THALASSEMIA

Blood transfusion versus hydroxyurea in beta-thalassemia in Iran: a cost-effectiveness study

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ABSTRACT

Introduction: Thalassemia intermedia is a type of anemia which has several treatments modalities. We aimed to study the cost effectiveness of two treatments, including blood transfusion and hydroxyurea, in patients with beta-thalassemia intermedia in south of Iran referred to a referral center affiliated to Iran, Shiraz University of Medical Sciences in 2015.

Materials and methods: This was a cost-effectiveness study which was conducted on 122 patients with beta-thalassemia intermedia. The indicator of effectiveness in this study was the reduction of growth disorder (normal BMI). Data analysis was done using SPSS 21, Excel 2010 and Treeage 2011. Finally, the one-way sensitivity analysis was performed to determine the robustness of the results.

Results: The average annual costs of blood transfusion and the use of hydroxyurea in 2015 were 20733.27 purchasing power parity (PPP)$ and 7040.29 PPP$, respectively. The effectiveness of blood transfusion was 57.4% while in hydroxyurea group was 60.7%.

Conclusion: The results showed that the cost effectiveness of using hydroxyurea was more than that of blood transfusion. Therefore, it is recommended that the use of hydroxyurea in the treatment of patients with beta-thalassemia intermedia would become the first priority, and more basic and supplementary insurance coverage for treating such patients using hydroxyurea should be considered.

KEYWORDS
Cost effectiveness; thalassemia intermedia; blood transfusion; hydroxyurea

Introduction

Thalassemia is a genetic chronic blood disorder caused by the synthesis deficiency of one or several chain of globin peptide [1] in which the patients are not able to produce sufficient amounts of globin chains [2]. Generally, about 5% of the world’s population is suffering from diseases related to the hemoglobin of which the thalassemia carriers are formed about 1.7% [3]. This disease starts with anemia and associates with changing the shape and problems of the bones, weakness and growth delay [4,5]. Also, we can consider the delayed growth, delayed sexual puberty, being short, atrophy and hypogonadism as the basic problems of these patients [6]. This disease should be called thalassemia syndrome as it has different types. What's more, any type of thalassemia has a wide range of clinical symptoms based on their severity [7]. Beta-thalassemia major (B-TM) is one of the most common genetic disorders in the world; some of these patients sometimes show milder form of the disease and are called intermedia [8].

Beta-thalassemia intermedia (B-TI) is a variant of beta thalassemia [9] in which the severity of anemia is less than thalassemia major; therefore, they are not regular transfusion-dependent and can hold their hemoglobin level at 8–6 g/dl without blood transfusions [10]. The usual treatment of B-TM is the regular blood transfusion [11]. But blood transfusion in addition to the risk of transmission of blood-borne diseases, gradually leads to iron overload disorder in vital organs such as the liver and heart, which can cause premature death [6]. On the other hand, different medicines have also been used to treat patients with thalassemia; including Azacitidine, Zastdyyn, hydroxyurea, phenyl butyrate, busulfan [12], ferric chloride, erythropoietin and chorionic gonadotropin that increase the patients’ hemoglobin levels [13]. However, most experience in the effect of pharmacological medicine interventions in the increase of Hbf (fetal hemoglobin) production is related to the use of hydroxyurea in B-TI patients [12,14].

Hydroxyurea is an antineoplastic medicine [15] and has fewer side effects than other used medicines and it has seen that it can increase the total hemoglobin level and Hbf in some patients with thalassemia intermedia [12]. The therapeutic use of hydroxyurea in thalassemia started in 1994 and several studies have been conducted on the effects of its use in patients with thalassemia [16]. The results of studies indicate that after treatment with hydroxyurea in patients with beta-

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thalassemia, the need for blood transfusions and the serum ferritin are significantly reduced [12,17,18].

Bradai et al. [19] and Ansari et al. [20] in their study concluded that the hydroxyurea could replace blood transfusions in patients with thalassemia major and intermedia in terms of effectiveness. Moore et al. [21] also in their study found out that compared with placebo, the use of hydroxyurea in patients with sickle-cell anemia is cost effective [21]. But in some studies, the researchers have concluded that hydroxyurea causes some symptoms such as not having effect on hemoglobin, lethargy, severe nausea, heart problems, drop in platelets, and bone pain that cause treatment discontinuation [11].

