

Cholestyramine Use for Rapid Reversion to Euthyroid States in Patients with Thyrotoxicosis

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Cholestyramine (CS) is an ion exchange resin, which binds to iodothyronines and would lower serum thyroid hormone level. The use of CS added to conventional antithyroid drugs to control thyrotoxicosis has been applied since 1980's, and several studies indicate that using CS in combination with methimazole (MZ) produces a more rapid decline in serum thyroid hormones than with only MZ treatment. Our recent retrospective review of five patients taking high dose MZ and CS, compared to age-, gender-, initial free thyroxine (T4) level-, and MZ dose-matched 12 patients with MZ use only, showed more rapid decline of both free T4 and triiodothyronine levels without more adverse events. CS could be safely applicable short-term adjunctive therapy when first-line antithyroid medications are not enough to adequately control severe thyrotoxicosis or side effects of antithyroid drug would be of great concern.

Keywords: Thyrotoxicosis; Graves disease; Cholestyramine resin

INTRODUCTION

Current medical treatment of hyperthyroidism consists of the antithyroid medication such as, methimazole (MZ) or propylthiouracil (PTU). In most cases, these medications restore euthyroidism in 1 to 2 months [1,2]. When conventional managements have failed, surgery or radioactive iodine is usually considered for alternative treatment modality. Literature reviews have reported a few cases that showed poor response to conventional therapy and required additional management [2,3]. Cholestyramine (CS), a bile salt sequestrant, has been used to lower cholesterol since the 1960s [4-6]. CS forms an insoluble complex with the bile acids, preventing the reabsorption from the intestines. It is also an ion exchange resin, which binds to iodothyronines and would lower serum thyroid hormone level.

Several studies demonstrated that using CS in combination with conventional antithyroid medication, MZ, or PTU, produces a more rapid decline of serum thyroid hormone [2,5,6]. We recently reported one thyrotoxic female patient who showed refractoriness to nearly all conventional antithyroid medications and finally underwent total thyroidectomy after short-term administration of CS and following achievement of near euthyroid state [7]. Herein we retrospectively evaluated the efficacy and safety of high-dose CS added to maximal dose of antithyroid drugs used in a short period to control thyrotoxicosis and not to increase the dose of antithyroid drugs.

METHODS

We retrospectively reviewed patients who were prescribed CS

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to control dyslipidemia, hyperbilirubinemia, and thyrotoxicosis from January 2014 to December 2014. Among these patients, we excluded the patients prescribed CS to control hyperlipidemia and hyperbilirubinemia only. We finally enrolled five patients (three women and two men, aged 18 to 64) because they took both high dose MZ (at least 30 mg) and CS (4 g three times a day, totally 12 g per day) during the initial short term to control severe thyrotoxicosis and checked thyroid function tests in a timely manner. We made up of control group in which patients with the age, gender, and initial free thyroxine (T4) levels matched to combination therapy group, received nearly the same dose of MZ within the same period, to evaluate the efficacy and safety of adding CS to high dose antithyroid drug.

RESULTS

Totally, five patients in combination therapy group and 12 in control group were included in this study and their clinical characteristics were described in Table 1. Among them, one patient who presented severe nausea and vomiting after taking high-dose MZ led to administration of CS to lower total dose of antithyroid drugs. Compared to age and gender matched control group with MZ-only use during the same period of

treatment, combination therapy group showed more rapid reduction of free T4 and triiodothyronine (T3) levels in nearly all subjects (Fig. 1), even though statistically insignificant differences due to the small number of study subjects. Judging from the changes in thyroid hormone levels associated with MZ plus CS, reduction of T3 levels was higher than that of free T4 levels (Table 1).

Combination therapy group reported only one minor pruritus which might be due to thyrotoxicosis by itself or adverse events of MZ so no CS-related adverse events were observed. On the other hand, control group showed one hepatitis and three pruritus, which were resolved after short-term medication.

DISCUSSION

CS's ionic exchange properties could decrease excessive thyroid hormone level by enhancing thyroid hormone clearance by enterohepatic circulation. By this mechanism of action, CS control thyrotoxic symptom effectively by reducing circulating hormone levels. Unfortunately, it is uncertain whether CS influences the clinical prognosis, such as remission rates and relapse rate.

This study showed more rapid improvement of thyroid hor-

Table 1. Four-Week Efficacy and Safety of Cholestyramine Added to Methimazole (MZ) vs. MZ Only

Variable	MZ+CS ^a (n=5)	MZ (n=12)	P value ^b
Sex, female/male	3/2	8/4	0.793
Age, yr	34.2±18.0	41.9±14.4	0.225
Baseline			
Free T4, ng/dL ^c	4.97±1.80	4.55±0.76	0.833
T3, ng/mL ^d	5.09±1.81	4.28±1.14	0.170
TSH, μ IU/mL ^e	0.007±0.001	0.019±0.04	0.955
Four weeks after treatment			
Free T4, ng/dL ^c	2.12±0.64	2.71±0.74	0.091
T3, ng/mL ^d	1.80±0.69	2.19±0.79	0.370
TSH, μ IU/mL ^e	0.007±0.001	0.048±0.15	0.737
Average change in free T4 (Δ), ng/dL ^c	2.85±1.44	1.84±0.91	0.399
Average change in T3 (Δ), ng/mL ^d	3.28±1.41	2.08±0.81	0.058
Dose of methimazole, mg	32.00±4.47	30±0.0	0.121
Described adverse events	1/5	3/12	
Details	Pruritus (1)	Hepatitis (1) Pruritus (3)	

Values are expressed as mean±SD.

