Treatment of deep vein thrombosis with continuous intravenous infusion of LMWH in children – an alternative to subcutaneous application when needed

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Summary: Incidence of thrombosis is age dependent with the lowest risk in the childhood. Children mostly suffer from vein thrombosis. Incidence of thrombosis in children is only 0.07/10 000, but it increases among hospitalized children (3.5/10 000). Subcutaneous administration of low molecular weight heparin (LMWH) is preferred treatment of deep vein thrombosis in children. In this study we present group of 33 children with deep vein thrombosis, who were treated with LMWH for their first thrombosis from 2003 till 2006. Twenty-one (63.6%) patients were treated with LMWH by continuous infusion and 12 (36.3%) patients by subcutaneous injection. Duration of the treatment with LMWH was modified in accordance with the course of thrombosis (monitored by Doppler ultrasound with compression) with median of 15 days in patients treated by continuous infusion and 18.5 days when treated subcutaneously. Median dose of LMWH for intravenous and subcutaneous application was 240 IU/kg/24 h and 215 IU/kg/24 h respectively. The administered dose of LMWH was modified to achieve and maintain required therapeutic antiXa level within the range of 0.5–1 IU/ml. The treatment with continuous infusion led to total recanalisation of the occluded vein in 3 cases (14.3%), partial recanalisation was achieved in 15 (71.4%) patients. Three (14.3%) patients were without any recanalisation. The treatment by subcutaneous injection led to total recanalisation of the vein in 4 cases (33.3%), partial recanalisation was seen in 4 (33.3%) patients. Four (33.3%) patients were without any recanalisation. The difference in the outcomes of the therapy between both groups appears to be statistically significant (p = 0.041, nonparametric Mann-Whitney test). We have not noticed any severe adverse event of the treatment in any of our patients. Our results support the hypothesis that the treatment of DVT with continuous infusion of LMWH might be efficient and safe alternative to subcutaneous application in those children in whom we want to avoid subcutaneous administration from certain reasons.

Key words: deep vein thrombosis – LMWH – thrombosis – antiXa

Léčba trombózy u dětí pomocí kontinuální intravenózní infuze – možná alternativa k subkutánnímu podání tam, kde je třeba

Souhrn: Incidence trombózy je věkově závislá, s nejnižším rizikem v dětství. Děti většinou trpí trombózou žilní. Její výskyt je v běžné dětské populaci 0,07/10 000, mezi hospitalizovanými dětmi pak ve vyšším počtu 3,5/10 000. Při léčbě hluboké žilní trombózy u dětí je preferován nízkomolekulární heparin (LMWH). Nejčastější formou podání LMWH je subkutánní aplikace. V naší práci prezentujeme soubor 33 dětí s hlubokou žilní trombózou, které byly v letech 2003–2006 léčeny pomocí LMWH pro první žilní trombózu. Dvacet jedna (63,6%) pacientů bylo léčeno nízkomolekulárním heparinem kontinuální infuzí. Dvanáct (36,3%) pacientů bylo léčeno LMWH subkutánní aplikací. Délka léčby LMWH byla modifikována dle vývoje trombu (monitorace Doppler sono s kompresí). Průměrná délka léčby u pacientů, kterým byl LMWH podáván kontinuální infuzí, byla 18,7 dní, medián 15 dní. U pacientů léčených LMWH subkutánní aplikací byla průměrná délka terapie 28,2 dní, medián 18,5 dne. Průměrná podávaná dávka LMWH na kg a den u pacientů léčených kontinuální infuzí byla 250,7 IU/kg/24 hod, medián 240 IU/kg/24 hod, u pacientů léčených LMWH subkutánní aplikací potom průměrná dávka 223,1 IU/kg/24 hod, medián byl 215 IU/kg/24 hod. Dávka LMWH byla v průběhu terapie upravována dle hodnot antiXa k udržení požadované terapeutické hladiny 0,5–1 IU/ml. Během podávání LMWH kontinuální infuzí byla hluboká žilní trombóza kompletně odstraněna u 3 (14,3%) pacientů a alespoň částečně odstraněna u 15 (71,4%) pacientů. U 3 (14,3%) pacientů nebyla odstraněna vůbec. U pacientů léčených subkutánně byla trombóza kompletně odstraněna ve 4 (33,3%) případech, u 4 (33,3%) pacientů jen částečně a u 4 (33,3%) pacientů odstranění trombózy nedošlo. Rozdíl ve výsledku léčby se vzhledem ke způsobu podání LMWH jeví jako statisticky významný (p = 0,041, test Mann-Whitney). Krvácení jako nežádoucí účinek léčby LMWH jsme v našem souboru nezaznamenali. Tato práce má upozornit na fakt, že intravenózní léčba hluboké žilní trombózy u dětí formou kontinuální infuze LMWH může být bezpečnou a efektivní alternativou léčby subkutánní tam, kde je to zapotřebí. Je spojená s kratším poločasem LMWH, může být využita zejména u hospitalizovaných dětí s permanentním intravenózním přístupem a u těch, které jsou ohroženy rizikem krvácivých komplikací.

