Journal of Critical Care 29 (2014) 362–366

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Recombinant human thrombopoietin improves platelet counts and reduces platelet transfusion possibility among patients with severe sepsis and thrombocytopenia: A prospective study☆

Qin Wu, MD, Jianan Ren, MD, FACS*, Xiuwen Wu, MD, Gefei Wang, MD, Guosheng Gu, MD, Song Liu, MD, Yin Wu, MD, Dong Hu, MD, Yunzhao Zhao, MD, Jieshou Li, MD

Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China

ARTICLE INFO

Keywords:
Recombinant human thrombopoietin
Thrombocytopenia
Severe sepsis
Platelet counts

ABSTRACT

Introduction: Thrombocytopenia is prevalent in patients with severe sepsis, and it is associated with mortalities. Effectively adjunctive treatment might be needed to reverse low platelet counts (PCs). With a growing understanding of thrombocytopenia, recombinant human thrombopoietin (rhTPO) is considered a promising beneficial drug. The present study was dedicated to evaluate the efficiency of rhTPO in improving PCs in patients with severe sepsis.

Materials and Methods: We performed a prospective study in patients with severe sepsis between March 2012 and February 2013. All enrolled patients were divided into rhTPO group and control group, depending on whether rhTPO was prescribed or not. Platelet counts and other parameters were measured initially and in the following 15 days.

Results: Totally, 72 patients (38 in the rhTPO group and 34 in the control group) were included. All enrolled parameters exhibited no significant differences between groups at the baseline. Platelet counts showed a significant increase over time in both groups. Faster improvement of PCs in the rhTPO group was observed with a significant difference. Less platelet transfusion occurred in patients who received rhTPO in our study, as well. No drug-related adverse event during the rhTPO therapy was recorded.

Conclusion: The use of rhTPO in combination with conventional medical therapies could significantly improve the PCs in patients with severe sepsis and thrombocytopenia and effectively reduce the platelet transfusion possibility.

1. Introduction

Severe sepsis is one of the major health care problems affecting millions of people around the world [1]. As a systemic host response to invading pathogens such as bacteria, it has a wide influence on major organs, resulting in disorders of physiological processes.

Defined as the *platelet counts* (PCs) in peripheral venous blood less than 100×10^9/L, thrombocytopenia is one of the commonest laboratory abnormalities frequently encountered in patients with severe sepsis [2,3]. The incidence of thrombocytopenia in intensive care unit has been well reported to vary from 23% to 41% [4,5]. It has been further revealed that thrombocytopenia is directly linked to the mortality of patients with severe sepsis for the correlation with functional disorders in coagulation [5,6].

With a growing understanding of platelet (PLT) functions, special attention has been caught during the management of patients with severe sepsis [7,8]. On the basis of complex pathogenesis, PLT transfusion is recommended for reversing the low PCs of patients in several studies [8,9]. However, PLT transfusion is usually debated in thrombocytopenic critically ill patients for multiple risks transfusion brings such as infectious or immune complications. What is worse is that, recently, there has been a shortage of blood products around the world.

As a humoral growth factor originally identified for its ability to stimulate proliferation and differentiation of megakaryocytes, recombinant human thrombopoietin (rhTPO) participates in modulating the homeostatic potential of mature PLT by influencing the response to several stimulates [10,11]. It has been proven to be effective in PLT stimulating among patients with idiopathic thrombocytopenic purpura (ITP), indicating a possibility of rhTPO as a substitution in the management of severe sepsis to reduce possibilities for PLT transfusion [12].

Several studies have illustrated the changes of circulating thrombopoietin (TPO) level in critically ill patients [13,14]. However, until now, the effectiveness of rhTPO as a complementary drug in

☆ The work was supported by grants from National Natural Science Foundation of China (81270478).Competing interests: The authors declare that they have no competing interests.

* Corresponding author. Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, 305 East Zhong Shan Rd, Nanjing 210002, China. Tel.: +86 25 80860437.

E-mail address: JiananR@gmail.com (J. Ren).

0883-9441/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.11.023

patients with severe sepsis remains uncertain. To assess the potential roles of rhTPO in improving PCs and reducing PLT transfusion possibility among patients with severe sepsis, we performed a prospective investigation.

2. Patients and methods

2.1. Study design

This prospective study was carried out in the Department of Surgery, Jinling Hospital, Nanjing, China, from March 2012 to February 2013. It was approved by the ethics committee of Jinling Hospital. A written informed consent was obtained from all enrolled patients, which was mainly consisted of the following items: (1) the nature of the procedure, including the reason that the patient was suggested to be enrolled in the current study, when and how the drugs would be prescribed, and timing of blood collections; (2) the relevant benefits, risks, and uncertainties related to the interventions; and (3) assessment of understandings and acceptance of the interventions by the patient.

All adult hospitalized septic patients whose PCs were less than 100×10^9/L at their admission were eligible for inclusion. The criteria for severe sepsis were a modification of those defined by surviving sepsis campaign. Detailedly, *SIRS* was defined by 2 or more of the following conditions: temperature higher than 38°C or lower than 36°C, heart rate more than 90 beats/min, respiratory rate more than 20 breaths/min or $Paco_2$ less than 4.26 kPa, or white blood cell (WBC) count greater than 12×10^9/L or less than 4×10^9/L. Also, *sepsis* was defined as a systemic response to infection including the criteria of SIRS plus microbiological evidence of a focal infection and/or a positive blood culture. *Severe sepsis* was defined as sepsis associated with organ dysfunction including thrombocytopenia.