CS, cholestyramine; T4, thyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone.

^aTotally 12 g per day of cholestyramine were administrated; ^bP value for Mann-Whitney U test and chi-square test; ^cNormal range is 0.89 to 1.76 ng/dL;

^dNormal range is 0.6 to 1.81 ng/mL; ^eNormal range is 0.55 to 4.78 μ IU/mL (lowest detectable values was 0.008 μ IU/mL).

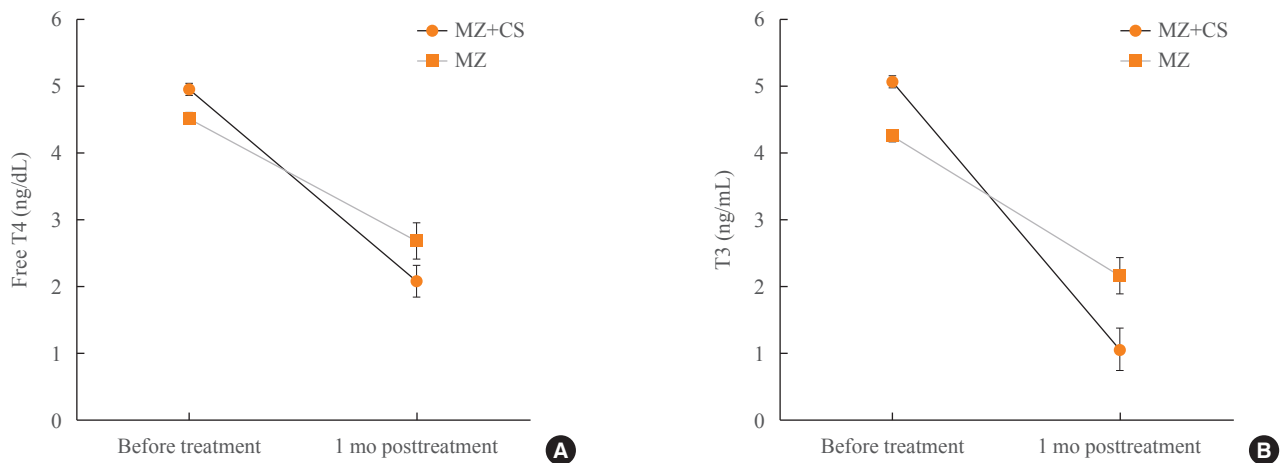


Fig. 1. Remarkable improvement of (A) free thyroxine (T4) and (B) triiodothyronine (T3) levels over 4 weeks of 12 g cholestyramine (CS) combined therapy to methimazole (MZ), compared to MZ only in patients with thyrotoxicosis.

mone level by adding high-dose CS to conventional MZ therapy without more adverse events, compared to MZ therapy only. Sebastian-Ochoa et al. [2] reported that totally 12 g per day of CS with MZ for 4 weeks resulted in more rapid decline in all thyroid hormone levels. In our study, we adopted the same protocol, which is 12 g a day of CS combination with MZ for 4 weeks. Rapid decline in all thyroid hormones, especially total T3 decline was observed after 4 weeks of treatment as a consequence of the combination treatment. Our study results are very similar to those of Mercado et al. [4], who reported that total T3 reduction as well as free T4 was observed in CS treated group. However, in the study of Mercado et al. [4] T3 levels declined for the second 2 weeks of the study after 1 week of washout period, not for the first 2 weeks. Unfortunately, we were unable to observe the declining pattern of T3 level during the study.

Our study subjects took nearly 30 mg of MZ, which might be conventional maximal dose [8,9], without any dose escalation above that. Usually, adverse events of antithyroid drug are dose-dependent [10] so those may have more adverse events who should take more antithyroid drug above maximal conventional dose as in 30 mg of MZ. Due to the combination of CS to patients who already took high dose of MZ, we could control thyrotoxicosis without adding another doses of MZ or experiencing adverse effects.

Combination therapy by antithyroid drugs with different side effect profiles will be a safer choice to reduce high levels of thyroid hormone. Major adverse effects of CS are constipation and abdominal discomfort. Fortunately, none of the patients complained of typical symptoms during the treatment with CS.

Considering one of the clinical manifestations of thyrotoxicosis is diarrhea, constipation as an adverse effect of CS seems to be even favorable. However, we need more sample size to validate the effect of CS and to estimate the risk and benefit of use of CS.

Limitations of our study include that the sample size is too small to demonstrate statistically significance of the efficacy and safety of CS. Our result only implicates the tendency to rapid decrease in free T4 and T3 level with CS use without major side effects. Another limitation is that we measured the change of TSH-receptor-antibody (R-Ab) level for only two patients in case group and three patients in control group. TSH-R-Ab measurement is another critical cues to evaluate the improvement of thyrotoxicosis. Unfortunately, TSH-R-Ab levels were not measured at follow-up in most cases so we could not obtain any clinical meaning from these facts.

In conclusion, CS could be safely applicable adjunctive therapy for 4 weeks when first-line antithyroid medications are not enough to adequately control severe thyrotoxicosis or side effects of antithyroid drug would be of great concern at the initial stage of treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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