Klíčová slova: hluboká žilní trombóza – LMWH – trombóza – antiXa

Introduction

The incidence of VTE – venous trombembolic event (deep vein thrombosis, pulmonary embolism) is age dependent with the lowest risk occurring in children [1–3]. The estimated incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the general pediatric population is 0.07/10 000 and 5.3/10 000 among hospital admissions [4–6].

DVT/PE develops in children often as a secondary complication of other

underlying disorders or in children with hereditary prothrombotic risks [7]. Idiopathic VTE occurs in less than 1% of newborns and in less than 5% of children compared to approximately 40% of adults [7–10]. Children less than one year of age and teenagers are at higher risk for VTE [7,8,10].

Patients with hereditary prothrombotic risk factors in heterozygous form and without any other acquired prothrombotic risk factors, which might potentiate each other, have very seldom their first thrombosis during childhood. Whereas patients with risk factors in homozygous form or with combination of same in heterozygous form have thrombosis during early childhood frequently [11].

The most frequent acquired prothrombotic risk factors in children are malignancy, indwelling central venous lines (CVL), prematurity in neonates, sepsis, surgery – especially orthopaedic, injury or trauma including burns, hormonal therapy, vascular anomalies, autoimmune diseases, endocrine diseases and nephrotic syndrome.

Low molecular weight heparin (LMWH) is currently the standard treatment of DVT in children for its more predictable pharmacokinetics and better bioavailability than unfractionated heparin [12]. It is also associated with lower risk of heparin induced thrombocytopenia (HIT), bleeding and/or osteoporosis [13]. Another alternatives include unfractionated heparin, coumarins, pentasacharides and under specific circumstances also thrombolytics.

Patients and Methods

In The Children's University Hospital Brno there were 45 children treated for venous thrombosis with LMWH from 2004 till 2006. We excluded 3 children with superficial vein thrombosis, 5 children who died because of their underlying disease during the treatment, 1 patient who has not had thrombophilia screening done, 1 patient who was transferred to another hospital with no sufficient feedback regarding his treatment outcome, 1 patient who was referred from regional hospital and his medical records were not complete and 1 patient who was treated by local thrombolysis. We assessed 33 patients treated by LMWH for deep vein thrombosis. Twenty one of them were treated by continuous infusion (CI). Twelve (57.1%) of them were boys and 9 (42.9%) were girls. Twelve patients were treated by subcutaneous (SC) application, 8 (66.7%) girls and 4 (33.3%) boys. The age range varied from newborns to 18 years and was comparable in both groups (Fig. 1).

