Feasibility, Safety and Outcome of Recanalisation Treatment in Childhood Stroke

Running head: Recanalisation Treatment in Childhood Stroke

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Abstract

Objective

Intravenous thrombolysis and endovascular therapy (IVT/EVT) are evidence-based treatments for adults with arterial ischemic stroke (AIS). However, randomized controlled trials in pediatric patients are lacking. This study aimed to describe feasibility, safety, and outcome of IVT/EVT in children with AIS.

Methods

Retrospective study (01/2000–12/2015) of a multicenter, population-based consecutive cohort of patients aged 1 month – 16 years diagnosed with AIS presenting with a pedNIHSS ≥4. Clinical and radiological data of patients receiving IVT/EVT were compared to those receiving standard care (SC) using linear regression to adjust for potential confounders. EVT included intraarterial thrombolysis and/or mechanical thrombectomy. Outcome was assessed 6 months after stroke using the pediatric stroke outcome measure (PSOM).

Results

Overall, 150 patients (age 7.1+/-4.9 years, 55 [37%] females) presented with a pedNIHSS of ≥4. Recanalization treatment was performed in 16 [11%], of whom 5 [3%] were treated with IVT and 11 [7%] with EVT. Patients receiving recanalization treatment were older (mean age 11.0 versus 6.9 years, p=0.01) and more severely affected (median pedNIHSS 13.5 versus 8.0, p<0.001). Death and bleeding complications did not differ between the two groups. Median (IQR) PSOM 6 months after AIS was 2.5 (1–4.3) and 1(0–2) in the IVT/EVT and SC groups, respectively (p=0.014). However, after multiple linear regression analysis, only higher baseline pedNIHSS remained associated with an unfavorable outcome (p<0.001).

Interpretation

Recanalization treatment is feasible and seems to be safe in severely affected pediatric AIS patients. The assessment of efficacy of IVT/EVT in pediatric stroke patients requires larger studies.

Introduction

Childhood arterial ischemic stroke (AIS) is a devastating disease affecting approximately 2–5:100,000 children per year. It is associated with significant morbidity and mortality and carries a high socioeconomic burden.[1-3] For adults, there are now highly effective treatment options for acute AIS consisting of intravenous thrombolysis or endovascular therapy (EVT), i.e. endovascular thrombolysis or mechanical thrombectomy. In particular, intravenous thrombolysis (IVT) with alteplase has been shown to significantly reduce disability in stroke patients without increasing mortality if given up to 4.5 hours after symptom onset.[4] Recently, endovascular thrombectomy in combination with best medical therapy has been shown to be highly effective in AIS patients with a large vessel occlusion in the anterior circulation, with a number needed to treat of 2.6.[5]

In contrast to the adult population, evidence from randomized studies of recanalization treatments in children is lacking. The prospective randomized controlled trial TIPS (thrombolysis in pediatric stroke) failed to recruit patients due to late arrival at hospital, diagnostic delay and the lack of established acute stroke programs.[6, 7] Further trials assessing recanalization treatment in pediatric stroke patients are unlikely considering the clinical and ethical difficulties in randomizing pediatric stroke patients who are candidates for the treatment and also with regard to the overwhelming efficacy of these therapies in adults.[8]

Stroke etiologies in children differ from those in adults and therefore, results cannot simply be extrapolated to pediatric stroke patients. Most centers agree on the use of aspirin or heparin for the treatment of acute stroke in children with AIS. The use of recanalization treatment, i.e. IVT or EVT in pediatric AIS has been reported.[9-15] However, population-based data on recanalization treatments in pediatric stoke patients are lacking. Therefore, we aimed to assess feasibility, safety and outcome of AIS patients treated with IVT/EVT in the population-based Swiss NeuroPediatric Stroke Registry (SNPSR).

Methods

Study Design and Study Population

This is a cohort study of consecutive pediatric AIS patients included in the SNPSR. The SNPSR is a nationwide prospective registry that includes all pediatric AIS patients living in Switzerland.[1, 3] All children aged 1 month to 16 years diagnosed with AIS between 2000 and 2015 who had a pediatric National Institutes of Health Stroke Scale (pedNIHSS) score $\geq$4 at presentation were included. Patients with neonatal stroke or cerebral venous thrombosis were excluded. AIS was defined as a new focal neurological deficit with ischemic lesion visible on magnetic resonance imaging (MRI) in the corresponding vascular territory. Patients who received recanalization treatment, i.e. IVT, endovascular pharmacological and/or mechanical treatment or a combination of both – later called the recanalization group – were compared to those receiving standard care (SC).

