Shalet SM, Beardwell CG. Single daily dose short term carbimazole therapy for hyperthyroid Graves' disease. Clin Endocrinol (Oxf) 1983;18(6):557–61.
11. Sriussadaporn S, Pumchumpol W, Lertwattanarak R, Kunavisarut T. Efficacy of Once Daily versus Divided Daily Administration of Low Daily Dosage (15 mg/Day) of Methimazole in the Induction of Euthyroidism in Graves' Hyperthyroidism: A Randomized Controlled Study. Int J Endocrinol 2017;2017:2619695.
12. Mafauzy M, Wan Mohamad WB, Zahary MK, Mustafa BE. Comparison of the efficacy of single and multiple regimens of carbimazole in the treatment of thyrotoxicosis. Med J Malaysia 1993;48(1):71–5.
13. Gupta SK, Mithal A, Godbole MM. Single daily dose of carbimazole in the treatment of hyperthyroidism. Natl Med J India 1992;5(5):214–6.
14. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag 2008;4(1):269–86.
15. Ehret MJ, Wang M. How to increase medication adherence: What works? Ment Health Clin 2014;2(8):230–2.
16. Siddiqui MF, Hasnain S, Batool Z, Qazi MH, Imtiaz M, Fatima I, *et al*. Clinical effectiveness of Carbimazole and Propylthiouracil for Hyperthyroidism in Patients of Punjab, Pakistan. Adv Life Sci 2014;2(1):10–5.

Submitted: May 23, 2020	*Revised: February 10, 2021*	*Accepted: February 12, 2021*

Address for Correspondence:

Rashid Usman, Department of Surgery, CMH Lahore Medical College and CMH Hospital Lahore-Pakistan
Cell: +92 333 488 5445
Email: drrashidusman@yahoo.com