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

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SUMMARY
Introduction Hepatic veno-occlusive disease (VOD) is a life threatening complication after stem cells transplantation (SCT). Its prediction, precise diagnosis and treatment remain unclear.
Objective Our goals were to determine the incidence, outcome and changes in haemostatic parameters in patients with VOD. Also, we tried to determine coagulation disturbances and their practical significance in early diagnosis of such patients.
Methods We prospectively evaluated all consecutive VOD patients after SCT, aged 3 months to 17 years, from February 2004 to July 2008 treated at the Mother and Child Health Institute of Serbia "Dr Vukan Čupić" (IMD). All patients were diagnosed according to the Seattle criteria. The values of PT, aPTT, fibrinogen, FVIII, AT and vWF were measured on the day prior to the initiation of conditioning regiment and on the days 1, 7 and 14 from the moment of VOD diagnosis. Laboratory testing was performed in the IMD haemostasis laboratory and results were statistically evaluated.
Results During the study period 74 SCT were performed at IMD. VOD developed 11 patients; 10 of 46 were autologous and 1 of 28 allogeneic SCT patients. In our group of patients the incidence of VOD was 14.8%. VOD was classified as mild in 7, moderate in 1 and severe in 3 patients. At the moment of establishing the diagnosis all patients had a significantly increased activity of vWF, FVIII and fibrinogen, and decreased AT. All of them were dependent on platelet transfusions.
Conclusion Platelet transfusion dependence suggests coagulation activation with great significance and indicates a possible development of VOD. Our results also suggest that monitoring coagulation parameters levels in the first five days from the establishment of diagnosis may have a significant predictive value for VOD outcome.
Keywords: veno-occlusive disease; stem cell transplantation; children; coagulation

INTRODUCTION

Liver veno-occlusive disease (VOD) is a clinical syndrome characterized by hepatomegaly, fluid retention and hyperbilirubinaemia [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 complication 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 are 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 thrombolitic 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 thromboplastic time (aPTT), coagulation factors I, VIII and vWF, and antithrombin levels prior to starting conditioning regiment and time trend of this 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 1×10^9/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 regiment 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.

In order to present the patients, the methods of explorative and descriptive statistical analyses were used. Also, we graphically showed the mathematically averaged levels of parameters given in the function of time, for the basal values (the day 0 on the graphics) and days 1, 7 and 14.

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 osteopetrosis in 1 patients. Six patients received busulphan and melphalan in the conditioning regiment, 2 received thiothepa and melphalan, and 3 different combinations of chemiotherapeutic 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 regiment 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.

Table 1. Main characteristics of stem cell transplantation in patients with veno-occlusive disease

Patient	Age (months)	Sex	Disease	Status	Transplantation type	Conditioning regiment	VOD form therapy		Outcome
1	36	M	NB IV CS	RP	Auto	Bu-Mel	Severe	S+D	R
2	47	F	NB IV CS	RP	Auto	Bu-Mel	Mild	S	R
3	29	M	NB IV CS	R	Auto	Bu-Mel	Moderate	S+D	R
4	11	M	NB IV CS	R	Auto	Bu-Mel	Moderate	S+D	R
5	195	M	NHL	R III	Auto	TT-Mel	Severe	S+H	R
6	135	M	PNET	RP	Auto	TT-Mel	Moderate	S+D	R
7	21	F	NB IV CS	RP	Auto	Bu-Mel	Moderate	S+D	R
8	190	M	NHL	RP	Auto	Bu-Mel-TT	Severe	S+D	R
9	3	F	OP	AD	Allo	Flu-Bu-TT-Cy-ATG	Moderate	S+D	Death
10	40	M	NB IV CS	R	Auto	Bu-Mel	Moderate	S+D	R
11	100	M	AML	R	Auto	Bu-Mel-Cy	Moderate	S+D	R

M – male; F – female; NB IV CS – neuroblastoma IV clinical stage; NHL – non-Hodgkin limphoma; PNET – primitive neuroectodermal tumour; OP – osteoporosis; AML – acute myeloid leukaemia; R – remission; RP – partial remission; AD – active disease; Bu – busulphan; Mel – melphalan; TT – thiotepa; Flu – fludarabin; Cy – cyclophosphamide; ATG – anthytimocite globuline; S – sympthomatic therapy; D – defibrotid; H – heparin

