Central venous line-related thromboembolism is common in children with non-high risk acute lymphoblastic leukaemia

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Children with acute lymphoblastic leukaemia face increased risks of thromboembolism, and major risk factors for this serious treatment-related toxicity are central venous lines, asparaginase and steroids. Central venous lines have become standard care in paediatric oncology, facilitating therapy and improving patients' quality of life. However, up to half of the children with acute lymphoblastic leukaemia will develop asymptomatic central venous line-related thromboembolism (1, 2). We assessed the rate of symptomatic and asymptomatic central venous line-related thromboembolism, using ultrasonography and lineograms, in children with non-high-risk acute lymphoblastic leukaemia.

Of 51 children consecutively diagnosed with non-high risk acute lymphoblastic leukaemia at Oslo University Hospital from September 2009 to August 2013, 47 were included in the study. Informed signed consent was obtained from parents and children over 12 years old. The Regional Committee for Medical and Health Research Ethics South-East Norway and the hospital's Data Protection Officer approved the study.

The children had central venous lines inserted at the time of diagnosis and were treated according to the non-high risk arms of the 2008 Nordic Society for Paediatric Haematology and Oncology acute lymphoblastic leukaemia protocol (3). Pegylated asparaginase was administered intramuscularly at 1,000 units/m² starting in week five. Patients were included after induction therapy on day 29 of the protocol, at the time of risk group stratification for further treatment and just before introduction of asparaginase. They were followed until week 35 of the treatment protocol. Symptomatic thromboembolism was identified by clinical evaluation, verified by

image analysis and led to treatment. Also, significant thromboembolism diagnosed *post mortem* was included. Screening for asymptomatic thromboembolism was performed by a paediatric radiologist on day 79, a time point when all patients came to Oslo University Hospital for bone marrow evaluation, and week 35, 2-4 weeks after the last asparaginase injection. Ultrasonography was performed with a Philips IU 22 (Philips Healthcare, Eindhoven, The Netherlands) or GE Logic E9 (GE Healthcare, Illinois, USA). The subclavian and internal jugular veins were examined in two planes with colour Doppler and greyscale imaging, with and without compression (2). Lineograms were performed using a Phillips MD4 Multidiagnost Fluoro (Philips Healthcare). Up to 10 mL of 270 mg I/mL iodixanol (GE Healthcare) was injected manually at 2-3 mL/s into the central venous line during fluoroscopic capture of six images per second. The physicians were kept blinded to the results of the protocolled image analyses during the study period, as asymptomatic thromboembolism was not considered indication to anticoagulation treatment.

Persistent central venous line-related thromboembolism was defined as positive findings on both ultrasonography examinations and used when analyzing risk factors. Three patients withdrew before the second ultrasonography exam and were excluded from further analysis, and one patient died, but was included on an intention to treat basis.

Statistical analyses were performed using Fisher's exact test and bootstrap confidence intervals were calculated for categorical variables. We used logistic regression for continuous variables. We used SPSS Statistics, version 23 (IBM Corp, New York, USA).

Five of the 47 children developed symptomatic thromboembolism. Three were related to central venous lines and occurred during consolidation or delayed intensification: two with line dysfunction and one with chest pain and pulmonary embolism. A fourth child developed cerebral sinus vein thrombosis during delayed intensification. All four were treated with low molecular weight heparin and one with additional recombinant tissue plasminogen activator. They all had partial or complete recoveries. A fifth child died of candida septicaemia with right pulmonary embolism during maintenance treatment.

There were 31/47 (66%) patients with asymptomatic central venous line-related thromboembolism at the first ultrasonography, with a 95% confidence interval (95% CI) of 52-80, and 29/43 (67%, 95% CI 53-82) at the second. None were occlusive. Asymptomatic thromboembolism was persistent in 21/44 cases (48%, 95% CI 33-63), and the patient characteristics are grouped by the presence or absence of persistent central venous line-related thromboembolism in Table 1. In the univariate analysis, persistent cases were associated with increasing age, with an odds ratio (OR) of 1.24 (95% CI 1.03-1.50, $p=0.02$). There was also a trend towards association with $>0.1\%$ minimal residual disease in the bone marrow on day 29 (OR 6.88, 95% CI 0.91-15.9, $p=0.09$). The result was consistent when adjusted for age and gender. There was a trend towards association between persistent central venous line-related thromboembolism and implanted central venous lines (OR 4.20, 95% CI 0.82-16.2, $p=0.13$), but this trend disappeared when adjusted for age. There was no association between symptomatic and asymptomatic central venous line-related thromboembolism ($p=1.00$).