Low molecular weight heparin was administered to patients by intravenous (IV) pump Infusomat (Braun, Firana, Ivac) at the dose of 80 IU/kg/8 h diluted in normal saline. Rate of infusion was 1 ml per hour. Continuous infusion was interrupted maximally for 2 hours and only in exceptional situations such as Doppler ultrasonography. Second group was treated with s.c. injection standard way. The chosen starting dose (240 IU/kg/24 h) was the recommended therapeutic dose for dalteparin, which we have used in all of our patients. In patients younger 5 months we used the same initial dose. Further dosing was tailored individually for each patient to reach the required antiXa level. The study, including genetic investigation for inherited thrombophilia risks was authorized by local ethical committee.

Before starting the treatment our aim was to perform full thrombophilia work-up in all patients. Blood samples were taken by qualified nurses into the Sarstaedt tube as requested by Standard operational procedures valid in University Hospital Brno at the time of the investigation. (University Hospital Brno is certified in accord with the norm ISO 9000:2001.)

These tests were performed: antithrombin plasmatic level assessment (Accucolor AT III Kit, Trinity Biotech, Ireland); assessment of mutation F V Leiden by PCR method (East-Port Praha, The Czech Republic); assessment of mutation FII G20210A by PCR method (East-Port Praha, The Czech Republic); assessment of polymorphisms of methylentetrahydrofolate reductase by PCR method (East-Port Praha, The Czech Republic); protein C plasmatic level assessment (Sta Staclot protein C, Diagnostika Stago, France); protein S plasmatic level assessment (Asserachrom Total protein S, Sta Staclot Protein S, Diagnostika Stago, France); homocystein plasmatic level assessment (Homocystein Bio-Rad, Bio-Rad Laboratories, USA); lipoprotein a plasmatic level assessment (Lpa Roche, Roche, Switzerland).

Deep vein thrombosis was diagnosed with Doppler ultrasonography (Siemens, type Antarez, linear probe VFX 15–3, 10MHZ), increased D-dimmer level (STA Liatest D-Di, Diagnostica STAGO, France) and by clinical examination: tenderness, pain and swelling at the site of thrombosis, positivity „plantar" sign and/or positive Hommans sign when applicable.

Efficiency of the treatment was monitored by the regression of clinical symptoms which were assessed and recorded during regular ward rounds, as well as by repeated Doppler ultrasonography (week 1, week 2 and week 6 after the diagnosis of the thrombosis) together with D-dimmers testing. AntiXa levels (Coamatic Heparin, Chromogenix, Italy) were monitored daily at least during first five days of the treatment, but majority of the patients had longer monitoring of antiXa levels.

In patients treated by continuous infusion samples for antiXa level measurements were taken twelve hours after dose adjustment and/or change and in patients treated by subcutaneous injection 3–4 hours after application following such a change. In accord with those levels the dose of LMWH was modified to keep antiXa within required intervals. The aim was to achieve as stable as possible antiXa level.