Table 2. Baseline values ($\bar{X}$±SD)

Parameter	Hb (g/l)	Plt ($\times10^9$/l)	PT (%)	aPTT (s)	AT (%)	FI (g/l)	FVIII (%)	vWF (%)
Day 0 values	100±11	178±62	91±14	19±3	114±22	4±1.5	115±26	143±32

Table 3. Values at the veno-occlusive disease onset ($\bar{X}$±SD)

Parameter	Hb (g/l)	Plt ($\times10^9$/l)	PT (%)	aPTT (s)	AT (%)	FI (g/l)	FVIII (%)	vWF (%)
Day 1 values	89±9	14±8	75±21	35±5	84±18	5.5±0.4	84±96	208±38

We treated them differently according to the form of the disease, one with supportive therapy only, one with supportive (controlled cristaloid 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).

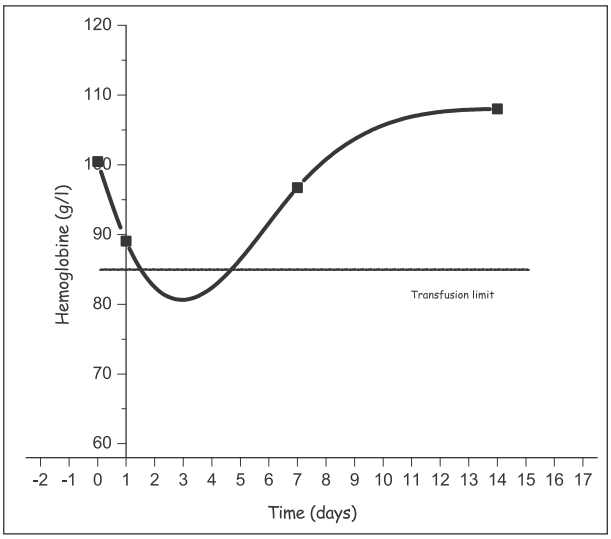
The graphics clearly show that haemoglobin level was below transfusion level from day 1-5 (Graph 1) and platelets level from day 1-7 (Graph 2). At that time the need for haematological support was very intensive.

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.

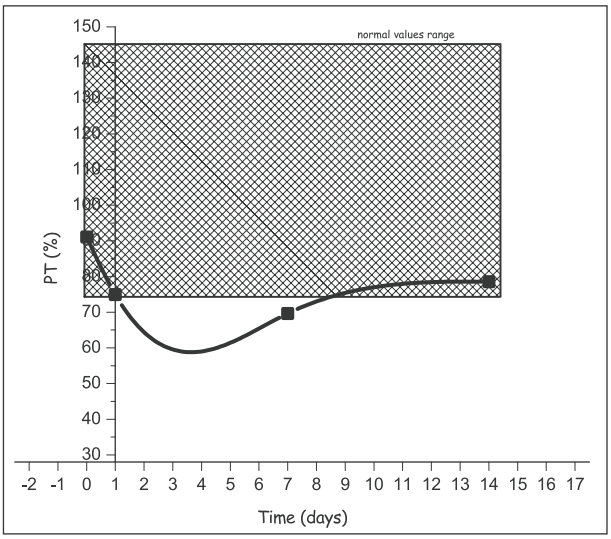
Contrary to expected, liver failure was not associated with high average levels of fibrinogen, at least for the first 5 days of VOD. During several next days they decreased to normal at the moment of clinical signs resolution (Graph 5). The curves representing the level of AT, vWF and FVIII obviously 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