Variables at Stroke Onset

Baseline characteristics (i.e. demographic data, vascular risk factors, laboratory findings), treatment modalities, and time from symptom onset to diagnosis and treatment were recorded. Stroke severity was assessed using the pedNIHSS. Patients diagnosed before 2011 were scored for pedNIHSS retrospectively.[16, 17] All patients underwent MRI or computed tomography imaging to rule out intracranial hemorrhage, and MR angiography to assess the site of vessel occlusion.

Intravenous and endovascular therapies for children were adapted based on international and institutional guidelines for adult stroke patients. In general, IVT was performed with either full-dose (0.9 ml/kg body weight) or 2-thirds-dose (0.6 ml/kg body weight) of intravenous tissue plasminogen activator (tPA) within 4.5 hours after symptom onset. In patients with basilar artery occlusions, or in selected cases, extended time windows were applied based on imaging. EVT was performed if: 1) diagnosis of ischemic stroke was established; 2) baseline pedNIHSS score was ≥ 4 points; 3) hemorrhage on cranial CT or MRI was excluded; 4) vessel occlusion correlated with the neurological deficit; and 6) no

individual clinical or premorbid conditions or laboratory findings contraindicated thrombolysis.[18, 19] However, the final decision on treatment was at the discretion of the neuropediatricians, neurologists and interventional neuroradiologists on call.

Digital subtraction angiography was performed via the transfemoral approach. Endovascular recanalization procedures consisted of a combination of techniques such as intraarterial pharmacological treatment (urokinase, n = 2; iv tPA, n = 12; eptifibatide, n = 1) or mechanical thrombectomy. Device selection depended on occlusion pattern and operator preference: mechanical recanalization was performed using thromboaspiration and stent retrievers. Immediately after IVT and/or EVT all patients were transferred to the pediatric intensive care unit. Twenty-four hours after treatment, or earlier in the case of clinical deterioration, a CT or MRI scan was performed. Recanalization rates were classified as complete, partial, or no recanalization by the responsible neuroradiologists. Symptomatic intracerebral hemorrhage (sICH) and asymptomatic intracerebral hemorrhage (aICH) were classified according to the European Cooperative Acute Stroke Study (ECASS) III study protocol.[20, 21] Non-thrombolysed patients were transferred either to the pediatric intensive care unit or to the pediatric ward. They were treated, according to the discretion of the responsible neuropediatrician, mainly with aspirin and/or heparin.

Etiology of stroke was assessed using the Cascade classification.[22] Complete stroke workup was defined according to the recommendations in the SNPSR and included echocardiography, MRI and vessel imaging of head and neck as well as screening for infection, metabolic disease, coagulation pathology and vasculitis. Complications assessed were as follows: malignant middle cerebral artery infarct (MMCAI), sICH, aICH, any bleeding, or stroke-related mortality.[19] Neuropediatricians examined all patients 6 months after stroke onset. Disability was scored using the pediatric stroke outcome measure (PSOM), in some cases retrospectively.[23-25]

Statistical analysis

We primarily assessed feasibility, safety and outcome of recanalization treatment in pediatric AIS patients 6 months after AIS treatment. Secondary outcomes included the PSOM at

discharge and 2 years after AIS, treatment-related complications, and stroke-related mortality. Variables were summarized descriptively by treatment type for all the patients included and no imputation of missing variables was performed. Between-group comparisons for categorical variables were made using the Chi-Square or Fisher's exact test, as appropriate, and for continuous variables using the Wilcoxon rank sum test. Adjustment for potential confounders was performed using a multiple linear regression model. Besides modality of treatment (recanalization treatment versus SC), variables included in the linear regression model were chosen according to the results from univariate analysis (p<0.2). We performed two subgroup analyses: the first controlled for initial pedNIHSS; i.e. eliminated patients in the SC group with a pedNIHSS below 10. The second compared patients treated with thrombolysis (IVT and IAT) to endovascular thrombectomy (use of MT). A 2-sided p-value of <0.05 was considered statistically significant. Analysis was performed using R (version 3.1.2 – R Core Team (2014)). The SNPSR was approved by the cantonal ethics boards and by the Swiss Ministry of Health. All patients and/or their legal guardians participating in the SNPSR provided written informed consent. In addition, the approval of the Swiss Ministry of Health allows for the collection of basic information on all Swiss pediatric stroke patients.

