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Short Communication

Combined Chelation Therapy and Survival of Beta-Thalassemia Major: A Retrospective Cohort Study

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Keywords

- Combined therapy
- Survival analysis
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Abstract

Background: There recently are multiple different iron-chelation regimens among thalassemia patients in Iran. The aim of our study was evaluated the efficacy of combined chelation therapy on survival time of the beta-thalassemia major patients.

Methods: A retrospective cohort study was performed on 667 beta-thalassemia major patients in Shiraz, **Iran.** Using a predetermined checklist data were collected from their medical records. For analysis, patients were divided into two groups (exposure variable); one drug (single-agent therapy) and two or more drugs (combination therapy). Dependent variable is survival time following combination therapy. We used Kaplan-Meier curves and Cox proportional hazards model to identify the effect of combined therapy against mortality of the patients.

Results: Both crude (HR=0.30, 95%CI: 0.19, 0.43) and adjusted (HR=0.52, 95% CI: 0.31, 0.86) hazard ratios showed that combination therapy was significantly associated with decreased risk of mortality. The 10-year, 20-year and 40-year survival rates for patients with combination therapy were 99%, 93% and 78%, respectively. However, the 10-year, 20-year and 40-year survival rates for patients receiving single agent therapy were 98%, 74% and 47%, respectively.

Conclusion: The findings of this study showed that the combination therapy is associated with lower risk of mortality. Future prospective studies are needed in future to examine this association to achieve the maximum accuracy of the results.

INTRODUCTION

Thalassemia, with about 60,000 individuals born annually [1], is a severe inherited anemia arising from the failure of hemoglobin synthesis [2]. Long term survival of the patients is related with regular blood transfusion [3]. This treatment can result to some major complications such as iron overload [4], cardiac [5] and endocrine disorders [6]. Iron overload is the primary cause of mortality and morbidity in thalassemia major despite advances in chelation therapy [7].

Numerous clinical studies have indicated that iron chelation therapy is the main objectives of clinical management of the thalassemia patients [8,9]. Desferrioxamine has been the standard drug for iron chelation therapy [10]. The efficacy of combined chelation therapy with deferoxamine and deferiprone has been shown in literature [7, 11,12].

In Iran, multiple different iron-chelation regimens including monotheray, combined and alternative sequential regimens are used [13-15]. To our knowledge, this is the first study to evaluate the efficacy of combined chelation therapy on survival time of beta-thalassemia major patients who receive one drug at a time (single-agent therapy) compared with patients who receive two or a combination of drugs (combination therapy).

MATERIALS AND METHODS

A retrospective cohort study was conducted on patients with beta thalassemia major attending in referral hospitals, Shiraz, Iran in 2014.

According to census methods, data were collected from patients' medical records using a predetermined checklist including sex, education level, marital status, consanguinity, ferritin & hemoglobin level, type of iron chelation drugs (Deferoxamine (Desferrioxamine), Deferiprone, Deferasirox (Exjade), Desferal or Esferal), and the presence of accompanied diseases.

Survival time (person-year) was calculated from the date of birth to September 2014 (end of study). The Kaplan-Meier analysis was used to estimate the survival function .The log-rank test was used to compare the survival curves across the subgroups. A univariate and multivariate cox proportional hazards model was also used to identify the effect of combined therapy against mortality of the patients. For this purpose, patients were divided into two groups; one drug (single-agent therapy) and two or more drugs (combination therapy). In the multivariate analysis, the effect of gender, ferritin and hemoglobin level, accompanied diseases, consanguinity, marital status and education variables were adjusted. All statistical analyses were performed at 0.05 significance levels by using the statistical software, Stata, version 11 (StataCorp, College Station, TX, USA).

RESULTS AND DISCUSSION

This study included 667 beta-thalassemia patients with 183 (27.4%) death cases and 0.3 % of data (two cases) were missing. The total median age of subjects was 43.1 years (range: 0.08–47.0 years). The average age was 43.1 years (ranged from 0.08 to47.0 years) for the subjects. The average observed age at death was 18.4 years (ranged from 4.9 to43.2 years).The median follow-up for the entire study was 14474.4 person-years, and the incidence rate was 1.2 per 100 person-years.

Half of the subjects were female, and nearly 10% of the subjects were married. Almost one third of the patients were diagnosed with co-morbid conditions. The combination therapy was observed in 34.8% of the patients. Other characteristics of beta-thalassemia major patients, including ferritin and hemoglobin levels, consanguinity and education are shown in [Table 1].

