Prevalence and predictors of cardiac and liver iron overload in patients with thalassemia: A multicenter study based on real-world data

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ABSTRACT

Prevalence of cardiac and liver iron overload in patients with thalassemia in real-world practice may vary among different regions especially in the era of widely-used iron chelation therapy. The aim of this study was to determine the prevalence of cardiac and liver iron overload in and the management patterns of patients with thalassemia in real-world practice in Thailand. We established a multicenter registry for patients with thalassemia who underwent magnetic resonance imaging (MRI) as part of their clinical evaluation. All enrolled patients underwent cardiac and liver MRI for assessment of iron overload. There were a total of 405 patients enrolled in this study. The mean age of patients was 18.8 ± 12.5 years and 46.7% were male. Two hundred ninety-six (73.1%) of patients received regular blood transfusion. Prevalence of cardiac iron overload (CIO) and liver iron overload (LIO) was 5.2% and 56.8%, respectively. Independent predictors for iron overload from laboratory information were serum ferritin and transaminase for both CIO and LIO. Serum ferritin can be used as a screening tool to rule-out CIO and to diagnose LIO. Iron chelation therapy was given in 74.6%; 15.3% as a combination therapy.

1. Introduction

Thalassemia is the most common cause of iron overload in many countries. In Thailand, the prevalence of thalassemia is approximately 1% or 500,000 cases [1]. Ineffective erythropoiesis, which results in abnormal iron metabolism, and blood transfusion together lead to iron accumulation in several organs, resulting in organ dysfunction and serious complications like liver dysfunction, heart failure and endocrine abnormality - especially in patients with regular blood transfusion

[2,3]. Iron overload of the heart is the leading cause of death in patients with thalassemia [4]. Estimation of iron accumulation within the body and an understanding of iron kinetics is essential in the management of thalassemia patients [2,5]. Iron overload in the liver is more common than cardiac iron overload and liver overload begins earlier in the course of the disease [6]. Serum ferritin is commonly used to reflect total body iron stores, is easy to use, and is inexpensive. However, there are some disadvantages, including increased serum ferritin with inflammation, decrease serum ferritin with ascorbate deficiency, and a

variable or nonlinear relationship between serum ferritin level and iron overload [7].

Magnetic resonance imaging (MRI) has been proposed as a better method for assessing body iron overload especially in the liver and the heart [8–10]. MRI has been incorporated into many standard practice guidelines for management of patients with thalassemia [7,11]. MRI can also be used as a guide for adjusting iron chelation therapy regimen [12–14]. Survival of patients with thalassemia is significantly improved with iron chelation treatment [15]. Since the development and introduction of iron chelation therapy, most patients with thalassemia were now treated early in the course of their disease, which has helped to prevent complications associated with iron overload [16,17]. Diagnosis of liver and cardiac iron overload in Southeast Asia is has previously been based on patient clinical information plus serum ferritin level. Although MRI has been used in clinical trials, this may not accurately reflect real-world prevalence or outcomes. As such, information regarding the prevalence of iron overload in clinical practice in Southeast Asia is limited. As such, the aim of this study was to determine the prevalence and predictors of hepatic and cardiac iron overload and the management patterns of patients with thalassemia in real-world practice in Thailand.

2. Materials and methods

2.1. Study patients

We studied thalassemia patients aged 8 years or older who were referred for liver and cardiac MRI for assessment of iron overload. A total of 8 hospitals located across Thailand participated in this study. Five out of 8 participating hospitals had MRI systems. The 3 remaining sites without MRI referred cases to a research site which is one of the participating hospitals with an MRI system. This study was approved by the institutional review boards of all participating centers and written informed consent was obtained from all participants prior to their enrollment in this study. MRI scans were performed during the 2011 to 2015 study period. Patients were excluded if they were 1) unable or unwilling to provide informed consent; 2) unable to have MRI assessment of heart and liver iron accumulation; 3) unwilling to share clinical data; or 4) pregnant.

2.2. Clinical information and laboratory data

The following clinical information were collected and recorded: 1) demographic information; 2) height and weight; 3) medical history; 4) transfusion history; 5) medications; and, 6) chelation treatment. The following laboratory data (within 6 months) were collected and recorded: 1) hematocrit and blood cell count including differential; 2) blood chemistry, including fasting plasma glucose, creatinine, and liver function test; and, 3) serum ferritin.