Results

Description of the Cohort

A total of 216 children were diagnosed with an AIS during the study period and 150 patients (mean [SD] age 7.1 [4.9] years, 55 [37%] females) with a pedNIHSS of ≥4 were included in this analysis. Sixteen of the 150 patients (11%) received IVT or EVT. Recanalization treatment was not used in any patient with a pedNIHSS <4. Baseline characteristics of the cohort are presented in Table 1. Stroke etiology remained undetermined in 64 (42.7%) patients; 18% had a stroke with a cardioembolic origin and 17.3% had a focal cerebral arteriopathy. One hundred and twenty patients (80%) had an anterior circulation stroke, of whom 17 (11.3%) developed a MMCAI. Overall, four patients (2.7%) died because of the

stroke. Median PSOM during follow-up was 1.0 (interquartile range [IQR] 0.5–2.5) at all time points of assessment, i.e. at discharge, 6 and 24 months after AIS.

Description of Patients in the Recanalization Group

Detailed information on the 16 patients (mean [SD] age 11.0 [4.3] years, 31.2% female, median [IQR] pedNIHSS 13.5 [11.5–21.3]) who received recanalization treatment is given in Table 2. All but one patient (patient 5) were diagnosed within 12 hours after symptom onset; however 4 patients were treated more than 6 hours after symptom onset. All these patients had an occlusion of the basilar artery. Three patients had a stroke due to unilateral focal cerebral arteriopathy and 4 patients due to cardioembolism. Stroke etiology remained undetermined in the remaining nine patients. Of the latter, 3 had risk factors associated with childhood stroke (Evans syndrome with hemolysis and homozygous MTHFR mutation in patient 6, decreased protein S in patient 8, and elevated lipoprotein a in patient 15). Five patients (31.2%) had a basilar artery occlusion, 7 (43.8%) an MCA and 4 (25%) an ICA occlusion. Five patients (31.2%) were treated with IVT only and five patients received intraarterial pharmacological treatment either with tPA or urokinase. The remaining 6 patients were treated with mechanical thrombectomy; one of these patients received pretreatment with IVT and 4 patients received additional intraarterial pharmacological treatment. Only one patient was treated with mechanical thrombectomy alone.

Complications of recanalization therapy occurred in two patients (12.5%): one patient experienced an asymptomatic ICH and one mucosal bleeding. Furthermore, 5 patients developed an MMCAI requiring hemicraniectomy and one of these patients died due to massive herniation. The indication for hemicraniectomy was based on evolving mass effect due to infarct growth and malignant edema over 24-48 hours post stroke. There was neither any evidence of hemorrhages nor reinfarctions in these patients. The pedNIHSS of patients with MMCAI ranged between 14–21. Recanalization was assessed immediately after the intervention in those patients receiving endovascular treatment and within the first 24 hours in those receiving IVT. Complete recanalization at follow-up was seen in 4 (25%), partial in 6

(38%) and no recanalization in 4 (25%) patients. Information on recanalization rates was lacking for 2 (12%) patients. None of the patients developed a new thrombus. All patients who showed no recanalization at follow-up had been treated with IVT more than 6 hours after symptom onset. Median (IQR) PSOM 6 months after stroke was 2.5 (1.0–4.3). Overall, the use of recanalization treatment increased over the years of the study (Figure 1). The comparison of patients treated with thrombolysis, i.e. IVT and IAT, and endovascular thrombectomy, i.e. use of MT, did not reveal any statistically different results (table 3).

Comparison of Recanalization Treatment with Standard Care

Significant differences were noted between patients who received recanalization treatment and those who did not: in univariate analysis patients who had recanalization treatment were older (p = 0.001), had a higher baseline pedNIHSS (p<0.001), and a shorter time interval from symptom onset to diagnosis (p<0.001). However, stroke etiology and the site of vessel occlusion did not differ between the 2 groups (Table 1). Overall, in univariate analyses bleeding complications did not occur significantly more frequently in patients who had recanalization treatment than in patients receiving SC, whereas MMCAI was diagnosed in 5 patients (31.2%) in the recanalization group compared to 12 (9%) in the SC group (p = 0.012). Median (IQR) PSOM at 6 months was 2.5 (1.0–4.3) in the recanalization and 1.0 (0–2.0) in the SC group (p = 0.014; Table 1). However, in a multiple regression analysis after adjusting for age, baseline pedNIHSS, diagnostic delay and modality of treatment, only higher baseline pedNIHSS was associated with a higher PSOM 6 months after stroke, but not recanalization treatment (Supplementary table 1). Eliminating the impact of initial pedNIHSS by excluding patients with an initial pedNIHSS of <10 in the SC group, the PSOM 6 months after stroke did not differ anymore between groups (table 4 and supplementary table 2).