On the other hand, the total cost of treating thalassemia two hematology clinics of Iran, Tabriz in 2009 was estimated at €1730.52 per patient/year [22]. Wang et al. [23] in their study have estimated the annual costs of hydroxyurea therapy usage for patients are equal to $11072; and also Moore et al. [21] in their study have indicated that the annual average cost per patient taking hydroxyurea was $16,810. Economic evaluation is one of the scientific techniques that is used by the policymakers to determine the effective intervention. The economic analysts in the health sector use the comprehensive expression of economic evaluation for the economic analysis of different solutions. One of the tools that are used in the health sector is the cost-effectiveness analysis. Cost-effectiveness analysis is the most common form of economic evaluation in the health sector, where the costs are measured as monetary units, but the effectiveness of health care interventions and programs are shown as a non-material real scale [24].

According to what mentioned above, about the rate of thalassemia and the huge costs that this disease may impose on the patients and the community on the one hand, and on the other hand, as the researcher failed in her search to find a similar study on the evaluation and comparison of the cost effectiveness of the use of blood transfusion treatment and the use of hydroxyurea medicine in patients with thalassemia, the aim of this study was to determine the cost effectiveness of blood transfusions compared with hydroxyurea in patients with B-TI in south of Iran referred to a referral center affiliated to Iran, Shiraz University of Medical Sciences in 2015. Due to lack of the similar studies in this regard, using the results of the pilot study conducted by researchers in the field of thalassemia disease complications in the two groups of patients taking hydroxyurea and blood transfusions whose complication rates were 56 and 34%, respectively, and considering $a = 0.05$, and the power of 70%, a sample size of 61 patients in each group were determined using the following formula:

\[
n_1 = n_2 = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2[p_1(1 - p_1) + p_2(1 - p_2)]}{(p_1 - p_2)^2}
\]

The inclusion criteria included: patients who were willing to participate in the study, have more than 10 years old, the patients taking at least 2 years of blood transfusion therapy, and the patients using hydroxyurea therapy at least for 5 years. Based on these inclusion criteria, patients in each group were selected using convenience sampling method during 6 months.

**Effectiveness**

The effectiveness indicator in this study was the growth disorder in patients with B-TI which was studied after the use of blood transfusions and hydroxyurea therapy measured using a researcher-made checklist of the effectiveness. In other words, to determine the effectiveness of the mentioned treatments, the indicator of not having growth disorder in the form of normal BMI was used [25]. To complete the effectiveness checklist, the researcher accompanied by a hematologist used the medical records of the patients. It should be noted that the patients were distinguishable from one another using a code above the form and checklist used for gathering required data.

**Costs**

To collect the costs data in this study, a data collection form was used that consisted of two parts. The first part was related to the studied patients’ demographic information such as age, sex, marital status, etc.; and the second part was related to the information of the therapeutic–diagnostic costs such as laboratory, radiology, visit, medicines, etc. It should be noted that in order to collect the data on medical costs, the Bottom Up method was used [26]. Also, in order to international comparison, the costs were changed into international dollars using the purchasing power parity (PPP) $ exchange rate of 11222.4 Rials per 1 $ [27].

In the present study, given that the criteria for calculating the costs were from the perspective of the society, the required data were collected by interviewing the patients and reviewing their medical records. The direct medical costs (including the average costs
of outpatient, inpatient, medicine, para-clinical testing, and diagnostic services), direct non-medical costs (including the costs of transportations, the food eaten by the patient and his family during the visits in medical centers and the costs of staying in other cities in order to treatment), and the indirect costs (including the time of being absent from the office and workplace due to receiving medical care or, in other words, the potential production lost caused by being referred to the hospitals as the outpatient or inpatient which was evaluated by using the human capital approach) were calculated.

This study was approved by the Medical Ethics Committee of Iran, Shiraz University of Medical Sciences. Also, all the patients participating in the study completed the informed consent form. They were free to participate in the study and in case of unwillingness to continue participation in the project, they could withdraw the study. Moreover, they were assured that their information would remain confidential. It should be noted that, finally, all studied patients completed the study.

To analyze the collected data and performing the one-sided sensitivity analysis, SPSS 21.0, Excel 2010, and Treeage 2011 were used; and the amounts of costs, effectiveness, and cost effectiveness had been calculated for the two treatment strategies for 1 year of 2015.

**Results**

The results showed that most of the patients were female (63.1%), at the age group of 21–30 years (73%), single (76.2%), urban (82%), with a 1–4 household members (49.2%), with the basic Taamin Ejtemaee insurance coverage (46.7%) and without supplementary insurance coverage (91%), at the education level of diploma (35.2%), and were not the heads of households (87.7%). The results of the direct medical costs, direct non-medical costs and indirect costs in the patients with thalassemia intermedia separately in the two blood transfusions and hydroxyurea therapies have been shown in Table 1. In other words, the total costs of the blood transfusion therapy consisted of 97.25% direct medical costs the most of which were related to the medicines, 0.78% of the costs were for non-medical direct costs most of which was related to the transportations, and the indirect costs were 1.97%.

