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Original Article

Deferiprone effectiveness in thalassemia major children with or without hepatitis B or C virus infection: a non-randomized study

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Abstract

Background A high incidence rate of hepatitis B or C virus infection is found among thalassemia children in Indonesia. This may influence deferiprone effectiveness.

Objective To determine the effectiveness of deferiprone in thalassemia children with or without hepatitis B or C virus infection.

Methods A non-randomized clinical study was performed at Thalassemia Center Jakarta. Subjects were thalassemia children with serum ferritin level >1000 ng/mL who had hepatitis B or C virus infection. A match control pair was recruited based on similar duration of transfusion therapy, thalassemia type, and initial serum ferritin level. All subjects received initial deferiprone dose of 50 mg/kg/day for 3 months. Those whose ferritin decreased ≥10% continued to receive deferiprone of 50 mg/kg/day for the following 3 months. Otherwise, deferiprone dose was adjusted to 75 mg/kg/day.

Results Forty-eight subjects were recruited. After 3 months of treatment, 16/24 subjects without and 6/24 subjects with hepatitis B or C had their ferritin level decreased ≥10%. Mean ferritin serum level of all subjects after 6 months was significantly reduced from 4734 (SD 2116) to 3695 (SD 1709) ng/mL. Lower mean deferiprone dose, lower mean post-study ferritin serum level and higher mean percentage of ferritin serum level decrement were found in subjects without hepatitis B or C infection than those with infection.

Conclusions Deferiprone 50-75 mg/kg/day for 6 months is effective in reducing serum ferritin level of thalassemia major children; it is more effective in thalassemia children without hepatitis B or C virus infection. **[Paediatr Indones. 2010;50:105-12]**.

Keywords: *deferiprone, thalassemia, hepatitis B, hepatitis C, effectiveness*

Thalassemia is one of the most common genetic disorders in the world with estimated patients of 1.67% of the world's population.[1] In 2008, there were 1435 patients registered at Thalassemia Center Cipto Mangunkusumo Hospital Jakarta, with 70-80 new patients each year.[2] Thalassemia is a disorder where one or more globin chain production is reduced. This ineffective erythropoiesis results in mild to severe degree of anemia. Packed red cell transfusion is still the mainstay management to ensure child's optimal growth and development. Iron overload is an inevitable consequence of regular transfusion, which leads to organ dysfunction.[1,3] Iron chelation therapy has been widely known to increase survival. Deferoxamine (DFO) is the conventional parenteral iron chelating agent. However, low compliance rate is found with DFO therapy due to its relatively difficult administration.[4] The first oral iron chelating agent, deferiprone, has been proven to have comparable

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effectiveness and safety with DFO and has been claimed to be superior to DFO in reducing cardiac iron overload.[4,5]

Thalassemia patients in Indonesia face another problem of high incidence of transfusion-associated hepatitis B or C virus infection rate. In 2008, there were 112 patients noted to have been positively infected with hepatitis C.[2] This chronic infection is suggested to influence the effectiveness of iron chelation therapy. On personal observation in Thalassemia Center Jakarta, thalassemia patients with chronic infection, particularly hepatitis B or C virus infection, do not have serum ferritin level reduction as good as those without infection, while receiving similar adequate iron chelation therapy.[6] Studies on deferiprone effectiveness in thalassemia patients in Indonesia and the effect of hepatitis virus infection status on the therapy are still limited. This study aimed to determine the effectiveness of deferiprone in reducing iron overload in thalassemia major children and to compare the effectiveness of deferiprone on thalassemia subjects with or without hepatitis B or C virus infection.

Methods

A non-randomized clinical trial was performed in Thalassemia Center Jakarta in 2008-2009. Subjects were children (≤ 18 year-old) diagnosed with thalassemia major (based on hemoglobin analysis, including thalassemia-β homozygote and thalassemia β/HbE patients with severe clinical manifestations) recruited consecutively with serum feritin level >1000 ng/mL, neutrophil count >1000/μL, and platelet count <150,000/μL who had hepatitis B/C virus infection (determined by positive anti-HCV, HbsAg, or total anti HBc). The exclusion criteria consist of renal impairment, liver failure, heart failure, pregnant and lactating woman. A match control pair was recruited purposively based on similar duration of transfusion therapy, thalassemia type, and initial serum ferritin level. All subjects received initial deferiprone dose of 50 mg/kg/day for 3 months; thereafter the ferritin serum level was evaluated. Those whose ferritin decreased ≥10% continued to receive deferiprone of 50 mg/kg/day for the following 3 months. Otherwise, deferiprone dose was adjusted to 75 mg/kg/day. After the second three months, complete laboratory evaluation was perfomed. Data was analyzed using SPSS for windows version 17.0 program, with $P<0.05$ considered significant. Ethical clearance was obtained from Ethical Committee Faculty of Medicine University of Indonesia.