Discussion

Whether IVT and endovascular treatment approaches are feasible, safe and effective in children who have had an acute ischemic stroke is currently one of the most pressing questions in pediatric stroke research. The main findings of our population-based series of consecutive pediatric AIS patients treated with various recanalization approaches were: 1) recanalization treatment is feasible, and 16 out of 150 acute stroke patients with a pedNIHSS of ≥4 were treated with either IVT or EVT; 2) complications did not occur more frequently in patients who received recanalization treatment; 3) patients who received IVT and EVT had suffered a more severe stroke were more severely affected; 4) mortality did not differ between the 2 treatment groups and, 5) in multivariate analysis, stroke severity, as evaluated by pedNIHSS, was the only significant predictor of unfavorable outcome according to PSOM.

Rates of Revascularization Procedures

This population-based cohort study supports the view that recanalization therapy in children is used rarely (~10%); however, an increase in its use over time was noted (Figure 1). The most likely reasons for the low usage are lack of evidence available from randomized controlled trials, late presentation, diagnostic delay and uncertainty regarding safety and clinical efficacy. In our cohort, one-third of patients were diagnosed more than 24 hours after symptom onset; thus, recanalization treatment was no longer possible. Even though we observed an increase in early presentation over time, resulting in a higher proportion of pediatric AIS patients being diagnosed and treated early, there is still an urgent need to increase awareness of stroke in the pediatric population to allow more pediatric AIS patients to be evaluated for recanalization treatment (Figure 2).

Revascularization techniques

The use of the different revascularization techniques was performed individually according to the discretion of the interdisciplinary team on call. Performing a subgroup analysis comparing the use of thrombolysis to endovascular thrombectomy we could not show any statistically significant difference regarding recanalisation rates and outcome. However, the potential

impact of the technique on outcome is important and requires further attention in future studies focusing on pediatric stroke treatments.

Safety

One of the major concerns of neuropediatricians about the use of acute recanalization techniques in children relates to their safety, e.g. the potential for disabling or even fatal bleeding complications. However, no severe or fatal treatment-related complications occurred in our study, which is in line with previous reports.[9, 10, 12] Rates of hemorrhagic transformations and mortality did not differ between the 2 treatment groups. Furthermore, no complications occurred during endovascular procedures. This finding is in line with those of recent reviews reporting low complication rates in children who received endovascular treatment for AIS. This is important as stroke etiologies in children differ from adults and therefore the results of randomized controlled trials cannot simply be extrapolated to pediatric stroke patients.[26] Children more often have strokes due to an underlying arteriopathy, especially of inflammatory origin, which might increase the risk of bleeding complications during endovascular procedures, due to vessel fragility. In our cohort we had only one patient with FCA who underwent endovascular treatment and, therefore, no firm conclusions regarding its influence on outcome are possible. However, vascular fragility and risk of hemorrhage needs to be considered and weighted carefully against a potential benefit of a recanalisation treatment in this specific patient population. Future research should include consideration of stroke etiology when assessing recanalization techniques.

Four patients received IVT more than 4.5 hours after symptom onset and none of these patients recanalized. No bleeding complications occurred in these patients, but they also showed no clear benefit from IVT. Therefore, in pediatric stroke patients, as in adults, the benefit of IVT more than 4.5 hours after stroke is questionable.

Severity of AIS

Patients receiving IVT and EVT were more severely affected than those receiving SC (pedNIHSS 13.5 versus 8.0; $p<0.001$). MMCAI is a serious concern in patients suffering from a large anterior circulation stroke. In our cohort, development of MMCAI occurred in 17 patients (i.e. 17% of all MCA strokes) and was more frequent in patients receiving recanalization treatment than in the SC group. The frequency of MMCAI ranges between 1.3–18% in pediatric AIS patients and is associated with higher baseline pedNIHSS as shown in our cohort.[27-29] Therefore, the higher frequency of MMCAI in the recanalization group is likely to be an epiphenomenon of more severe infarcts, rather than a complication attributable to the treatment modality itself.

Mortality

Mortality in patients treated with recanalization techniques was not higher than in the SC group, despite a higher baseline pedNIHSS. Compared to the SOC group, patients receiving recanalization treatment had a worse neurological outcome at discharge and 6 months post-stroke (Table 1). However, after adjusting for age, baseline pedNIHSS and diagnostic delay, treatment modality was not a predictor of unfavorable outcome. The initial severity of the stroke was the only relevant factor associated with unfavorable outcome. This finding was confirmed by a subgroup analysis controlling for initial pedNIHSS.