In addition, of the total costs of hydroxyurea therapy, 92.64% were direct medical costs among which the highest costs were related to the medicine, 3.66% of that was non-medical direct costs among which the highest costs were related to the transportations, and 3.7% had been spent on the indirect costs.

The results of the effectiveness investigation of the therapies on the patients with B-TI have been presented in Table 2. As the results show, the effectiveness or the percentage of the normal BMI in blood transfusion therapy and hydroxyurea were 57.4 and 60.7%, respectively.

The results of cost-effectiveness analysis obtained from the collected data based on the percentage of patients with normal BMI in the studied strategies have been presented in Table 3. As it can be seen in Table 3 and Figure 1, the use of hydroxyurea compared with the blood transfusions was less expensive and more effective and, therefore, the blood transfusion therapy has been dominated. The results of Table 4 which are the extracted findings from Table 3 and

| Table 1. The average total costs of treatment by the blood transfusions and the use of hydroxyurea therapy per each B-TI patient in south of Iran in 2015. |
|---|---|---|---|
| Type of the treatment | Blood transfusion Mean (PPP $) | Hydroxyurea Mean (PPP $) |
| Type of the costs | Direct medical costs | 16307.65 | 5560.05 |
| | Blood transfusion | 2562.27 | 35.04 |
| | Visit | 575.63 | 203.16 |
| | Laboratory | 405.13 | 337.25 |
| | Diagnostic and treatment services | 189.64 | 266.54 |
| | Hospitalization | 121.89 | 119.76 |
| | Direct non-medical costs | 141.88 | 209.02 |
| | Transportation | 20.53 | 48.58 |
| | Accommodation and food | 189.64 | 266.54 |
| | Indirect costs | 408.62 | 260.86 |
| | Potential production lost due to the absence from work to receive medical care | 20733.27 | 7040.29 |

| Table 2. The results of the comparison of body mass index (BMI) between the B-TI patients using blood transfusion and those using hydroxyurea in south of Iran in 2015. |
|---|---|---|---|
| BMI categories | Frequency | Percent of frequency | Frequency | Percent of frequency |
| Underweight (< 18.5) | 20 | 32.8 | 20 | 32.8 |
| Normal (18.5–24.9) | 35 | 57.4 | 37 | 60.7 |
| Overweight (25–29.9) | 6 | 9.8 | 4 | 6/6 |
| Obese (more than 30) | 0 | 0 | 0 | 0 |
| Total | 61 | 100 | 61 | 100 |

| Table 3. Comparison of the costs and effectiveness of the blood transfusion and use of hydroxyurea in patients with B-TI in south of Iran in 2015. |
|---|---|---|---|
| Type of the treatment | Effectiveness and cost | Blood transfusion Mean | Hydroxyurea Mean |
| | The mean of total costs (PPP $) | 20733.27 | 7040.29 |
| | Effectiveness | 57.4 | 60.7 |
| | Incremental cost-effectiveness ratio (ICER) | The use of hydroxyurea = The dominant strategy |
Figure 1 show that the use of hydroxyurea therapy compared with the blood transfusion was more cost effective.

Also, the results of Table 4, which have been obtained from Table 3 and Figure 1, show that the use of hydroxyurea was more cost effective in comparison with blood transfusion, and as a result, the blood transfusion therapy had been dominated.

The results of sensitivity analysis in Figure 2 also show that the results of ICER has had the highest sensitivity to the effectiveness of blood transfusions (E1) and the lowest sensitivity to the costs of using hydroxyurea (c2). Therefore, by increasing the effectiveness of blood transfusion and considering that in this case, the ICER level significantly decreased compared with the baseline and turns to negative, it can be said that by increasing the effectiveness of blood transfusion (normal BMI), the amount of cost savings increases and the decision making about the cost effectiveness of blood transfusion compared with the hydroxyurea can be done with more certainty.

**Discussion**

Due to the limited resources in health systems around the world, the demand for the economic evaluation of the health care programs and strategies is increasing steadily [28]. The health care system of Iran is also responsible for financing the medical care for more than 25 thousand patients with thalassemia major and intermedia, hence, it is necessary to allocate resources efficiently [29]. According to the present study findings, the average costs per patient in blood transfusion and taking hydroxyurea were annually equal to $20733.3 and $7040.3, respectively.