The effect of combined therapies on survival in beta-thalassemia major patients is shown in [Table 2]. Both crude and adjusted hazard ratios showed that combination therapy was significantly associated with decreased risk of mortality. In crude analysis, the combination therapy was associated with 70% lower risk of mortality (HR=0.30, 95%CI: 0.19, 0.43). While, after controlling for other variables (gender, ferritin and hemoglobin levels, accompanied diseases, consanguinity, marital status and education), the adjusted hazard ratio of death was 0.52 (95% CI: 0.31, 0.86).

The crude and adjusted survival rates for the beta-thalassemia major patients and for combined therapy are shown in [Figure 1] and [Figure 2] respectively. The survival rate was longer in patients treated with combination therapy than in single agent therapy (P=0.001). The 10-year, 20-year and 40-year survival rates for patients with combination therapy were 99%, 93% and 78%, respectively. However, the 10-year, 20-year and 40-year survival rates for patients receiving single agent therapy were 98%, 74% and 47%, respectively.

We found that 34.8% of the patients with beta thalassemia major received combined iron chelation therapy. The 10-year, 20-year and 40-year survival rates for patients with combination therapy were 99%, 93% and 78%, respectively. However, the 10-year, 20-year and 40-year survival rates for patients with single-drug therapy were 98%, 74% and 47%, respectively. According to the data from Iranian studies, there has been a clear improvement of survival rate in the thalassemia patients during the past decades [16,17].

The crude analysis found that combined iron chelation therapy is associated with 70% lower risk of mortality, and the strength of the association was reduced to 48% in the adjusted model. On the other hand, after controlling for the other variables including gender, ferritin and hemoglobin levels, comorbid diseases, consanguinity, marital status and

Table 1: Characteristics of beta-thalassemia major patients.

	Alive (%)	Dead (%)	Total (%)
Gender			
Male	223(68.6)	102(31.4)	325(48.7)
Female	261(76.3)	81(23.7)	342(51.3)
Marital status			
Single	432(81.8)	96(18.2)	528(90.6)
Married	50(90.9)	5(9.1)	55(9.4)
Consanguinity			
No relation	243(85.0)	43(15.0)	286(49.1)
Relationship	238(80.4)	58(19.6)	296(50.9)
Education			
<Diploma	165(79.0)	44(21)	209(37.3)
Diploma	318(90.6)	32(9.4)	351(62.7)
Accompanied diseases			
No	386(92.3)	32(7.7)	418(71.3)
Yes	98(58.3)	70(41.7)	168(28.7)
Hemoglobin level (g/dl)			
<9.5	177(59.8)	119(40.2)	296(44.5)
>9.5	307(83.2)	62(16.8)	369(55.5)
Ferritin level (ng/mL)			
<2500	330(85.3)	57(14.7)	387(58.5)
>2500	153(55.6)	122(44.4)	275(41.5)
Ferritin (Mean ± SD)	2251.2(1518.7)	3206.7(1319.3)	2509.6(1526.8)
Combined therapy			
One drug	281(64.6)	154(35.4)	435(65.2)
Two drugs	174(85.7)	29(14.3)	203(30.4)
3 or more	29(100)	0(0)	29(4.4)

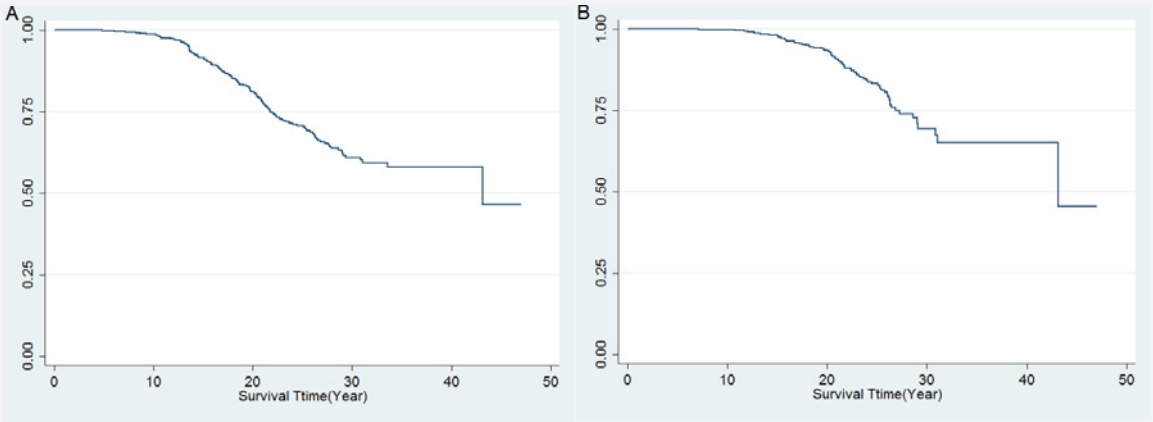

Figure 1 Kaplan-Meier survival curve of the beta-thalassemia major patients: A) Overall survival curve, B) Adjusted for gender, ferritin and hemoglobin level, accompanied diseases, consanguinity, marital status and education.