Outlook

Evidence from randomized trials as to whether recanalization techniques in pediatric patients are safe and clinically effective is needed. However, a previous prospective randomized controlled trial (TIPS) failed to recruit patients, and further trials assessing recanalization treatment in the pediatric stroke population are unlikely. This is because of the clinical and ethical difficulties in randomizing pediatric stroke patients against the background of overwhelming evidence for a very strong treatment effect in adults. Therefore, alternative approaches such as large international prospective treatment registries allowing for data pooling and matching are urgently needed to gain further insights into optimal treatment regimens for pediatric stroke patients. In the meantime, standardized treatment protocols and

recommendations should be developed and implemented to provide guidance for neuropediatricians treating pediatric stroke patients.[7]

A major strength of our study is the population-based nature of the SNPSR and the relatively large sample size. One major limitation is the inhomogeneous cohort, with anterior and posterior circulation stroke patients treated with different treatment modalities. Another is the absence of standardized protocols in the different centers. Some patients with basilar artery occlusion were thrombolysed more than 6 hours after symptom onset, which is not evidence based in the adult population. The small sample size, especially in the interventional treatment group, clearly restricts the statistical power of comparisons and multiple regression. Therefore, non-significant findings have to be interpreted with caution. Furthermore, treatment approaches have dramatically changed during the past 10 years and, given the sample size, we were not able to restrict the analysis to the past 5 years. Finally, to assess efficacy of recanalization treatment, a more homogeneous cohort, standardized assessment of recanalization status and a matched analysis would have been valuable.

Conclusions

Recanalization treatment appears to be a feasible and safe treatment option for pediatric AIS patients. A large proportion of such patients are still diagnosed too late, missing the opportunity to be assessed for recanalization treatment options. Previous attempts have shown that a randomized controlled trial of acute stroke treatment in pediatric patients is not feasible. Therefore, larger prospective population-based registries are needed to allow for matching and data pooling to identify those patients most likely to benefit from recanalization treatment.

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Author contributions

"SB, AD, UF and MS contributed to the conception and design of the study; SB, AD, AM, CB, JG, AM, AD, MA, JK, JF, AH, OM, JW CP, EF, UF and MS contributed to the acquisition and analysis of data; SB, AD, CB, UF and MS contributed to drafting the text and preparing the figures."

Potential conflicts of interest

Nothing to report.

Legend of abbreviations:

ACA: anterior cerebral artery
BA: basilar artery
CE: cardioembolic
FCA: focal cerebral arteriopathy
IAT: intrarterial thrombolysis
ICA: Internal carotid artery
ICH: intracerebral hemorrhage
IVT: intravenous thrombolysis
MCA M1: M1 segment of the middle cerebral artery
MCA M2: M2 segment of the middle cerebral artery
MMCAI: malignant middle cerebral artery infarction
MT: mechanical thrombectomy
NA: not available
PCA: posterior cerebral artery
PICA: posterior inferior cerebellar artery
PSOM: pediatric stroke outcome measure
SCA: superior cerebellar artery
SVA: small vessel arteriopathy
ttm: treatment
UE: undetermined etiology

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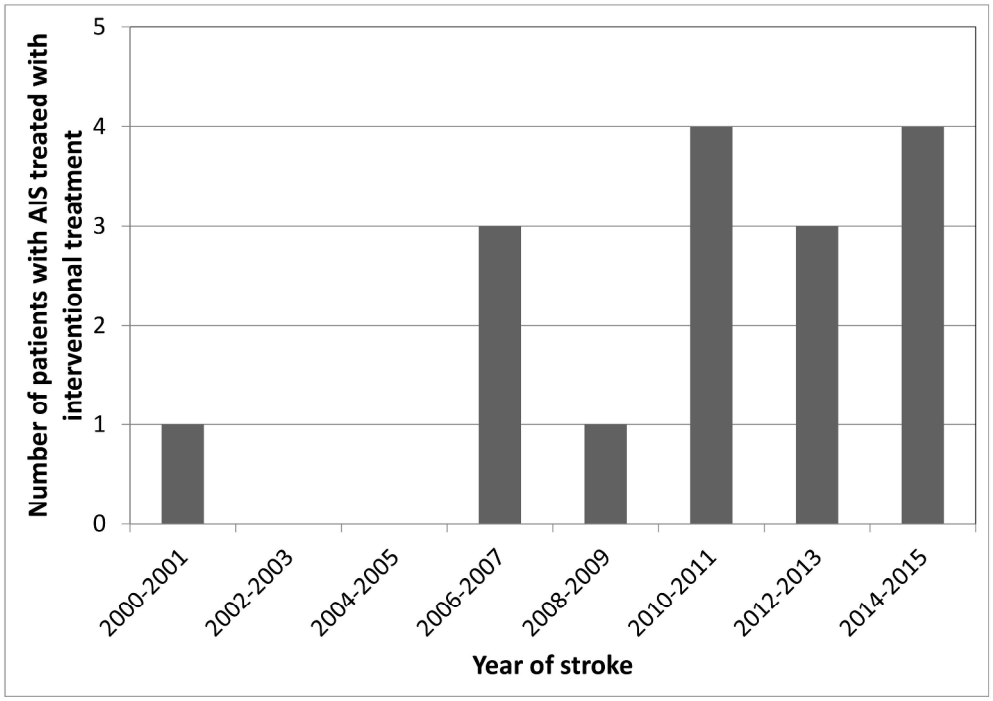
Figure legends

Figure 1 shows the frequency of recanalization treatment per 2-year period during the study.