Platelet levels were monitored during the whole time of the treatment to

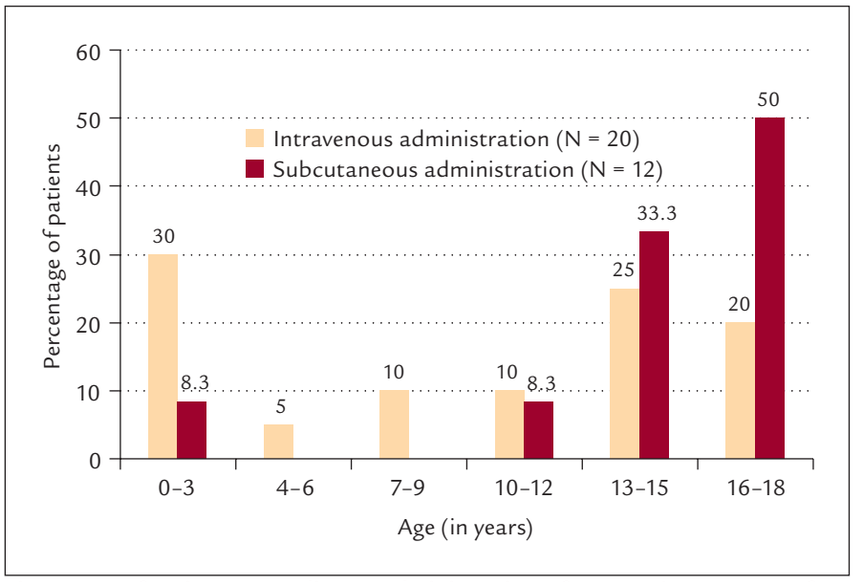

Fig. 1. Age of patients according to administration of LMWH (percentage of patients).

	N	Average	Median	Minimum	Maximum	p – level
intraveous administration	21	18.7	15.0	5.0	444.0	0.726
subcutaneous administration	12	28.2	18.5	6.0	94.0	

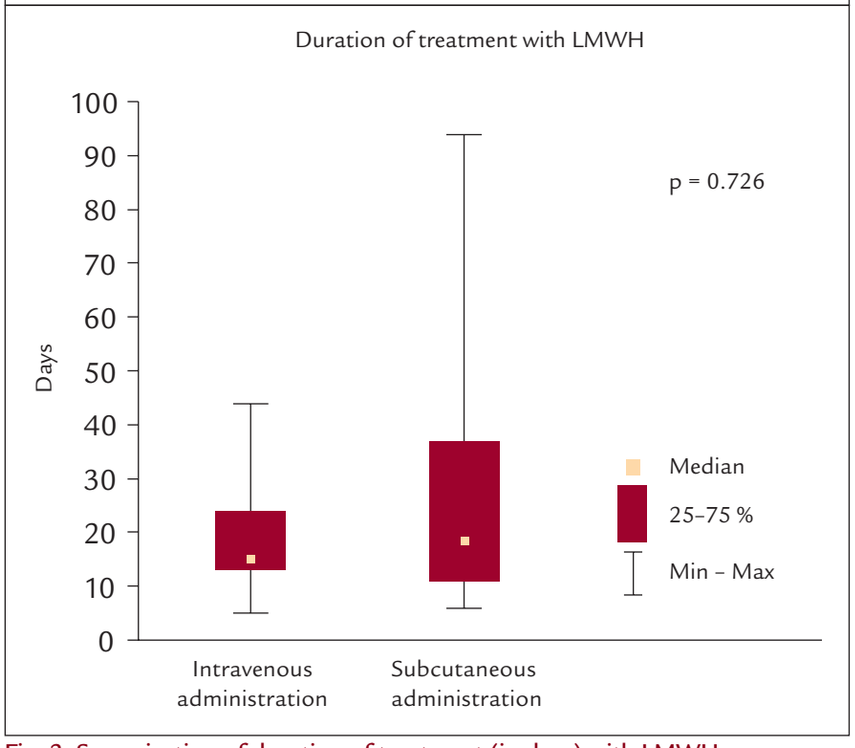

Fig. 2. Sumarization of duration of treatment (in days) with LMWH.

avoid possible bleeding complications in patients with low platelets treated with heparins. None of the patients in both groups had a kidney disorder therefore there were no supposed differences in antiXa clearance. Liver tests were not monitored regularly and/or intentionally in our patients. The treatment with LMWH was stopped when recanalisation of the vein was achieved or the thrombus has been organised and unchanged during two consecutive Doppler ultrasound examinations. Patients were then switched to prophylactic treatment for at least 3 months to prevent re-occurrence of the thrombus. The safety of the treatment was clinically assessed by nurses who recorded possible bleeding or other adverse events related to the LMWH into patients charts.

No patients were treated with thrombolytics or other anticoagulants than those, mentioned above.