Results

There were 48 subjects recruited in this study, consisted of 24 subjects with hepatitis B or C virus infection, and 24 subjects without hepatitis B or C virus infection (**Figure 1**).

There were 30 boys and 18 girls aged 3-17 years. Sixteen subjects were proved to have history of hepatitis B virus infection (positive total anti-HBc), 7 subjects were infected with hepatitis C virus (positive anti-HCV), and 1 subject had both. Mean transfusion volume (ml/kg) during study period in both groups was similar. Mean serum ferritin levels, mean pre-transfusion hemoglobin levels, as well as other supporting examinations parameter in both groups were comparable (**Table 1**).

During 6 months of treatment, the compliance rate was ranged between 72-100%. Mean compliance rate was similar between both groups (82.5 (SD 9.3) vs. 84.2 (11.3) in group with and without hepatitis B or C virus infection respectively).

Treatment with deferiprone of 50 mg/kg/day for the first three months resulted in reduced mean serum ferritin level from 4734 (SD 2116) ng/mL to 4570 (SD 1900) ng/mL. After three months, 22/48 subjects showed reduced ferritin level ≥10% of whom deferiprone dose continued to be given on dose of 50 mg/kg/day. The remaining 26 subjects had their dose increased to 75 mg/kg/day. Serum ferritin level evaluation after the second three months of therapy with dose of 50-75 mg/kg/day showed significant decrement (**Table 2**).

Mean decrement of serum ferritin level was 1039 (SD 1038) ng/mL or 21 (SD 19)% from the initial value. As shown in Figure 1, only 6/48 subjects who still did not have their serum ferritin level reduced ≥10% after deferipone therapy of 75 mg/kg/day, 1/6 subject who was infected with both hepatitis B and C virus infection had her serum ferritin level increased, and 5/6 subjects