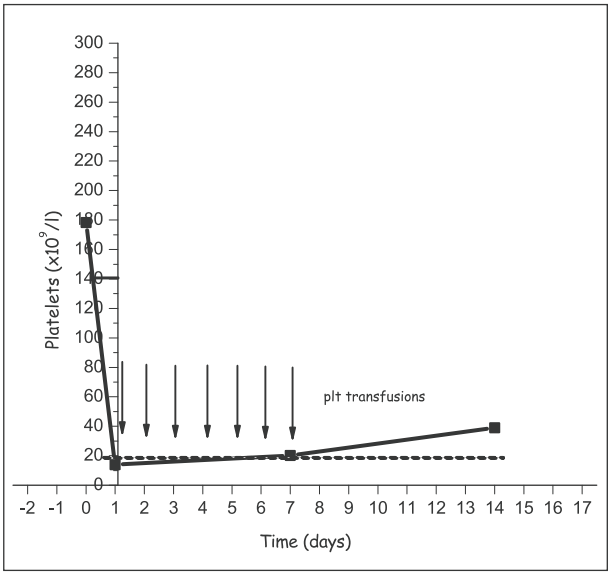
VOD is caused by hepatocyte and sinusoidal endothelium vessel damage that can occur early after SCT and, in severe form, it may lead to liver failure, hepatorenal syndrome,



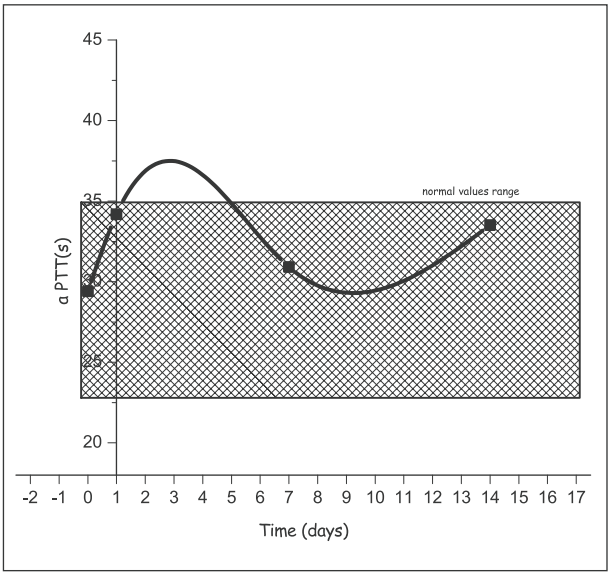
Graph 1. Average trend values of haemoglobin



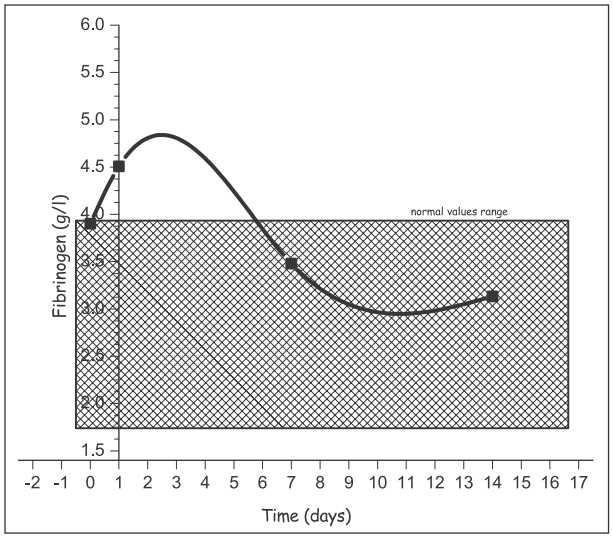
Graph 3. Average trend values of PT



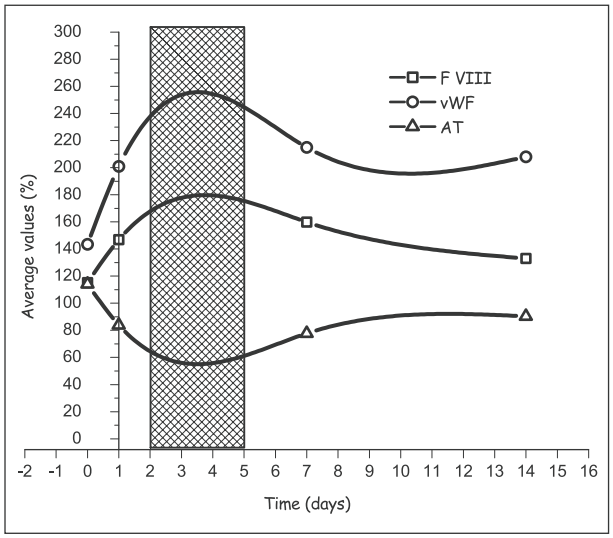
Graph 2. Average trend values of platelets