Statistics – methods and data processing

Descriptive statistics such as mean, median, minimum and maximum values were used for comparison of duration of treatment, dose of LMWH and level of antiXa. Differences between continuous variables were tested using nonparametric Mann-Whitney test whereas for assessment of associations between categorical variables Spearman test for frequency tables was used. As a level of statistical significance $\alpha = 0.05$ was adopted. Graphical visualization was performed using box-plots generated by software STATISTICA for Windows 7.1.

Results

None of the patients in both groups was free of any prothrombotic risk. Those, who had no acquired risk had at least one inherited and vice versa. Detailed analysis of acquired and inherited thrombophilia risks in our patients goes beyond the scope of this manuscript which is focused on efficacy and safety of the treatment with LMWH when administered by continuous infusion. However no significant difference neither in acquired nor inherited risk factors was found between two groups of our patients.

Average duration of the treatment in patients with CI of LMWH was 18.7 days, median was 15 days (range

	N	Average	Median	Minimum	Maximum	p – level
intraveous administration	21	250.7	240.0	200.0	300.0	0.024*
subcutaneous administration	12	223.1	215.0	200.0	282.5	

*statistically significant result

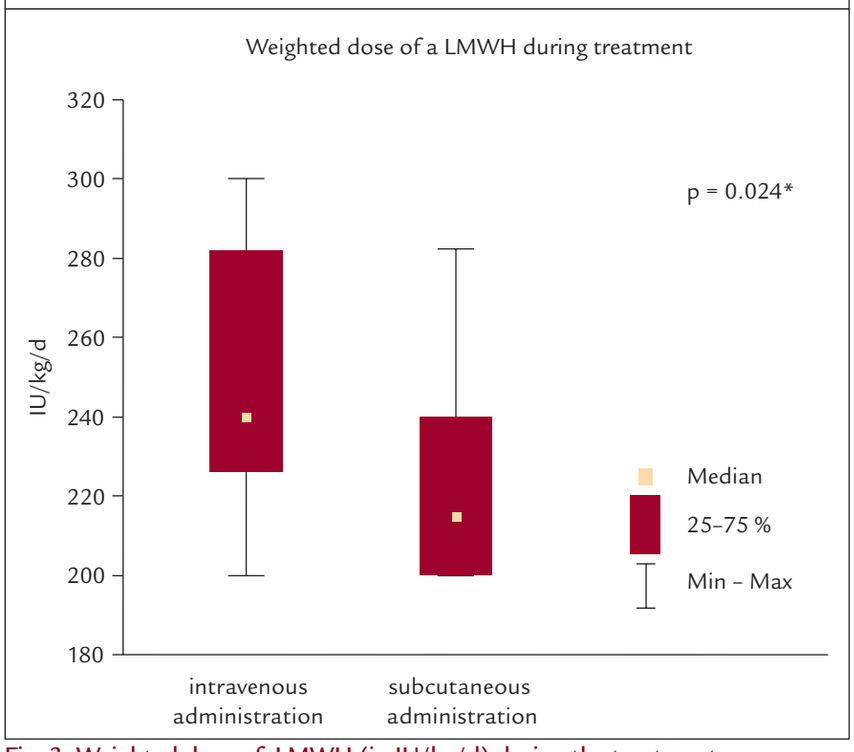

Fig. 3. Weighted dose of LMWH (in IU/kg/d) during the treatment.

5 to 44 days). In patients treated with LMWH by SC application the average duration was 28.2 days, median 18.5 days (range 6 to 94 days). **The difference in the duration of the treatment between those two groups was not statistically significant** (Fig. 2).

Average dose administered per kg per day to reach required antiXa level in the group treated with LMWH by CI was 250.7 IU/kg/24 h, median 240 IU/kg/24 h. In patients treated with LMWH by SC average dose was 223.1 IU/kg/24 h with median 215 IU/kg/24 h.

We found statistically significant difference in the average weighted daily dose of LMWH between patients treated with LMWH by continual infusion and patients treated with LMWH by subcutaneous injections (p = 0,024) (Fig. 3).