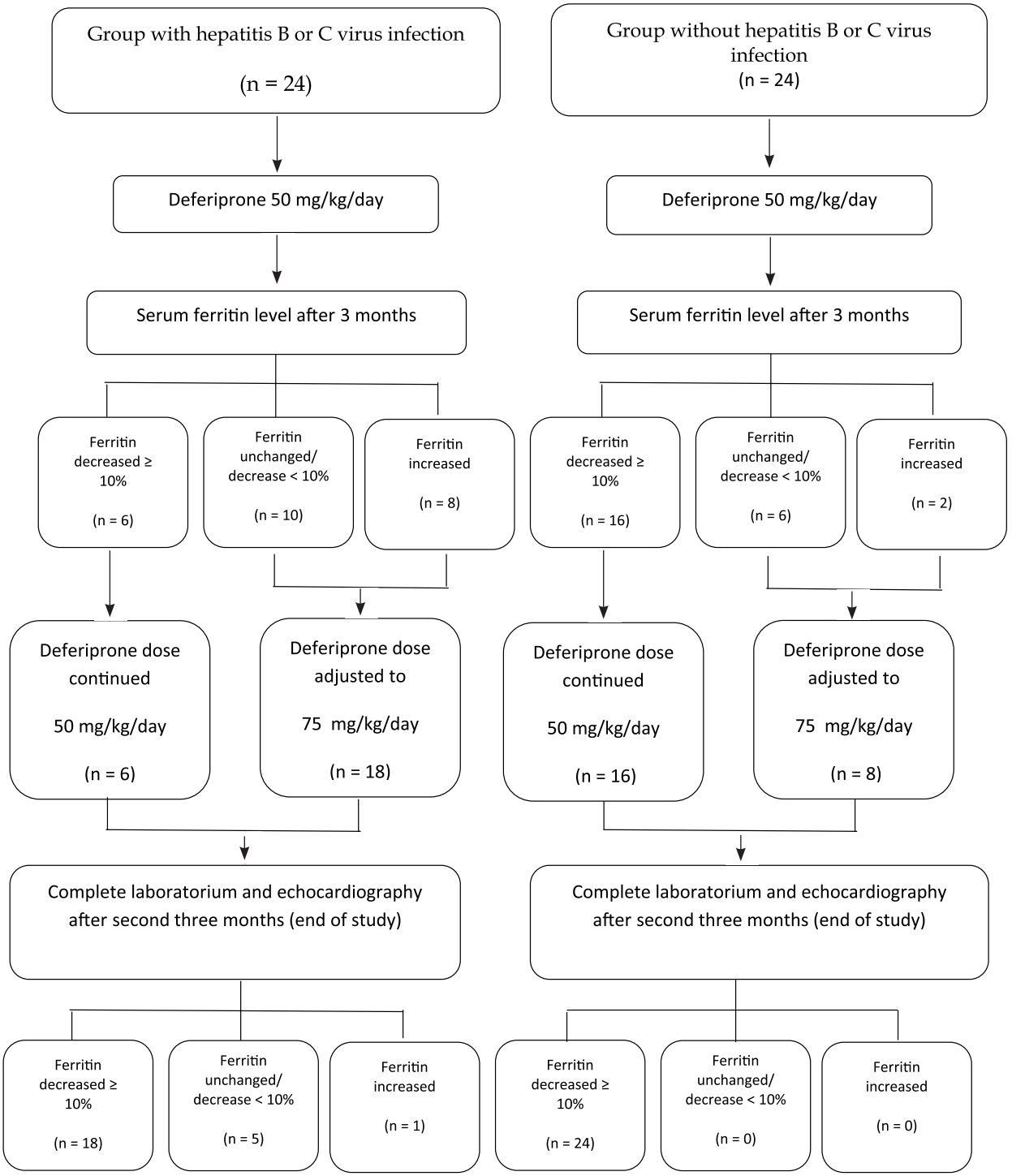

Figure 1. Flow of study subjects

Table 1. Characterisics of study subjects

Characteristics	Group with hepatitis B or C virus infection (n=24)	Group without hepatitis B or C virus infection (n=24)
Sex		
Male	15	15
Female	9	9
Thalassemia type		
Thalassemia-β homozygote	18	18
Thalassemia-β/HbE	6	6
Age, mean (SD) year	12.2 (3.5)	10.4 (3.7)
Transfusion duration, mean (SD) year	9.5 (4.4)	8.8 (3.9)
Nutritional status (based on MUAC/age)		
Well-nourished	6	5
Malnourished	13	15
Severe malnourished	5	4
Hepatitis B imunization status		
Complete (≥ 3x)	9	19
Incomplete (<3x)	15	5
Transfusion volume during study, mean (SD) ml/kg	115 (27)	114 (15)
Initial serum ferritin level, mean (SD) ng/mL	4725 (2186)	4744 (2091)
Pre-transfusion Hb, mean (SD) g/dL	7.2 (0.8)	7.7 (1.0)
Initial supporting examinations parameter, mean (SD)		
- White blood cell (/mL)	8913 (15,557)	8817 (7147)
- Absolute neutrophil count (/uL)	3881 (3625)	4883 (3994)
- AST(U/L)	51.0 (22.0)	43.5 (17.0)
- ALT(U/L)	57.7 (33.9)	47.0 (26.4)
- Ureum (mg/dL)	20.3 (6.0)	22.9 (8.3)
- Creatinine (mg/dL)	0.4 (0.18)	0.4 (0.13)
- Ejection fraction (%)	69.4 (6.6)	69.6 (5.0)

Table 2. Deferiprone therapy results

Parameter	Before study (n=48)	End of study (n=48)	P
Mean serum ferritin level (SD), ng/mL	4734 (2116)	3695(1709)	<0.001^

^Wilcoxon test

with hepatitis B virus infection had their serum unchanged/decreased <10%.

Table 3 shows decrement percentage of mean serum ferritin level in the control group is higher than in the group with hepatitis B or C virus infection (P = 0.011). In addition to that, group with hepatitis B or C virus infection needed larger mean deferiprone dose than control group (P=0.020).

When further classified based on hepatitis virus type, mean serum ferritin level in subjects with hepatitis C virus infection was higher than those with hepatitis B infection and than control **(Table 4).**

Adverse events of deferiprone 50-75 mg/kg/day resulted in adverse events of included nausea, vomiting, leukopenia, neutropenia, and increased liver enzymes in some subjects. Nausea and vomiting were generally found only in the first month of therapy, except in one subject who continued to experience them through the third month. Leukopenia and neutropenia could be found at anytime during study period. Neutropenia of 990/μL was found in one subject without hepatitis B or C virus infection on the last laboratory examination. There was no agranulocytosis (ANC <500/μL) found. No arthropathy was reported. The numbers of adverse

Table 3. Comparison of deferiprone therapy results between two groups

Parameter	Group with hepatitis B or C virus infection (n=24)	Group without hepatitis B or C virus infection (n=24)	P
Mean initial serum ferritin (SD), ng/mL	4725 (2186)	4744 (2091)	0.648^
Mean serum ferritin after 6 months therapy (SD), ng/mL	3939 (1855)	3452 (1550)	0.032*
Mean difference percentage (SD), %	14 (22)	27 (11)	0.011*
Mean deferiprone dose needed (SD), mg/kg/day	68 (12)	58 (12)	0.020^