In general and based on the results of this study, the average direct medical costs of patients using blood transfusion therapy were higher than the average direct medical costs of patients taking hydroxyurea. This increase is mainly due to the higher costs of medicines, tests, blood transfusions and the number of physician visits in the treatment with blood transfusion.

Also, the average indirect costs of blood transfusion were higher than the use of hydroxyurea. As the patients using blood transfusion have more number of visits and hospitalization; thus, they were away from their work longer. But the average non-medical direct costs of blood transfusions had been more than hydroxyurea. This difference in the current study was due to the fact that the majority of patients using hydroxyurea were non-native of Shiraz, so the costs of their travel and accommodation and food

**Table 4.** The results of comparing the cost effectiveness of blood transfusion and use of hydroxyurea in patients with B-TI based on BMI.

| Strategies         | Eff  | incEff | Costs (PPP $) | incrCost | incrCE | Subset        |
|--------------------|------|--------|---------------|----------|--------|---------------|
| Hydroxyurea        | 0.607| 0      | 7040.3        | –        | –      | Undominated   |
| Blood transfusion  | 0.574| -0.033 | 20733.3       | 13693    | -414,939| Abs. dominated|

Eff: Effectiveness; incEff: incremental effectiveness; incrCost: incremental costs; incrCE: incremental cost effectiveness.
had been more. The results of the studies conducted by Riewpaiboon et al. [30], Wang et al. [23], Sattari et al. [22], and Moore et al. [21] confirm those of the present study results.

In addition, the highest and lowest costs of patients who used the hydroxyurea in this study were, respectively, related to the direct medical costs (92.64%) and the non-medical direct costs (3.66%). In the patients who were under the blood transfusion therapy, the highest costs were related to the direct medical costs (97.25%) and the lowest ones were related to the direct non-medical costs (0.78%), respectively. The results of the Scalone et al.’s study [31] are also in line with our findings on the highest costs in the B-TI patients using blood transfusions, but unlike the present study results that the direct costs of non-medical therapies were the lowest costs, the indirect costs were the lowest in the study of Scalone et al.

Also, the results of the current study showed that the effectiveness and the normal percentage of BMI in the patients with blood transfusion and the use of hydroxyurea were 57.4 and 60.7%, respectively. As a result, the use of hydroxyurea therapy was more effective than treatment with blood transfusion. The results of Bradai et al. [19], Yavarian et al. [11], Steinberg et al. [32] and Ansari et al. [20] confirm the present study results.

Generally and based on the results of investigating the costs and effectiveness of blood transfusion and use of hydroxyurea, it can be concluded that the use of hydroxyurea, in comparison with blood transfusion, was less expensive and more effective; so, the use of hydroxyurea treatment is more cost effective or dominant. The results of Moore et al. and Kosarian et al. [15,21] are similar to those of the present study.

In this study, the one-sided sensitivity analysis was performed to verify the results of the economic evaluation whose results can be a determining factor in the results of economic evaluation.

According to the results of the Tornado diagram, it can be said that with increasing the effectiveness of blood transfusion (i.e. normal BMI), the amount of cost saving increases further. Thus, the decision making on the cost effectiveness of using hydroxyurea in comparison with the blood transfusion would be along with more certainty. Considering the results of the sensitivity analysis, it can be concluded more certainly that the use of hydroxyurea treatment for the studied patients was more cost effective and could achieve the better outcomes.

The same as the other studies, this study had a series of limitations; including conducting a cross-sectional study, as well as the defects in some of the patients’ medical records in the data on the medication dosages prescriptions for the patients. What’s more, although due to the use of hydroxyurea in patients with B-TI in other medical centers in Iran, the results of this study can be generalized to the other medical centers in Iran, the study findings cannot be generalized to the other countries without considering some items; such as the amount of cost coverage by their insurance organizations, their maximum government’s willingness to pay the costs of the most cost-effective treatment strategies, etc.

Figure 2. Tornado Analysis Diagram of the sensitivity analysis of the cost-effectiveness of blood transfusion vs. hydroxyurea in patients with B-TI in the south of the country in 2015.
In conclusion, based on the results and findings of the study, it can be concluded that hydroxyurea therapy in patients with B-TI was more cost-effective strategy than blood transfusion. Therefore, it is recommended that the use of hydroxyurea in the treatment of these patients would become the first priority, and more basic and supplementary insurance coverage for treating such patients using hydroxyurea should be considered.

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