The LMWH dose was adjusted to achieve and maintain required antiXa levels during the treatment. Required therapeutic range of antiXa level was 0.5–1 IU/ml. In group of patients treated with LMWH by CI average antiXa level achieved by the treatment described above was 0.53 IU/ml, median 0.52 IU/ml. In patients treated with LMWH by SC application average antiXa level was 0.66 IU/ml, median 0.71 IU/ml. **The difference between summarized level of antiXa in patients with CI and SC administration of LMWH was statistically significant (p = 0,044)** (Fig. 4).

In the group treated with LMWH by CI the treatment with therapeutic dose led to complete recanalisation of the affected vein in 3 (14.3%) patients and to partial recanalisation in 15 (71.4%) patients. Only in 3 (14.3%) patients the treatment with therapeutic dose of LMWH did not lead to recanalisation. In patients treated by subcutaneous application the complete recanalisation appeared in 4 (33.3%) children. In 4 (33.3%) patients treatment led only to partial recanalisation and in 4 (33.3%) patients did not lead to any recanalisation at all. Above mentioned **results of the therapy seem to be significantly different between patients treated with IV and SC LMWH** (p = 0,041) (Fig. 5).

In patients treated by CI we have not recorded any adverse event neither any bleeding complication nor decreased platelet counts which could be related to heparin treatment. Patients treated by SC application had bruises after application recorded.

Discussion

The aim of this pilot project was to point out alternative way of thrombosis treatment in children. In these days the standard treatment of DVT is subcutaneous application of LMWH. These well-established recommendations result especially from REVIVE study, which has proven LMWH to be as effective and even more safe compared to unfractionated heparin.

We compared the efficacy and safety of DVT treatment with LMWH by CI and SC application in two groups of patients with similar age ranges and types of primary diagnoses. In those treated with LMWH by CI the initial treatment with full therapeutic dose of LMWH led to at least partial recanalisation of thrombosis in 85.7% of children. In patients treated with SC application we were not able to recanalize the thrombosis in 33.3% of our patients. The difference in the outcomes of the therapy between both groups appears to be statistically significant (p = 0.041).

We can speculate that the reason for better results with CI could be lower median dose of LMWH (IU/kg/day) and/or wider range of antiXa levels and thereby less stable antiXa levels in

	N	Average	Median	Minimum	Maximum	p – level
intraveous administration	21	0.53	0.52	0.26	0.87	0.044*
subcutaneous administration	12	0.66	0.71	0.20	0.93	

*statistically significant result

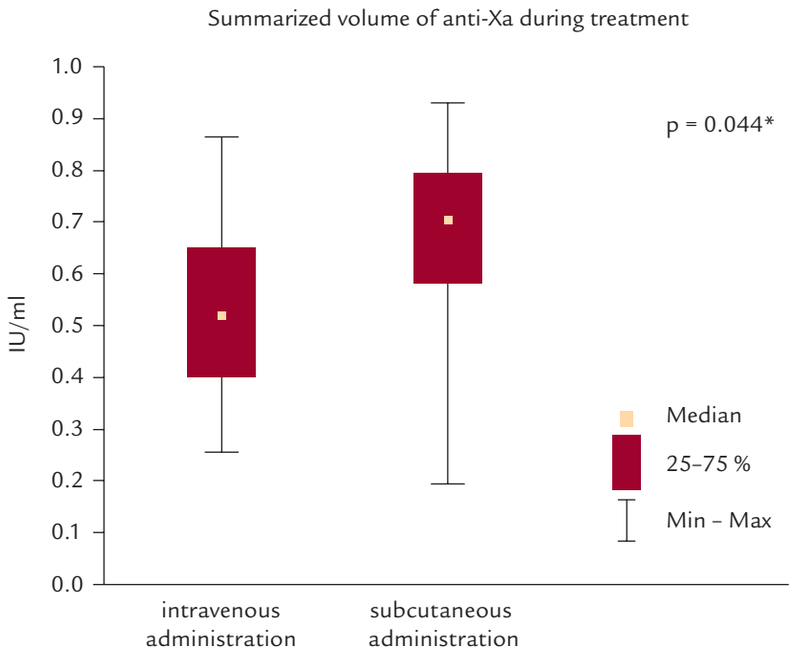

Fig. 4. Summarized level of antiXa (in IU/ml) during treatment.

