Coagulation Disturbances in Paediatric Patients with Hepatic Veno-Occlusive Disease after Stem Cells Transplantation

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INTRODUCTION

Liver veno-occlusive disease (VOD) is a clinical syndrome characterized by hepatomegaly, fluid retention and hyperbilirubinemia [1]. It is a serious complication after high doses of chemotherapy and/or radiotherapy and immunosuppressive treatment. Also, it is an early complication after stem cells transplantation (SCT), one of the most frequent complications and one of the leading causes of death in this group of patients [2]. In paediatric population the incidence of VOD is between 5-40%, mortality rate around 40% and, according to the recent studies, it is several times higher comparing with adults [2, 3].

The precise mechanism of VOD and the place of damage are not completely clear yet; it is, most probably, the result of sinusoidal endothelial cell damage followed by hepatocyte necrosis and coagulation activation. All these thee processes are highly increased after being followed by cytokine activation, especially tumour necrosis factor α and interleukin 1β [1]. First pathohistological findings have been seen in zone 3 of hepatic acinus as a progressive and concentric narrowing of small intrahepatic venules associated with necrosis of hepatocytes in the centrilobular areas. A lasting sinusoidal obstruction with cell detritus and erythrocytes consecutively leads to sinusoidal fibrosis and obliteration [4].

The diagnosis of VOD relies on the combination of certain clinical signs, and most of transplantation teams use Seattle or Baltimore criteria, which are similar. The Seattle criteria requires two of the following three physical or laboratory findings: 1) jaundice or bilirubin level >34 μmol/L; 2) hepatomegaly or right upper quadrant pain of liver origin or; 3) sudden weight gain of more than 5% above baseline caused by either fluid accumulation or ascites [5]. For clinical practise it is very useful to add ultrasound findings of gallbladder thickening of more than 4 mm and platelet transfusion dependency together with the mentioned well known clinical signs [6].

Some of the authors think that VOD is the result of coagulation disarrangements after sinusoidal and central venous endothelial injury, the consecutive increase of tissue factor concentration and initiation of coagulation cascade. This process is contributed to the decrease of natural anticoagulants levels such as protein C and antithrombin and high levels of circulating procoagulant cytokines [7, 8]. In patients with VOD level of tissue plasminogen activator is increasing, however fibrinolysis is decreased and there are even higher levels of plasminogen activator inhibitor type 1. Besides, heparin and antithrombin concentration infusions has not shown to be efficient in the prevention and treatment of VOD, and thrombolytic therapy is successful in just a minority of patients [9-12].

OBJECTIVE

Our goals were to determine the incidence, risk factors, changes in haemostatic parameters and outcome in
paediatric patients with VOD. We measured levels of platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), coagulation factors I, VIII and vWF, and antithrombin levels prior to starting conditioning regimen and time trend of these values on the day 1, 7 and 14 from the VOD onset. Also, we tried to determine coagulation disturbances in these patients and their practical significance in early diagnosis.

METHODS

We prospectively evaluated all consecutive VOD patients after SCT, aged 3 months to 17 years during a 4-year period, from February 2004 to July 2008. All were treated in the Bone and Marrow Transplantation Unit of the Mother and Child Health Institute of Serbia “Dr. Vukan Čupić” (IMD) and were diagnosed according to the Seattle criteria and based on ultrasound findings of gallbladder thickening over 4 mm. From particular medical histories we collected all necessary information regarding age, diagnosis, previous treatment and dates of liver and kidney damage prior to SCT.

All patients were placed in protective isolation from the start of conditioning therapy until hospital discharge. Prophylactic medications included oral acyclovir from admission for next six months, fluconasol when the patient’s absolute neutrophil count was above 1×10⁹/L and ursodiol for minimum next 30 days.

The values of complete blood count, PT, aPTT, fibrinogen, FVIII, AT and vWF were measured on the day prior to starting the conditioning regimen and on the days 1, 7 and 14 from the moment of VOD diagnosis. Laboratory testing was performed at the IMD, in haematology and haemostasis laboratories and results were statistically evaluated.