The exclusion criteria were as follows: (a) patients who were prescribed chemotherapeutic, glucocorticoid, or heparin before or in our study; (2) patients who had a history of ITP or such immunologic diseases; (3) pregnant patients; (4) patients who were definitely diagnosed as having acute gastrointestinal hemorrhage; and (5) patients who have a history of bone marrow, lung, liver, kidney, pancreas, or small bowel transplantation.

All enrolled patients were divided into ITPO group (intent to receive rhTPO therapy) and INTPO group (intent not to receive rhTPO therapy) according to the will of the patients of their families. The same treatments were initiated in both groups, except for rhTPO therapy. Fluid resuscitation was performed according to the guideline launched by Surviving Sepsis Campaign. Volume and frequency of fluid boluses were recorded. Patients who could not stand the adverse effect of the treatment would discontinue our study.

The criteria for PLT transfusions in our study were documented as PCs below 15×10^9/L. Thromboembolic events were systematically evaluated. The occurrence of myocardial infarction/ischemia, ischemic stroke, deep vein thrombosis, or pulmonary embolism is required for a detailed report. If any abnormal symptoms are present, computed tomographic scan is performed as soon as possible. Patients remained in the ITPO and INTPO groups at the end of our study were defined as the *rhTPO group* and *control group*, respectively. Laboratory tests were performed before treatment (baseline) and every day after starting the treatment.

2.2. Thrombopoietin therapy

There were no written protocols for rhTPO therapy in severe sepsis until now. Recombinant human thrombopoietin (TPIAO; Shenyang Sunshine Pharmaceutical Company Limited [SUNSHINE], Shenyang, China) was subcutaneously injected in the rhTPO group after initial resuscitation. The dose was 15 000 U/d for initial stage and maintenance stage. The subcutaneous injection would be terminated when PCs restored to a normal level (PCs $>100 \times 10^9$/L). Also, administration of rhTPO would be stopped if patients had received PLT/blood transfusion. Time from sepsis onset to treatment with rhTPO is within 24 hours. This rhTPO therapy was limited to 15 days.

According to the criteria that were used to evaluate the efficiency of rhTPO in patients with ITP, a *successful rhTPO medical treatment* in our study was defined as PCs returned to or above a normal level ($>100 \times 10^9$/L) after initiation of the rhTPO treatment. The identical criterion was applied for accessing PCs changes in the control group. The *duration of rhTPO therapy* was defined as days from initiation to the ending. Fifteen days was applied in our study for those patients who did not terminate rhTPO therapy at the end of our study.

2.3. Data collection

For each enrolled patient, all of the following data were collected: primary diseases, Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA) score, body temperature, heart rates, WBC counts, C-reactive protein (CRP), red blood cell (RBC) counts, PCs, activated partial thromboplastin time (APTT), glutamic-pyruvic transaminase (GPT), and blood urine creatinine (Cr). White blood cell count and CRP were enrolled to indicate the inflammations and infections of whole body; APTT and international normalized ratio (INR) were collected for assessing coagulation functions; and GPT and Cr were enrolled for monitoring liver and renal functions respectively. Time from sepsis onset for measurement of all laboratory parameters was limited within 24 hours.

Venous blood for all laboratory tests was drawn between 5 AM and 6 AM. Laboratory values were calculated within 2 hours after blood collection. Baseline characteristics including age and sex were also collected.

2.4. Statistical analysis

Demographic data and laboratory parameters were summarized by frequency for categorical variables and means ± SD. Proportions were compared with χ^2 test or Fisher exact test. Continuous variables were tested by means of *t* test with normal distribution or Wilcoxon rank sum test with nonnormal distribution. Statically analyses were performed with GraphPad Prism Software (version 5.01; GraphPad, San Diego, Calif) and SAS software (SAS 9.1.3; SAS Institute Inc, Cary, NC). Surviving analysis was conducted for the time to the successful medical treatment according to whether rhTPO was used or not. Cases were censored in case of PLT/blood transfusion or loss to follow-up. A multivariate analysis of Cox proportional hazards regression model (backward, stepwise) was created to assess the influence of each variable on treatment success rate. A P value less than $<.05$ was considered statistically significant.

3. Results

3.1. Participants

A total of 107 patients were prospectively collected between March 2012 and February 2013, and 102 of them met the criteria (Fig. 1). Fifty-one patients were treated with rhTPO, whereas the others were not. Twenty-seven patients received PLT or blood transfusions. Three patients were excluded because of insufficient data that were needed for statistical analysis. These remaining 38 and 34 patients were defined as the rhTPO and control groups respectively, for further statistical analysis.

Table 1 demonstrated the demographic data of patients in the rhTPO and control groups. Accompanied by a male predominance, the medium ages were 53.16 and 49.29 years in these 2 groups. The most common cause for severe sepsis in our study was gastrointestinal fistula. The most common sites of infection were the abdomen and lung, with mixed pathogens or gram-negative organisms accounting