Fig. 5. Result of the treatment with LMWH.

	Complete recanalisation	Partial recanalisation	No recanalisation	p – level
intraveous administration (N = 21)	14.3 %	71.4 %	14.3 %	0.024*
subcutaneous administration (N = 12)	33.3 %	33.3 %	33.3 %	

*statistically significant result

This table shows percentage of patients in whom the treatment of LMWH in therapeutic doses led to complete recanalisation, partial recanalisation or no recanalisation respectively.

plasma of patients treated with LMWH via SC application. On the other hand median of antiXa levels measured after LMWH application was higher in the group of patients treated by SC application. However we have to bear in mind, that assessment of antiXa during SC treatment reflects only the maximal peaks of antiXa activity reached in vivo after bolus SC injection. In contrary, monitoring of antiXa during CI aims to reflect the stable steady state of antiXa activity in patients' plasma. Thus information provided is not fully comparable. It seems, that being guided by antiXa levels during treatment with LMWH via CI, we were able to reach better clinical results. To achieve the same or similar levels of antiXa we had to use different dosage for different ways of application of LMWH. Therefore it is probably not correct just to extrapolate the dose of LMWH for CI from the dose of LMWH administered subcutaneously. In other words we should further assess what is more important for the successful treatment: if more stable levels or higher peaks of antiXa levels. Further and more detailed study of the pharmacodynamics of LMWH during CI administration might put more light on that issue. Based on currently available results of this particular study, it however seems, that stability of antiXa levels in patients' plasma might be probably more important for favourable outcome of the treatment. The duration of treatment – average, minimal as well as maximal – was shorter in group of patients treated by CI, what might be considered an advantage for the patients, but the difference was not statistically significant.

In contrast to REVIVE study we have not recorded any severe adverse events in none of our patients. That finding, in certain way, also corresponds with results of U. Hoffman showing that even i.v. bolus application of LMWH is as safe as SC administration and it is not associated with higher risk of adverse events [14].

We understand that the results of this study do not enable us to draw any firm conclusions, mainly due to small number of patients and that it will be necessary to prove these results on larger cohort. In spite of that we have shown that the treatment of DVT with LMWH by CI in our group of patients was at least as effective and safe as SC application.

Conclusion

Based on results mentioned above and according to facts coming up in the discussion we believe that in our patients the treatment of DVT with LMWH by continuous infusion was non-inferior and in some aspects even more pro-

mising compared to the treatment by subcutaneous injection.

The treatment by CI might be advantageous especially in children admitted to the hospital, who have permanent intravenous access. By means of this treatment we can avoid repeated painful SC injections and thus increase child's quality of life. In children with very low weight, it might be difficult to dose LMWH subcutaneously precisely enough due to very small amount of the medication injected. Moreover in small children and neonates SC injections might be limited by body surface available for application. When administered by continuous infusion, LMWH has shorter half-life and this could be useful especially in patients with considerable risk of bleeding, for example patients with thrombocytopenia as shown in our patients with low platelet counts after chemotherapy, who had no bleeding complications related to LMWH administration. Moreover their parents appreciated the possibility to avoid painful SC applications. Based on our results guidelines for the treatment of deep vein thrombosis for both Department of Internal Medicine and Department of Paediatric Oncology were updated.

Abbrevations

LMWH – low molecular weight heparin, DVT – deep vein thrombosis, SC – subcutaneous, CI – continuous infusion, PE – pulmonary embolism, VTE – venous trombembolic event, TED – thrombembolic disease, CVL – central venous line, IV – intravenous

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