2.3. MRI protocol

The main center at Siriraj Hospital in Bangkok and 3 of the other 4 participating sites used a 1.5 T Philips Achieva XR Quasar Dual Gradient System (Philips Medical Systems, Best, The Netherlands). The fifth participating site used 1.5 T Siemens Aera System (Siemens AG, Munich, Germany).

The image acquisition started with cardiac exam, followed by liver exam. For examination of heart anatomy, the conventional black blood or inversion recovery pulse sequence was performed. Cine images were then obtained to study cardiac function. For iron study of the heart, the patient was scanned with the black-blood technique [18] which uses cardiac-gated multi-echo fast gradient sequence to acquire images within a single breath-hold time. An additional double inversion recovery pre-pulse was used to null the blood signal in the cardiac chamber. Images were acquired during diastole in a single mid-

ventricular short-axis slice with a slice thickness of 10 mm. Imaging parameters were a TR of 19 msec, 8 echo times from 2.6 to 16.7 msec with 2.0 msec steps, a matrix of 128 × 256, and field of view of 40 cm, which generated a voxel size of $3.1 \times 1.6 \times 10\ mm^3$. Inversion time (TI) was set to suppress the blood signal.

MRI scan of the liver was performed at the mid-hepatic slice with a multi-echo fast gradient-recalled echo sequence, which was acquired within a single breath-hold. Imaging parameters were repetition time (TR) of 80 msec, 20 echo times (1.1–16.3 msec with 0.8 msec increments), slice thickness of 10 mm, flip angle of 20 degrees, and field-of-view (FOV) of 40 cm, which yielded a voxel size of $3.1 \times 1.6 \times 10\ mm^3$. Due to a limitation associated with MRI acquisition, the maximum measurable R2* was approximately 1308 Hz, which is the reciprocal of the minimum TE used divided by 1.4, corresponding to a liver iron concentration of 33.4 mg/g dry weight [19].

2.4. Analysis of MRI

T2* images was analyzed by software developed from MATLAB software tool (The MathWorks, Inc., Natick, MA, USA) [18]. All myocardial T2* data were fit to a monoexponential curve without truncation or offset correction. Regions of interest (ROI) were defined manually from the interventricular septal region using a previously reported method [18]. Analysis was performed by MRI technologists with high experience in cardiac MRI. T2* results were reported using the median values of T2* which has been shown to be more precise than a mean value [18].

Liver iron overload was analyzed by an R2* which was measured by manually defining an ROI from the whole area of liver after excluding the major vessels. The liver data were offset corrected. A median value of R2* was reported. Liver iron concentration (LIC) was calculated using the formula described in an earlier report [20].

We have shown that intra- and inter-observer variability had a bias of 0.01 and 0.04 msec and a coefficient of variation of 1.5% and 2.4%, respectively [18]. Comparing data within site and inter-site measurement had a good reliability [21,22].

Cardiac iron status was divided into 3 groups according to T2*:, > 20 msec = no or minimal iron overload; > 10–20 msec = mild to moderate iron overload; and ≤ 10 msec = severe iron overload [6]. Liver iron status was divided into 4 groups, as follows: ≤ 3 = no iron overload; more than 3–7 mg/g dw = minimal iron overload; more than 7–15 mg/g dw = mild to moderate iron overload; and > 15 mg/g dw = severe iron overload [23]. For dichotomous comparisons, Iron overload of heart was defined as T2* ≤ 20 msec and iron overload of the liver was defined as LIC > 7 mg/g dw [6,24,25]. Patients were also classified into transfusion-dependent thalassemia (TDT) for patients who received regular transfusion and non-transfusion-dependent thalassemia (NTDT) for those who did not require regular transfusion.

2.5. Statistical analysis

Continuous data were compared by the Student's *t*-test for unpaired variables and are presented as mean ± standard deviation. Categorical data were compared by chi-square test or Fisher's exact test and are shown as number and percentages. Univariate and multivariate logistic regression analysis was performed to identify predictors for iron overload. A *p*-value of < 0.05 was regarded as being statistically significant.

3. Results

3.1. Prevalence of iron overload

A total of 405 patients were enrolled in this study. The mean age of patients was 18.8 ± 12.5 years and 46.7% were male. Overall, 21 patients (5.2%) had cardiac iron overload and 230 patients (56.8%) had