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Predictors of Good Clinical Outcome in Patients with Acute Stroke Undergoing Endovascular Treatment – Results from CERBERUS

Prediktory pozitivního léčebného výsledku u pacientů s akutní cévní mozkovou příhodou podstupujících endovaskulární léčbu – výsledky z registru CERBERUS

Abstract

Background: Endovascular therapy (EVT) with stent retrievers has been shown to be superior and safe (in the anterior circulation) in comparison to intravenous thrombolysis (IVT) alone or no specific therapy. We compared clinical outcome between patients undergoing EVT admitted directly to comprehensive stroke centers (CSCs) and patients transferred from primary stroke centers (PSCs) to a CSC. *Materials and methods:* Demographics, risk factors, and medical history of all consecutive EVT-treated stroke patients in collaborating stroke centers were collected. Patients were divided into three groups: treatment with IVT in a PSC before transfer to a CSC for EVT; treatment with IVT directly in a CSC with subsequent EVT in the same center; no treatment with IVT before EVT. Neurological status using the National Institutes of Health Stroke Scale (NIHSS) on admission and at day 7 and self-sufficiency using the modified Rankin Scale (mRS) at day 90 were assessed. Favorable clinical outcome was defined as an mRS score of 0–2. Follow-up computed tomography or magnetic resonance imaging was done to determine symptomatic intracerebral hemorrhage (SICH). *Results:* A total of 568 patients (313 males; mean age, 66.1 ± 13.2 years) were registered from January 2006 to the end of July 2015. Patients in all three groups did not differ in baseline characteristics except for the time to the start of EVT. The average delay of EVT start in patients transferred from PSC to CSC was 45 min. Subgroups did not differ significantly in SICH prevalence (overall prevalence 5.5%) and favorable clinical outcome (overall 46.7%). *Conclusion:* The benefit of direct transfer to a CSC merits further investigation. The present study showed that both approaches to stroke patient transport organization in the Czech Republic are comparably efficient and safe.

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M. Roubec[1], D. Krajíčková[2], J. Hommerová[3], P. Kešnerová[4], S. Klimošová[5], P. Rapantová[6], R. Herzig[2], D. Školoudík[1,7]
for the CERBERUS Study Group

Authors' affiliation are available at page 667.

Prof. David Školoudík, MD, PhD, FESO
Center for Research and Science
Department of Nursing
Faculty of Health Science
Palacký University Olomouc
Hněvotínská 3, 775 15 Olomouc
Czech Republic
e-mail: skoloudik@hotmail.com

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Souhrn

Úvod: Endovaskulární terapie (EVT) s použitím stent-retrieverů (v přední cirkulaci) již prokázala svou superioritu a bezpečnost ve srovnání se samotnou intravenózní trombolýzou (IVT) nebo žádnou specifickou terapií. Srovnali jsme klinický výsledek pacientů s ischemickou cévní mozkovou příhodou (iCMP) podstupujících EVT přijatých direktně do komplexních cerebrovaskulárních center (KCC) s pacienty transferovanými sekundárně z lokálních iktových center (IC) do KCC. *Metodika a pacienti:* Byly zaznamenány demografické údaje, rizikové faktory a zdravotní anamnéza všech konsekutivních pacientů léčených EVT ve spolupracujících iktových centrech KCC/IC. Pacienti byli rozděleni do tří skupin: léčba IVT v IC před transferem k EVT do KCC; léčba IVT přímo v KCC s navazující EVT v tomtéž centru; žádná IVT před EVT. Neurologický stav při přijetí a 7. den byl hodnocen za využití National Institutes of Health Stroke Scale (NIHSS). Soběstačnost pacientů 90. den byla hodnocena pomocí modifikované Rankinovy škály (mRS). Jako dobrý klinický výsledek bylo označeno skóre mRS 0–2. Kontrolní vyšetření výpočetní tomografií nebo magnetickou rezonancí byla provedena k vyloučení symptomatického intracerebrálního krvácení (SICH). *Výsledky:* Celkem 568 pacientů (313 mužů; průměrný věk 66,1 ± 13,2 roku) bylo zařazeno do registru od ledna 2006 do konce července 2015. Pacienti ze všech třech skupin se statisticky nelišili ve vstupních charakteristikách mimo času od vzniku příhody do zahájení EVT. Průměrné zdržení začátku EVT u pacientů transferovaných z IC do KCC činilo 45 min. Podskupiny se také statisticky nelišily ve výskytu SICH (celková prevalence 5,5 %) a dosaženém dobrém klinickém výsledku (celkově 46,7 %). *Závěr:* Benefit přímého transferu pacienta do KCC si zaslouží další sledování. Prezentovaná studie prokázala, že obě varianty organizace transportu pacienta s iCMP k EVT v České republice jsou srovnatelně efektivní a bezpečné.

