Advances in Bioresearch
Adv. Biores., Vol 8 (1) January 2017: 134-137

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.8.1.134137

Advances in Bioresearch

ORIGINAL ARTICLE

Evaluation of Omeprazole Effect on Iron Overload in Transfusion Dependent Patients with Thalassemia

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ABSTRACT
Background: Iron overload in transfusion-dependent patients with thalassemia is a major problem that causes high morbidity and mortality rates of these patients. Therefore, drugs that boost the effectiveness of iron-repellent agents can help in reducing the complications of iron overload. The aim of this study was to assess the effect of proton pump inhibitors on ferritin levels among patients with thalassemia on regular blood transfusion. Methods: In this single-arm clinical trial, 52 transfusion-dependent β-thalassemia patients older than two years-old who had inclusion criteria of the study and had been registered for at least six months in Dastgheib Thalassemia Outpatient Clinic (a referral center affiliated to Shiraz University of Medical Sciences) were evaluated from May 2013 to Nov 2013. The patients were treated with deferroxamine 40 mg/kg daily and omeprazole orally 20 mg/day for 3 months. Transfusion needs and hemoglobin levels were compared before and after omeprazole treatment. The patient's ferritin levels, hemoglobin, transfusion needs, frequency and volume, deferoxamine consumption and costs were compared before and after omeprazole treatment. Results: The mean volume and frequency of blood transfusion decreased significantly following omeprazole treatment (P < 0.001, p= 0.007). Omeprazole reduced the ferritin levels (p=0.027) and the number of deferoxamine vials before and after omeprazole treatment (P = 0.001). Omeprazole administration had no significant influence on hemoglobin levels. No serious adverse reaction was observed in patients. Conclusions: Omeprazole can be safely used in transfusion dependent β- thalassemia patients to decrease iron overload.
Keywords; *Omeprazole, Iron overload, Transfusion, Thalassemia*

Received 09/10/2016 Revised 08/11/2016 Accepted 30/12/2016

How to cite this article:
Soheila Z, Babak A, Javad D. Evaluation of Omeprazole Effect on Iron Overload in Transfusion Dependent Patients with Thalassemia. Adv. Biores. Vol 8 [1] January 2017: 134-137

INTRODUCTION

B-Thalassemia, as the most prevalent hereditary blood disorder, results from defective synthesis of β-globin chain which leads to ineffective erythropoiesis due to imbalance of α and non-α globin chains production [1]. Patients with β-thalassemia major require regular blood transfusions, as well as iron chelating agents in order to maintain a normal life [2-5]. Iron overload in patients with thalassemia major and intermedia is due to increased iron absorption from the gastrointestinal tract and blood transfusions. Iron absorption from the gastrointestinal tract reaches to10-15 times, up to 91%.This phenomenon is due to the relationship between gastrointestinal iron absorption and body hematopoietic system's need [2].
In thalassemia patients, excess iron in vital organs, even in mild cases of iron overload, increases the risk for diabetes mellitus, metabolic syndrome, liver disease (cirrhosis, cancer), heart failure, osteoporosis, hypothyroidism, hypogonadism, numerous symptoms and, in some cases, early death [3]. Gastric acid secretion enhances iron absorption in physiological and pathological conditions. Thus reducing or neutralizing gastric acid agents could theoretically decrease iron absorption.

Proton pump inhibitor (PPI) such as omeprazole, even for 7 days significantly reduces iron of food in patients with hemochromatosis [6, 7].
Achloridia induced by these drugs causes iron deficiency [8]. The iron malabsorption occurs during 3-4 years of continuous omeprazole administration [9]. Animal study showed that 4 weeks omeprazole therapy significantly reduces liver iron levels [10]. PPIs are also used for iron overload in patients with hemochromatosis but this has not been tried in transfusion dependent thalassemia with iron overload as yet.