Figure 2 shows the proportion of pediatric AIS patients diagnosed within 6 hours from symptom onset during the study period.



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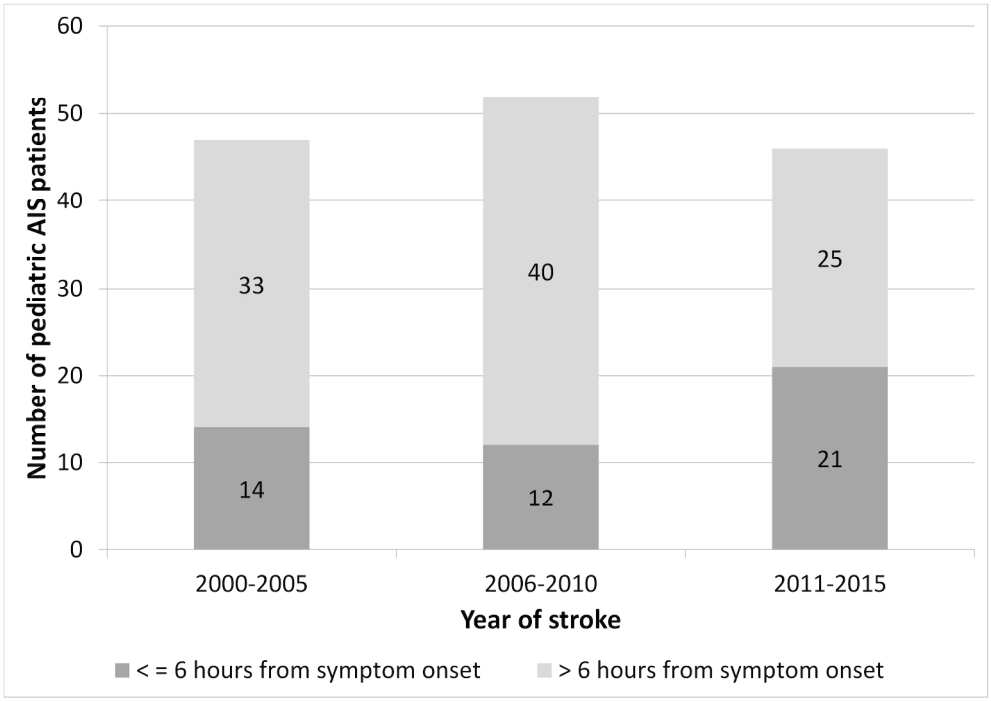

Figure 2 shows the proportion of pediatric AIS patients diagnosed within 6 hours from symptom onset during the study period.

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Table 1. Baseline characteristics of the cohort (pedNIHSS ≥4)