RESULTS

At our Centre, from February 2004 to April 2008, we performed 74 SCT, 28 allogenic and 46 autologous. From our result we could conclude that the incidence of VOD in our group of patients was 14.8%. In this study there were 11 patients (3 female and 8 male), mostly between 1-5 years old (two patients below 12 months, 5 in the group between 13-60 months and 4 between 61-200 months). The indication for SCT in most of the patients was neuroblastoma IV clinical stage (NB IV CS), 6 of them, also NHL in 2 patients, AML in 1 patient, PNET in 1 patient and malignant form of osteoporosis in 1 patients. Six patients received busulphan and melphalan in the conditioning regiment, 2 received thiothepa and melphalan, and 3 different combinations of chemotherapeutic drugs of which one patient also received antithymocyte globulin – ATG (I – busulphan, melphalan, thiothepa; II – fludarabin, melphalan and cyclophosphamide; III – fludarabin, busulphan, thiothepa, cyclophosphamide and ATG). The patients of younger age (below 5 years), the diagnosis NB IV CS and busulphan and/or melphalan in the conditioning regimen were under the most prominent risk factors in our group of patients. All children had normal liver and kidney function prior to SCT.

Among our patients with VOD there were 10 autologous and 1 allogeneic SCT. One patient had a mild form of VOD, 7 moderate and 3 had severe form of the disease.
We treated them differently according to the form of the disease, one with supportive therapy only, one with supportive (controlled crystalloid infusions, diuretics and painkillers) therapy and heparin, and most of them with supportive therapy and defibrotide (Table 1).

Haemoglobin level, platelet count together with the levels of PT, aPTT, FI, FVIII, vWF and AT were measured on the day prior to starting the conditioning regiment (day 0), and the baseline values of all mentioned parameters were within normal range (Table 2). On the onset day (day 1), we noticed decreased levels of haemoglobin, platelets, AT and PT, prolonged aPTT and increased levels of factors I, VIII and vW (Table 3).

We graphically presented mathematically averaged levels of the chosen parameters determined in the function of time – for the days 0, 1, 7 and 14 (Graphs 1–6).

The graphics clearly show that haemoglobin level was below transfusion level from day 1–5 (Graph 1) and platelets level from day 1–7 (Graph 2). At that time the need for haematological support was very intensive.

Also, PT values were decreased from day 1 to 5 (Graph 3), and aPTT was prolonged at the same time (Graph 4). There was no need either for the correction or for any kind of specific treatment based on the findings.

Contrary to expected, liver failure was not associated with high average levels of fibrinogen, at least for the first 5 days of VOD. During several next days they decreased to normal at the moment of clinical signs resolution (Graph 5). The curves representing the level of AT, vWF and FVIII obviously show that from the day 1–5 changes were most prominent, and the levels of vWF and FVIII were highly increased simultaneously with AT decrease (Graph 6). These counts were lower in second week of the disease.

DISCUSSION

VOD is caused by hepatocyte and sinusoidal endothelium vessel damage that can occur early after SCT and, in severe form, it may lead to liver failure, hepatorenal syndrome,
portal hypertension and, eventually to death due to multi-organ failure. As known, the incidence of VOD in paediatric population is between 5 - 40%. Possible reasons for the lower incidence of VOD in recent groups of patients as reported in the literature include lower dosages of conditioning chemotherapy, multi-institutional nature of studies and the use of different criteria for the diagnosis of VOD [13]. In this study the cumulative incidence of VOD is 14.8%; this is less than in other previous reports, and may be explained in part by the fact that all patients had a good performance status and normal liver function tests prior to transplantation [2].

The development of VOD has been associated with abnormalities in the coagulation cascade, such as the onset of procoagulant and hypofibrinolytic status. In view of this, the use of fibrinolitic and anticoagulant therapy may be indicated, but there is a considerable risk of subsequent haemorrhage, because of patients’ thrombocytopenia and high platelet transfusion requirement. Platelet transfusion dependency is one of the symptoms of VOD and low platelet count is not the result of thrombopoetin deficiency [2, 21]. In our patients, the decrease of platelet count occurred after completed conditioning regiments and increased platelet count in the engraphtment time. During the first 7 days of illness mean platelet values required transfusion in all patients. At the same time, haemoglobin level was low and it was the time for intensive haematological support. In the second week, average platelet count stepwise raised indicating the recovery of VOD patients.

Data from the literature have confirmed an active involvement of haemostasis in the pathogenesis of VOD, characterized by several coagulation parameter alteration
reflecting liver damage, endothelium dysfunction and thrombus generation. No clotting changes have demonstrated unequivocal specific role [14, 22]. The endothelial damage of sinusoids and hepatic venulas are initiating event that lead to a high production of TF and vWF, low levels of PC and AT, with activation of coagulation [20, 23]. In this context, we tested different haemostatic parameters with the aim of evaluating the existence of prothrombotic state during transplantation and VOD and its pathogenetic relevance.