* T-paired test, ^ Wilcoxon test

Table 4. Comparison of deferiprone therapy based on hepatitis virus type

Parameter	Sub-group hepatitis B virus infection (n=16)	Sub-group hepatitis C virus infection (n=8)	Group without hepatitis B or C virus infection (n=24)
Mean initial serum ferritin (SD), ng/mL	4612 (2086)	4950 (2509)	4744 (2091)
Mean serum ferritin after 6 months therapy (SD), ng/mL	3550 (1506)	4717 (2325)	3452 (1550)
Mean difference percentage (SD), %	20 (20)	2 (22)	27 (11)
Mean deferiprone dose needed (SD), mg/kg/day	66 (13)	72 (9)	58 (12)

Table 5. Deferiprone adverse events

Adverse events	Group with hepatitis B or C virus infection (n=24)	Group without hepatitis B or C virus infection (n=24)	Total (%) (n=48)
Nausea	4	5	9 (19)
Vomiting	4	4	8 (17)
Leucopenia (WBC<3000/uL)	4	5	9 (19)
Neutropenia (ANC <1000/uL)	0	1	1 (2)
Increased ALT 2-4x UNL	5	2	7 (15)
Increased ALT >4x UNL	1	1	2 (4)

WBC= white blood cells, ANC = absolute neutrophil count, UNL = upper normal limit

events between two groups are comparable (**Table 5**).

Discussion

The limitation of this study is that iron overload status and therapy effectiveness were assessed only by serum ferritin level examination. Although it is the most widely used parameter, ferritin value may be affected by acute conditions such as fever and infection. Another limitation is that compliance rate was obtained by history taking only in which inaccurate information might be given.

This study shows that initial serum ferritin level in subjects of both group was quite high, reflecting the poor chelating in the past. Serum ferritin level >2500 ng/mL is related to increased risk of cardiomyopathy. In this study, all subjects had good systolic and diastolic function based on echocardiography. However, Anderson et al[7] reported that echocardiography is not sensitive enough to detect early heart dysfunction due to iron overload. Ideally, every thalassemia patient >10 year old undergo MRI T2* examination to evaluate cardiac iron overload, but unfortunately, this test is not available in our center yet.

Compliance rate in this study was good in both groups (82.5 % and 84.2%). Olivieri et al[8] reported similar compliance rate of 85±3%, while Cohen et al[9] reported a higher rate of 93±8%. Previous iron chelation therapy with deferoxamine compliance rate in Thalassemia Center Jakarta was reported to be very low (<50%).[2] This may be due to difficulty in DFO administration and drug availability.

In this study, deferiprone therapy of 50 mg/kg/day for 3 months was effective in 22/48 (46%) subjects. After 6 months therapy, 42/48 (88%) subjects had reduced serum ferritin level ≥10%. Previous

published studies generally used larger dose of 75 mg/kg/day and performed longer monitoring (1-4 years).[9,10] Addis et al[11] in their meta-analysis defined long term study if perform ≥3 months with varied dose of 40-120 mg/kg/day. Mean initial serum ferritin in this meta-analysis was 3400 ng/mL, mean ferritin after study was 2600 ng/mL, and mean decrement percentage was 24%. Seventy six percent subjects had serum ferritin level reduction. Negative iron balance based on urine iron excretion measurement was successfully occurred in 51.8% subjects who were treated with deferiprone of ≥75 mg/kg/day. If subjects with lower dose (40-50 mg/kg/day) were also analyzed, the success rate became 45.1%.

Deferiprone dose of 50 mg/kg/day,used in this study, was the minimal initial dose suggested. This dose was applied in Thalassemia Center Jakarta because many patients came from underprivileged families. This study shows that this dose is effective in reducing serum ferritin level in 22/48 subjects. The difference of this study with previous studies was all subjects in this study were children, whereas other studies included adults. Besides, thalassemia-β/HbE subjects with severe clinical manifestation were also recruited, whereas other studies had more homogenous subjects of thalassemia β homozygote. Pootrakul et al[12] in their study of thalassemia-β/HbE subjects with thalassemia intermedia manifestation found that low dose of deferiprone (25-50 mg/kg/day) was effective in reducing iron overload.