	Whole cohort (150)	Recanalization ttm (16)	Standard ttm (134)	p-value*
Age (years), mean (SD)	7.1 (4.9)	11.0 (4.3)	6.7 (4.8)	**0.001**
Sex, f (%)	55 (36.7)	5 (31.2)	50 (37.3)	0.786
pedNIHSS, median (IQR)	8.0 (5.8-12-0)	13.5 (11.5-21.3)	8 (5-11)	**<0.001**
Fever, n (%)	11 (7.3)	0 (0)	11 (8.2)	1.0
Seizure, n (%)	39 (26.0)	5 (31.2)	34 (25.4)	1.0
Stroke classification, n (%)				0.685
SVA	5 (3.3)	0	5 (3.7)	
FCA	26 (17.3)	3 (18.8)	23 (17.2)	
bilateral arteriopathy	4 (2.7)	0	4 (3.0)	
aortic/cervical arteriopathy	17 (11.3)	0	17 (12.7)	
cardioembolic	27 (18.0)	4 (25.0)	23 (17.2)	
undetermined	64 (42.7)	9 (56.2)	55 (41.0)	
multifactorial	7 (4.7)	0	7 (5.2)	
Site of stroke, n (%)				0.415
Right	61 (40.7)	6 (37.5)	55 (41.0)	
Left	68 (45.3)	6 (37.5)	62 (46.3)	
Bilateral	21 (14.0)	4 (25.0)	17 (12.7)	
Site of proximal vessel occlusion				0.450
ICA	20 (13.3)	4 (25.0)	16 (11.9)	
MCA	100 (66.7)	7 (43.8)	93 (69.4)	
ACA	-	-	-	
PCA	10 (6.7)	-	10 (7.5)	
BA	15 (10.0)	5 (31.2)	10 (7.5)	
SCA/PICA	5 (3.3)	-	5 (3.7)	
Delay, n (%)				**<0.001**
<= 6h	47 (31.3)	12 (75.0)	35 (27.1)	
>6 - <=12h	18 (12.0)	3 (18.8)	15 (11.6)	
>12 - <=24h	29 (19.3)	0 (0)	29 (22.5)	
>24h	51 (34.0)	1 (6.2)	50 (38.8)	
Treatment, n (%)				NA
IVT	-	5 (31.2)	-	
IAT	-	8 (50.0)		
MT	-	3 (18.8)		
Complications, n (%)				
symptomatic ICH	0	0	0	
asymptomatic ICH	3 (2.0)	1 (6.2)	2 (1.5)	0.200
systemic bleeding	0	0	0	
any bleeding	2 (1.3)	1 (6.2)	1 (0.7)	0.070
MMCAI, n (%)	17 (11.3)	5 (31.2)	12 (9.0)	**0.012**
Stroke related mortality	4 (2.7)	1 (6.2)	3 (2.3)	0.377
PSOM, median (IQR)**				
Discharge, n=142	1.0 (0.5-2.5)	2.5 (1.8-5.0)	1.0 (0.5-2.0)	**0.007**
6 months, n=117	1.0 (0.5-2.0)	2.5 (1.0-4.3)	1.0 (0-2.0)	**0.014**
24 months, n=86	1.0 (0.5-2.0)	2.0 (0.5-3.0)	1.0 (0.5-2.0)	0.116

*p-value refers to univariate analysis between the IVT/ET and the standard ttm groups.

**calculated of all patients alive with available data, i.e. at discharge n=142 (15 in IVT/ET group), at 6 months n=117 (12 in IVT/ET group), at 24 months n=86 (11 in IVT/ET group)

Table 2. Characteristics of the patients receiving i.v. thrombolysis or endovascular treatment

Patient	Age at stroke (y)	Delay to diagnosis in hours	Type of intervention	Substance used	Stroke classification	Vessel involved	Baseline pedNIHSS	Complications	Recanalisation	PSOM discharge	PSOM 6 months	PSOM 24 months
1	13.8	6	IVT	tPA	FCA	ICA	10	none	No	2.0	1.5	1.0
2	15.6	3	IVT	tPA	UE	MCA M1	13	Asymptomatic ICH	Partial	5.0		
3	5.7	12	IVT	tPA	UE	BA	25	none	No	5.0	5.0	3.0
4	5.7	14	IVT	tPA	FCA	BA	24	none	No	6.0	5.0	5.0
5	5.8	48	IVT	tPA	CE	BA	25	Subcutaneous and mucosal bleeding	No	8.0	7.0	7.0
6	11.6	3	IAT	tPA	UE	MCA M1	7	none	Complete	0.5	0.0	0.0
7	14.8	3.5	Bridging and MT	tPA	UE	MCA M1	22	none	Complete	0.5	0.5	0.5
8	13.6	3	MT/IAT	Urokinase	UE	ICA	15	MMCAI hemicraniectomy	Complete	2.0	1.0	0.5
9	15.2	6	IAT	tPA	UE	MCA M1	14	MMCAI hemicraniectomy	Partial	4.0	6.0	6.0
10	14.1	3	MT/IAT	tPA	UE	ICA	17	MMCAI hemicraniectomy	Partial	2.5	2.5	3.0
11	2.1	2.5	MT/IAT	tPA	CE	MCA M1	8	none	Complete	1.5	1	1.5
12	8.9	4	IAT	tPA	UE	MCA M1, ACA	13	MMCAI hemicraniectomy	NA	5.0	3.5	
13	9.6	1	IAT	tPA	CE	MCA M1	12	none	NA	0.0		
14	14.8	4	MT	Eptifibatide	CE	BA	21	MMCAI hemicraniectomy	Partial	NA		
15	15.3	5	MT	-	UE	ICA	5	none	Partial	2.0		
16	9.7	10	IAT	Urokinase	FCA	BA	12	None	Partial	3.5	3.0	2.0