PT and aPTT in patients with VOD can be useful as readily available laboratory tests for coagulation factor level alteration [24]. The mean values of these parameters in our group were changed during the first week of VOD onset and were the reason of their decreased production instead of increased consumption. Low PT was followed by prolonged aPTT, especially pronounced during the first 5 days. Despite being unspecific, the levels of PT and aPTT are useful in diagnostics together with other laboratory signs of VOD. The mean levels of fibrinogen in the first week after VOD onset were strongly indicating the presence of its enhanced production and generation, probably in the subendothelium of hepatic venulas [20, 22, 23]. In the following week it was within the normal range. The Graphics obviously showed that in the first 5 days of the diagnosis the average values of FVIII and vWF were extremely high, coincidently with low levels of AT which suggested alterations of coagulation parameters, activation of coagulation cascade and microvascular thrombosis at the site of the damaged endothelium. To achieve a timely diagnosis, apply adequate therapy measures and perform the follow-up of the disease course; these parameters should be monitored regularly, especially during the first 5 days from the diagnosis of VOD. A study with a greater number of monitored parameters could be helpful in resolving prophylactic and therapeutic issues.

CONCLUSION

Younger patients with neuroblastoma have a significantly higher risk of VOD than patients with other malignancies. Also, busulphan and melphalan increase the risk of liver damage and patients who need them in the conditioning regimen should be very carefully monitored.

This study suggests that SCT is associated with the development of the state of moderate hypercoagulability, a probable consequence of marked endothelial damage. All these alterations create a potentially prothrombotic state, more pronounced in VOD. Lastly, the lesser incidence of 14.8% in our group and the moderate disease in the majority of patients suggest that increasing improvements in transplant strategies have reduced the risk and the severity of the disease that was the leading cause of morbidity/mortality at the beginning of transplantation era.

At the same time, haemoglobin decrease, low platelet number and platelet transfusion dependency show that the activation of primary haemostasis and possible VOD, PT and aPTT are not specific parameters for VOD, however observing AT, FVIII, vWF and fibrinogen levels have more precise diagnostic value. Repeated measurements of haematological and coagulation parameters during the first five days of VOD onset have a significant value for the diagnosis and, maybe, for the disease outcome.

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Поремеђаји коагулације код деца са венооклузивном болест јетре после трансплантације матичних ћелија хематопоезе

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КРАТАК САДРЖАЈ
Увод Венооклузна болест јетре (VOD) је тешка и потенцијално смртна компликација на коме трансплантације матичних ћелија хематопоезе (TMТХ). Прецизна дијагностика, лечење и предвиђање настанка ове компликације, међутим, још није потпуно разашљене.

Циљ рада Циљ рада је био да се утврде инциденти, промена параметара хемостазе и исход лечења болесника са VOD. Такође, испитивали смо постојање поремећаја коагулације и практични значај ових поремећаја за рано постављање дијагнозе.

Методе рада Просpekтивно истраживање је обухватало све болеснике узраста од три месеца до 17 година код којих је постављена дијагноза VOD после TMТХ у Институту за здравствену заштиту мајке и детета Србије „Др Вукањ Чупић” (ИМД) у Београду од фебруара 2004. до јула 2008. године. код свих је дијагноза постављена на основу Сијетл критеријума. Вреднoсти PT, aPTT, фибриногена, FVІІ, AT и вWF одређене су пре почетка режима кондиционарирања, а затим првог, седмог и четрнаестог дана од постављања дијагнозе VOD. Лабораторијсke анализе су обављене у Лабораторији за хемостазу ИМД; добијени резултати су потом статистички обрађени.

Резултати Током истраживања урађене су укупно 74 TMТХ. Код 11 болесника је дошло до развоја VOD, а код 2 до 46 аутолошких, а код једног до 28 апогеосних трансплантација. Инцидентица VOD у посматраној групи испитаника била је 14,8%. Код седам болесника дијагностикован је благ, код једног тежи, а код три тежак облик VOD. У тренутку постављања дијагнозе код свих болесника била је значајно повише активност vWF, FVІІ и фибриногена, а снижена AT. Сви болесници су били захваћени од трансплантације тромбоцитата.

Закључак Зависност од трансплантације тромбоцита указује на активацију коагулације с високом значајном, као и на могући развој VOD. Резултати истраживања такође показују да праћење нивоа параметара коагулације у првих пет дана од постављања дијагнозе може бити значајан у предвиђању исхода VOD.

Кључне речи: венооклузивна болест јетре; трансплантација матичних ћелија хематопоезе; деца; коагулација

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