MATERIALS AND METHODS

This single-blind clinical trial study was conducted at Hematology Research Center in Shiraz, southern Iran from May 2013 to Nov2013. 52 transfusion-dependent β-thalassemia patients who were older than two years and had been registered for at least six months in Dastgheib thalassemia outpatient clinic, which is a referral center affiliated to Shiraz University of Medical Sciences were included. All patients were on subcutaneous Deferoxamine (Novarits Pharmaceutical Company, Basel, Switzerland) 40 mg/kg/day for 5 days per week as iron chelation therapy. At first, placebo was started orally for 3 months. Omeprazole was started orally at a dose of 20 mg/day for 3 months and then placebo for 3 months including 2 trimesters. Ethics committee approval was obtained by the Research Advisory Council (RAC) at Shiraz University of Medical Sciences. Informed written consents were obtained from the participants.
The patients were informed about the probable benefit of omeprazole or placebo on reducing iron overload. The patients were visited every two weeks by a fixed attending hematologist for evaluation of their clinical and laboratory response. Complete blood count (CBC) was checked by a Sysmex KX-21 analyzer (TOA system, Japan) at every visit. Liver and renal function tests were performed monthly using Merck kits (Germany). Serum ferritin levels were measured by enzyme-linked immunosorbent assay (Dynex; Monobind Inc. Lake Forest, CA) every three months.
Those with abnormal uterine bleeding, hypersplenism, active hepatitis B or C infection on Interferon therapy, alloimmunization, serum ferritin above 4000 ng/dl, elevated liver enzymes more than 2 times normal range were excluded.
Complete blood count (CBC) was checked by a Sysmex KX-21 analyzer (TOA system, Japan) at every visit. Liver and renal function tests were performed monthly using Merck kits (Germany). Serum ferritin levels were measured by enzyme-linked immunosorbent assay (Dynex; Monobind Inc. Lake Forest, CA) every three months. Laboratory assessment was done before starting omeprazole and at the completion of the study.
All equipment used for the measurement of clinical variables was calibrated. At every follow-up, the remaining capsules of omeprazole and vials of deferoxamine were counted to evaluate therapeutic compliance. Toxicity monitoring was done according to the descriptions in the exclusion criteria.
Patients were assessed after 2 cycles, at the end of 3 months of co-administration of omeprazole (20 mg daily) and deferoxamine (40mg / kg/day for 5 days / week subcutaneously), and at the end of 3 months concurrent use of deferoxamine and placebo. The variables including serum ferritin, number and cost of deferoxamine, hemoglobin level, frequency, volume and cost of blood transfusion were assessed before and after omeprazole treatment. These values were compared together and with levels of a year ago. The ferritin levels of last year were obtained from patient's records.

STATISTICAL ANALYSIS

Data analysis was done by SPSS v. 17 (SPSS Inc. Chicago, IL, USA). Normality of data was assessed by Kolmogorov-Smirnov test. To compare quantitative variables in patients before and after treatment with omeprazole, paired samples t-test and Wilcoxon signed ranks test were used. Comparison of quantitative variables before and after omeprazole treatment was done by 1-way analysis of variance (ANOVA) and Kruskal-Wallis Test. Chi-square test was done to compare ratios among different groups. Two-sided P value < 0.05 was considered statistically significant.

RESULTS

The hemoglobin levels before and after administration of omeprazole were 9.78 ±0.94 and 10.00± 6.2 g/dl respectively (Wilcoxon non parametric test, Z =-1.725). There was not a statistical significant difference between hemoglobin levels before and after omeprazole treatment (p=0.085).
The mean volumes of blood transfusion before and after omeprazole consumption were 3019.01± 959.08 ml and 2707.34 ±820.56ml respectively (parametric t-test, CI: 95 %). Our study also revealed that, transfusion times before and after omeprazole treatment were 5.63 ± 1.12 and 5.07± 0.88 respectively (Z=-2.719). It means that, the transfusion needs and frequencies decreased significantly after drug

consumption (P = 0.001, p=0.007). Regarding consumption of the number of deferoxamine vials, the vials numbers before and after trial were 236.82 ±39.97 and 223.65 ±41.30, respectively, which was statistically significant (paired T-test, t=4.540, df = 51, p=0.001). The mean serum ferritin during 3months before and after omeprazole administration was 2043.60 ±1241.60 ng/dl and 1741.76 ±1217.17 ng/dl. respectively (parametric paired T-test, t = 2.272, df = 51, p = 0.027). This implies that omeprazole consumption may have significant effect on decreasing serum ferritin level. The mean serum ferritin level decreased significantly in the post-omeprazole periods (P = 0.021). The mean serum ferritin after administration of omeprazole compared with median serum ferritin of 1 year before trial were 1860.6±1915.64 ng/dl and 1741.76 ±1217.17ng/dl respectively (Student-t test, t = 0.559, df = 101, p = 0.577).There were no differences between serum ferritin and one year before administration of omeprazole.

Table1- Comparative data of thalassemia major patients with and without omeprazole therapy.