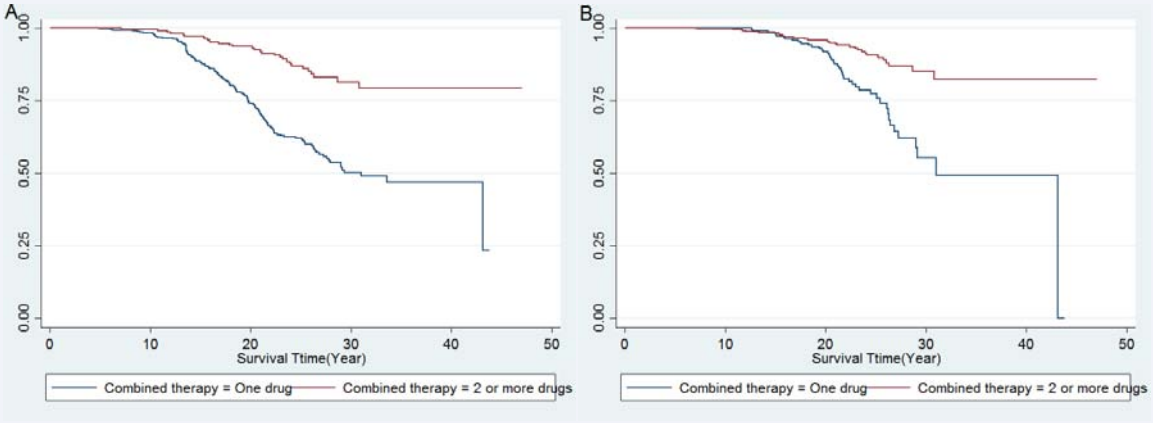

Figure 2 Kaplan-Meier survival curve of the beta-thalassemia major patients for combined therapy by A) Crude (P=0.001) and B) Adjusted for gender, ferritin and hemoglobin level, accompanied diseases, consanguinity, marital status and education (P=0.001).

Table 2: Crude and adjusted Cox regression analyses of effect of combined therapy on survival time in beta-thalassemia major patients.

		β	SE	Hazard Ratio	95% CI	P value
Crude	Combined therapy					
	One drug	0.00	-	1.00	-	-
	2 or more	-1.23	0.059	0.30	(0.19, 0.43)	0.001
Adjusted*	Combined therapy					
	One drug	0.00	-	1.00	-	-
	2 or more	-0.65	0.134	0.52	(0.31, 0.86)	0.012

Adjusted for variables: gender, ferritin and hemoglobin level, accompanied diseases, consanguinity, marital status and education

education, the multivariate analysis suggested that these were negative confounding variables. Similar studies reported that, there was no significant association between combined therapy and survival in patients with beta-thalassemia major. However, Telfer et al (2006) [18] conducted a survival study to identify the predicting factors of prolonged survival among thalassemia patients. They proposed that, no deaths were observed among patients using combination therapy, and there also was a great reduction in the mortality among these individuals [18]. Several studies reported the effects of combined chelation therapy in beta-thalassemia major patients. Some of the studies have found that the combination therapy has many beneficial effects on the treatment of the iron-loaded patients [12, 19-21]. Tsiapras et al [22] also showed that, left ventricular diastolic function significantly improves with combined therapy in patients with beta-thalassemia major. Results demonstrated that, this protective association may be related to some reasons. The combination therapy is not randomly allocated, in other words, combined therapy is selected for those patients considered most at risk, for example, patients with higher level of ferritin. In this

study, the mean serum ferritin level was significantly higher in the combined therapy group than in single agent therapy group, which is not in accordance with the previous studied, showing that the combination therapy is more likely to be useful in the lower level of ferritin [23].

LIMITATION

There was a potential limitation in the present study. The patients were treated with different drugs to obtain extensive iron depletion, and the evaluation of different treatment period was not possible.

CONCLUSION

The findings of this study showed that the combination therapy is associated with lower risk of mortality. Future prospective studies are needed in future to examine this association to achieve the maximum accuracy of the results.

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