Mean serum ferritin level after 6 months of deferiprone therapy was significantly higher in group with hepatitis B or C virus infection (P = 0.032) than in group without hepatitis B or C virus infection. Most (16/24) subjects without hepatitis B or C virus infection responded well to deferiprone of 50 mg/kg/day for 3 months. In contrast, most (18/24) subjects with hepatitis B or C infection needed increased dose. Eight subjects without hepatitis B or C virus infection had reduced serum ferritin level ≥10% after deferiprone therapy with adjusted dose of 75 mg/kg/day for 3 months. On the other hand, 1 subject with combination of hepatitis B and C virus infection still had increased ferritin level, and five other subjects with hepatitis B infection had decreased ferritin level <10%. These six subjects might need higher deferiprone dose (100 mg/kg/day) to reduce their iron overload.

Olivieri et al[10] reported liver fibrosis progression and increased liver iron concentration in five of forteen subjects who received deferiprone 75 mg/kg/day for a mean period of 4.6 years. Four of these five subjects were chronic hepatitis C patients and were older than the remaining subjects. Kowdley[13] analyzed this issue as a result of these two risk factors and lack of deferiprone effectiveness.

Mazza et al[14] in their study on 29 subjects aged 13-30 years (mean 22 years) with positive antibody to hepatitis C virus found that deferiprone 75 mg/kg/day for >12 months (14-32 months) was effective in reducing serum ferritin level. Ceci et al,[15] Cohen et al[9] and Maggio et al[16] whose studies' subjects were mostly hepatitis C positive also found that deferiprone 75 mg/kg/day was effective in reducing serum ferritin level, although no analysis was performed to compare the effectiveness between subjects with positive and negative antibody to hepatitis C.

Chen et al[17] in their study on 45 subjects (27 with hepatitis C virus infection, 18 without infection) discovered that deferiprone 75 mg/kg/day resulted in no significant difference in serum ferritin level between two groups.

In this study, subgroup analysis based on hepatitis virus type showed that subjects who had history of hepatitis C virus infection (n=8) required larger deferiprone dose than subjects who had history of hepatitis B infection and than control**.** Percentage of serum ferritin decrement between three groups were also different. Until currently, there is no particular study that can explain this phenomenon. Increased liver iron due to hepatitis C virus might be the reason why it is difficult to achieve negative iron balance although iron chelation has been administered in standard dose. Therefore, some subjects with hepatitis virus might need larger iron chelation dose.

Adverse events of deferiprone therapy occurred in this study was similar to those reported in previous studies. Nausea and vomiting were the most common adverse events (9/48, 19%), similar to study by Cohen et al[9] who found an incidence rate of 24%. These symptoms are usually resolved in the first week of therapy. In this study, 8/9 subjects improved after 1 month of therapy. Only 1/9 subject continued to experience nausea through the third month.

Neutropenia was reported in 5% patients receiving deferiprone, and was idiosyncratic and unpredictable

in nature.[9] In this study, leucopenia (white blood cells <3000/μL) was found in 9/48 subjects (19%), but neutropenia (absolute neutrophil count <1000/μL) was only found in one subject (2%). Agranulocytosis (absolute neutrophil count <500/μL) which may happen 0.5% pasien, was not found in this study.[9,18]

Nine of forty eight subjects (19%) had increased ALT >2x upper normal limit. Liver enzyme elevation is a common finding in deferiprone therapy, with incidence rate around 20%, occurs predominantly in the first 6 months of therapy, is usually temporary and generally does not require therapy modification.[15] Renal and heart function evaluation after study were between normal limits, comparable to previous studies where no renal or heart toxicity was found.[9]

One quite common adverse event (4-10%) found in other studies, namely arthropathy, was not found in this study. Risk factors to arthropaty include high dose of deferiprone, and high degree of body iron overload.[9,15] The low initial dose of deferiprone (50 mg/kg/day) used in this study may explain why no arthropathy was reported.

Adverse events rate between two groups were comparable. This is similar to study by Chen *et al* who did not found significant difference in adverse events rate between subjects with or without hepatitis C virus infection.[17] Increased serum ALT serum occurred in 3/24 subject without hepatitis B or C virus infection and 6/24 subjects with hepatitis B or C virus infection. Risk factor that increased serum ALT was hepatitis virus infection.[9]

We conclude that deferiprone 50-75 mg/kg/day for 6 months is effective in reducing serum ferritin level of thalassemia major children. Deferiprone is found to be more effective in thalassemia major children without hepatitis B or C virus infection than in those with hepatitis B or C virus infection, where lower dose is required, lower mean serum ferritin level after therapy and higher mean decrement percentage are obtained. There was no fatal adverse event found in this study. Number of adverse events between two groups are comparable.

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