Variables	With placebo	With omeprazole	P value
Hemoglobin g/dl	10	9.8	0.085
Serum ferritin	1860.61±915.64	1741.76±1217.17	0.027
Deferroxamine vials/patient	236.82± 41.30	223.65±39.97	0.001
Total Deferroxamine vials	**12315**	**11446**	0.001
Cost of deferroxamine	8127.9 Euro	7554.36 Euro	0.003
Number of Transfusion	5.63±1.12	5.07±0.88	0.007
Volume of transfusion/patient	3019.01±959.08	2707.34±820.56	0.001
Cost of *transfusions	1760 Euro	1584 Euro	0.002

*International Cost of preparation of 1 unit packed RBC is 176 Euro

DISCUSSION

Administration of omeprazole did not have a significant influence on hematological parameters such as hemoglobin, white blood cell, and red blood cell indexes on two trimesters of study, similar to previous studies even in long-term omeprazole administration, although hemoglobin increased 9.78g/dl to 10 g/dl (11).

Number of transfusion had significant decrease in the second trimester compared to the first trimester although in practice these values may be venial. This strategy probably improves with continuous use of omeprazole.

Continuous use of hydroxyurea by some patients with thalassemia causes chronic peptic ulcer. Therefore simultaneous use of omeprazole may help to decrease this adverse effect of hydroxyurea and indirectly reduce the number of transfusions in patients with thalassemia. Long-term use of omeprazole in these conditions can potentially be more effective to reduce the number of transfusions [12].

Omeprazole administration reduced transfusion volume in the second trimester compared to the first trimester.

The mean volume of blood transfusion before and after omeprazole treatment was 29700 and 25830cc milliliter, respectively. Regarding the price of each packed red cell unit, we have saved 43.66 Euros for each patient during 3 months omeprazole treatment. The median cost of transfusion with and without omeprazole was decreased approximately 21-fold.

Omeprazole reduces the number of used desferoxamine vials in the second trimester compared to the first trimester. Roughly, Omeprazole administration decreased the expense of deferroxamine vials for each patient with thalassemia about 2.3 Euros in a month. Omeprazole may be used in the context of the foreign exchange savings of transfusion expense.

Our study showed that, Omeprazole decreased ferritin in transfusion dependent thalassemia. According to our study, perhaps the use of short-term omeprazole demonstrates a minimal clinical difference but in Hutchinson's study long term drug administration had a clearly significant effect. Therefore, this defect may be resolved by use of long-term omeprazole therapy [6].It should be noted that good patient's compliance is needed for effective reduction of iron overload. Minimum dose of omeprazole was used, perhaps increase in omeprazole dosage even up to therapeutic dose range of Zolinger Ellison syndrome as in some studies, or administration of other omeprazole family members may improve PPI effect on Iron overload in transfusion dependent thalassemia patients [13, 14].

The majority of studies using this method were done in congenital hemochromatosis patients with abnormal Iron metabolism and Zolinger Ellison syndrome with normal Iron metabolism [6]. Studies

about congenital hemochromatosis indicated that these patients, despite the long-term omeprazole family drugs still need phlebotomy to maintain an acceptable ferritin level [13].

Our research showed that, concomitant use of PPIs and iron chelators may be effective as a co-helper in decreasing iron overload in thalassemia patients. Although this is one of the few prospective studies investigating the role of PPI in decreasing iron overload, our study faced some limitations. Use of cardiac and liver magnetic resonance imaging may be a more accurate method for better estimation of total body iron in thalassemia patients. The other limitation of our study was the relatively short study period to assess the long-term safety and efficacy of the drug. As most of the thalassemia patients refused to participate in the trial due to the possible adverse drug effects, we were forced to stop the trial after about 6 months and analyze the short-term effects of the drug. An education program is needed to convince transfusion-dependent thalassemia patients to consume omeprazole regularly and for a long time, since most of the thalassemia major patients are only adapted to iron chelators, and they hardly accept to share in other treatment regimens. It is noteworthy that we continued the study with a larger group of patients with better compliance to evaluate the long-term efficacy and safety of the drug, and the results will be issued in the future. In conclusion, omeprazole can be safely prescribed to some transfusion-dependent β-thalassemia patients in order to diminish their iron overload and may affect transfusion requirements.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS:

S. Zareifar contributed to design and concept of study and editing the manuscript. B. Abdolkarimi contributed to design and concept of study, data collection and editing the manuscript. J Dehbozorgian contributed to technical laboratory procedure and final discussion.

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