There were 7/47 (15%, 95% CI 5-25) and 4/41 (10%, 95% CI 1-19) positive lineograms at the first and second examinations, but no association between the lineogram and ultrasonography results ($p= 0.40$ and $p= 1.00$ for the first and second examinations respectively).

We found that asymptomatic central venous line-related thromboembolism was common in children with non-high risk acute lymphoblastic leukaemia. Between the two ultrasonography examinations some thromboembolisms disappeared and new ones appeared, demonstrating a dynamic process. There was no correlation with symptomatic thromboembolism. This finding is supported by the recent study by Jones et al. (4), demonstrating a low incidence of complications to asymptomatic central venous line-related thrombosis in critically ill children.

In contrast to the high number of positive ultrasonography examinations of the upper veins, very few patients had thromboembolic findings on lineograms, displaying only the catheter tip. According to the 2011 British Committee for Standards in Haematology guidelines, ultrasonography is recommended for initial assessment of central venous line-related thromboembolism in children (5).

The main limitation of this study was the low number of participants, which reduced the statistical power. However, the homogenous patient group, longitudinal design, and strict surveillance protocol provided important information about thromboembolism in children with non-high-risk acute lymphoblastic leukaemia.

Although there may be common risk factors for developing symptomatic and asymptomatic thromboembolism, we demonstrate that incidental findings of central venous line-related thromboembolism have limited clinical relevance. Routine

126 ultrasonography for thromboembolism should not be performed in non-high risk acute
127 lymphoblastic leukaemia patients unless clinically warranted.

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130 **Conflict of Interest**

131 No conflicting relationship exists for any author.

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153 **Table 1. Patient characteristics**

Persistent central venous line-related thromboembolism		No (n=23) n (%)	Yes (n=21) n (%)	Odds ratio*	95% CI	p-value*
Gender	Male	15 (65)	13 (62)			
	Female	8 (35)	8 (38)	1.15	0.31-4.41	1.000
Median age (years)		3.4 (2.0-15.2)**	6.5 (1.9-15.6)**	1.24	1.03-1.50	0.023
Down syndrome	No	23 (100)	19 (90)			
	Yes	0 (0)	2 (10)	-	-	0.222
Leukaemia phenotype	Pre B-cell	22 (96)	21 (100)			
	T-cell	1 (4)	0 (0)	-	-	1.000
Minimal residual disease day 29***	<0.1%	22 (96)	16 (76)			
	>0.1% to <5%	1 (4)	5 (24)	6.88	0.91-15.9	0.088
Treatment	Standard risk	17 (74)	12 (57)			
	Intermediate risk	6 (26)	9 (43)	2.13	0.58-9.56	0.342
Asparaginase****	PEG-ASP every 2 weeks	11 (48)	8 (38)			
	PEG-ASP every 6 weeks	8 (35)	12 (57)	2.06	0.55-8.75	0.343
Central venous line	External	21 (91)	15 (71)			
	Implanted port	2 (9)	6 (29)	4.20	0.82-16.2	0.126
Central venous line changed during study period	No	19 (83)	18 (86)			
	Yes	4 (17)	3 (14)	0.79	0.16-4.71	1.000
Symptomatic thromboembolism	No	20 (87)	19 (90)			
	Yes	3 (13)	2 (10)	0.70	0.16-4.31	1.000

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155 * Univariate analysis

156 ** Range

157 *** Minimal residual disease >5% lymphoblasts in the bone marrow at day 29

158 stratified the patient to the high-risk group and subsequently excluded them from this

159 study.

160 **** The 2008 acute lymphoblastic leukaemia protocol included randomisation of

161 pegylated asparaginase injections at two or six-week intervals after day 79. Patients

162 who developed allergies to pegylated asparaginase were treated with Erwinia

163 asparaginase.

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