Table 3. Comparison of different recanalisation techniques

	Thrombolysis (IVT/IAT) n=10	Endovascular Thrombectomy (MT) n=6	p-value
Age (years), median (range)	9.7 (5.7-15.6)	14.5 (2.1-15.3)	0.302
pedNIHSS, median (range)	13 (7-25)	16 (5-22)	0.957
Site of proximal vessel occlusion, n (%)			0.344
ICA	1 (10)	3 (50)	
MCA	5 (50)	2 (33.3)	
ACA	-	-	
PCA	-	-	
BA	4 (40)	1 (16.7)	
SCA/PICA	-	-	
Degree of recanalisation, n (%)			0.078
Complete	1 (10)	3 (50)	
Partial	3 (30)	3 (50)	
No recanalisation	4 (40)	0	
MMCAI, n (%)	2 (20)	3 (50)	0.486
Stroke related mortality, n (%)	0	1 (16.7)	0.790
PSOM, median (range)			
Discharge, n=15	4.5 (0-8.0)	1.8 (0.5-2.5)	0.108
6 months, n=12	3.5 (0-7.0)	1.0 (0.5-2.5)	0.074
24 months, n=11	2.5 (0-7.0)	1.0 (0.5-3.0)	0.255

Table 4. Baseline characteristics of the cohort (pedNIHSS <10 in control group)

	Whole cohort (66)	Recanalization ttm (16)	Standard ttm (50)	p-value*
Age (years), mean (SD)	8 (4.6)	11.0 (4.3)	7.0 (4.3)	**0.002**
Sex, f (%)	28 (42.4)	5 (31.2)	23 (46)	0.389
pedNIHSS, median (IQR)	12 (10-15.8)	13.5 (11.5-21.3)	12 (10-14.8)	0.26
Fever, n (%)	4 (6.1)	0 (0)	4 (8.0)	0.565
Seizure, n (%)	16 (24.2)	5 (31.2)	11 (22.0)	0.509
Stroke classification, n (%)				0.287
SVA	1 (1.5)	0	1 (2.0)	
FCA	10 (15.2)	3 (18.8)	7 (14.0)	
bilateral arteriopathy	1 (1.5)	0	1 (2.0)	
aortic/cervical arteriopathy	11 (16.7)	0	11 (22.0)	
cardioembolic	13 (19.7)	4 (25.0)	9 (18.0)	
undetermined	27 (40.9)	9 (56.2)	18 (36.0)	
multifactorial	3 (4.5)	0	3 (6.0)	
Site of stroke, n (%)				0.812
Right	22 (33.3)	6 (37.5)	16 (32.0)	
Left	29 (43.9)	6 (37.5)	23 (46.0)	
Bilateral	15 (22.7)	4 (25.0)	11 (22.0)	
Site of proximal vessel occlusion				0.075
ICA	11 (16.7)	4 (25.0)	7 (14.0)	
MCA	39 (75.5)	7 (43.8)	32 (70.3)	
ACA	-	-	-	
PCA	3 (4.5)	-	3 (6.0)	
BA	8 (12.1)	5 (31.2)	3 (6.0)	
SCA/PICA	5 (3.3)	-	5 (3.7)	
Delay, n (%)				**<0.015**
<= 6h	29 (46.0)	12 (75.0)	17 (36.2)	
>6 - <=12h	10 (15.9)	3 (18.8)	7 (14.9)	
>12 - <=24h	10 (15.9)	0 (0)	10 (21.3)	
>24h	14 (22.2)	1 (6.2)	13 (27.7)	
Treatment, n (%)				NA
IVT	-	5 (31.2)	-	
IAT	-	8 (50.0)		
MT	-	3 (18.8)		
Complications, n (%)				
symptomatic ICH	0	0	0	
asymptomatic ICH	2 (3.0)	1 (6.2)	1 (2.0)	0.388
systemic bleeding	0	0	0	
any bleeding	1 (1.5)	1 (6.2)	0	0.075
MMCAI, n (%)	16 (24.2)	5 (31.2)	11 (22.0)	0.452
Stroke related mortality	4 (6.2)	1 (6.2)	3 (6.2)	1.0
PSOM, median (IQR)**				
Discharge, n=65	2.0 (1.0-4.0)	2.5 (1.8-5.0)	2.0 (1.0-4.0)	0.323
6 months, n=62	1.5 (1.0-3.0)	2.5 (1.0-4.3)	1.5 (1.0-2.5)	0.275
24 months, n=61	1.8 (0.5-3.0)	2.0 (0.5-3.0)	1.5 (0.5-2.8)	0.619

*p-value refers to univariate analysis between the IVT/ET and the standard ttm groups.

**calculated of all patients alive with available data, i.e. at discharge n=65 (15 in IVT/ET group), at 6 months n=62 (12 in IVT/ET group), at 24 months n=61 (11 in IVT/ET group)