Graph 4. Average trend values of aPTT



Graph 5. Average trend values of fibrinogen



Graph 6. Average trend values of FVIII, vWF and AT

portal hypertension and, eventually to death due to multiorgan 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 low specificity and late onset of diagnostic clinical signs hinder early recognition and differential diagnosis of other liver diseases affecting transplanted patients [5]. Reasons for a higher VOD incidence in children could be due to intensive combination of alkylating agents involved in the conditioning regiments, as well as inherited and acquired illness specific in paediatric patients, which are well known risk factors for VOD development. According to different authors, younger patients have a greater risk for the development of this complication, because the onset of VOD predisponding paediatric diseases, such as neuroblastoma or the malignant form of osteopetrosis occurs at a very young age and, the highest incidence is exactly detected at this period of life [3, 13, 15, 16]. Most of our patients suffered from NB IVCS, which is in consistence with mentioned studies.

Busulphan was one induction medication found to be a potentially significant risk factor for the development of VOD. The proposed mechanism by which this medication may increase the risk is through glutation depletion in high doses [17]. Some recent studies showed that melphalan is VOD predisponding agent due to its metabolic pathway through the glutation enzyme system in the liver. Its toxic effects are amplified in combination with busulphan use [18, 19]. In our group of patients all children received protocols with either busulphan or melphalan, or both. Thus, we can conclude that these two chemiotherapeutic agents in conditioning regiments are serious risk factors for liver damage. It is important to notice that the majority of our patients had concurrently several risk factors for the development of VOD, which must be taken into consideration and evaluated before SCT in order to be prepared for adequate prevention and therapeutic measures.

Retrospectively, we confirmed that one patient had a mild form of the disease, 7 had moderate and 3 had a severe form of VOD. Preventively, all patients received oral ursodiol, a hydrophilic non-hepatotoxic bile salt, 13-15 mg/kg/BW [2, 20]. A number of studies have proved that ursodiol used alone could not prevent endothelial damage in most patients. Possibly, other kinds of preventive therapy with different mechanism of action are necessary to prevent VOD [20]. In this respect, same results we showed in our study. After the applied diagnostic and therapeutic measures, 9 patients completely recovered, while one died with clinical signs of multiorgan failure. The baseline laboratory values of the liver, kidney and coagulation parameters were within normal range in all patients, thus, we could not use them as anticipating and predictive outcome factors of VOD. Different kinds of therapeutic approaches we used were dependent on the clinical signs and condition of each patient.

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 fibrinolityc and anticoagulant therapy may be indicated, but there is a considerable risk of subsequent haemorrhage, because of patients' thrombocytopenia and high pletelet transfusion requirement. Platelet transfusion dependency is one of the symptoms of VOD and low pletelet 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 regiment 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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Поремећаји коагулације код деце са венооклузивном болести јетре после трансплантације матичних ћелија хематопоезе

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КРАТАК САДРЖАЈ

Увод Венооклузивна болест јетре (*VOD*) је тешка и потенцијално смртоносна компликација након трансплантације матичних ћелија хематопоезе (ТМЋХ). Прецизна дијагностика, лечење и предвиђање настанка ове компликације, међутим, још нису потпуно разјашњени.

Циљ рада Циљ рад је био да се утврде инциденција, промене 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 Проспективно истраживање је обухватило све болеснике узраста од три месеца до 17 година код којих је постављена дијагноза *VOD* после ТМЋХ у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић" (ИМД) у Београду од фебруара 2004. до јула 2008. године. Код свих је дијагноза постављена на основу Сијетл критеријума. Вредности *PT*, *aPTT*, фибриногена, *FVIII*, *AT* и *vWF* одређене су пре почетка режима кондиционирања, а затим првог, седмог и четрнаестог дана од постављања дијагнозе *VOD*. Лабораторијске анализе су обављене у Лабораторији за хемостазу ИМД; добијени резултати су потом статистички обрађени.

Резултати Током истраживања урађене су укупно 74 ТМЋХ. Код 11 болесника је дошло до развоја ВОД, и то код десет од 46 аутологних, а код једног од 28 алогених трансплантација. Инциденција ВОД 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 повишена активност *vWF, FVIII* и фибриногена, а снижена *AT*. Сви болесници су били зависни од трансфузија тромбоцита.

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

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

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