M. Roubec[1], D. Krajíčková[2], J. Hommerová[3], P. Kešnerová[4], S. Klimošová[5], P. Rapantová[6], R. Herzig[2], D. Školoudík[1,7] for the CERBERUS Study Group

[1] Comprehensive Stroke Center, Department of Neurology, University Hospital Ostrava, Czech Republic
[2] Comprehensive Stroke Center, Department of Neurology, Charles University Faculty of Medicine and University Hospital Hradec Králové, Czech Republic
[3] Comprehensive Stroke Center, Department of Neurology, Faculty of Medicine Charles University and University Hospital Plzeň, Czech Republic
[4] Comprehensive Stroke Center, Department of Neurology, Faculty of Medicine Charles University and University Hospital Praha Motol, Czech Republic
[5] Comprehensive Stroke Center, Department of Neurology, Regional Hospital Liberec, Czech Republic
[6] Stroke Center, Department of Neurology, Vítkovice Hospital, Ostrava, Czech Republic
[7] Center for Research and Science, Department of Nursing, Faculty of Health Science, Palacký University Olomouc, Czech Republic

Objectives

Acute occlusion of large cerebral arteries is usually associated with severe neurologic deficit and low chance for early recanalization with intravenous thrombolysis (IVT) [1]. In 2015, endovascular therapy (EVT) with stent retrievers has been shown to be superior and safe (in the anterior circulation) in comparison to IVT alone or no specific therapy [2–9]. Hence, this method should now be considered for all patients with acute ischemic stroke with occlusion of large cerebral vessels (if the timing is favorable). EVT requires changes to the protocol for acute management of stroke, pre-hospital care, communication and treatment organization with primary stroke centers (PSCs) and comprehensive stroke centers (CSCs). The goal is to determine optimal management for stroke patients with large-vessel occlusion.

Stroke care in the Czech Republic has changed considerably during the last 20 years. Since 1998, IVT treatment has started to be used routinely in selected neurology departments for acute ischemic stroke. Several hospitals built specialized stroke units providing comprehensive care for stroke patients from the very beginning, whereas other hospitals collaborated with (usually internal) intensive care units (ICUs). EVT has been used in the Czech Republic since 2005, mostly in university hospitals, rarely in local hospitals.

In 2010, a national two-level network of acute stroke care was created. Initially, this was a network of 32 PSCs providing acute stroke care (multi-modal diagnostics, care in a stroke unit, IVT administration, early rehabilitation, primary/secondary preventive care and treatment of common complications) and collaborating with the nearest CSC. CSCs also provide EVT, complex neurosurgical care and consultations to PSCs and local neurological departments for preventive and follow-up care with regard to cerebrovascular disease (second level, 13 CSCs).

Each PSC has a target population (≈250,000–500,000 inhabitants) to care for based on geography and population density. Stroke care is provided by a neurologist and each PSC must have a Stroke Unit. The admission work-up does not differ between PSCs and CSCs, and always comprises neurologic examination, basic laboratory tests, computed tomography (CT) or magnetic resonance imaging (MRI) and, in all patients suitable for IVT or EVT, additional computed tomography angiography (CTA) or magnetic resonance angiography (MRA). The typical work-up time in the submitted patient population (January 2006 until the end of July 2015) is consistent with the door-to-needle time (DNT) for IVT and is ≈55 min. There is usually one CSC in each region/territorial unit of the Czech Republic (14 regions, including the capital city Prague) that collaborates with PSCs in the same area (on a geographical basis) and covers a population of 800,000–1,200,000 inhabitants. The distances and travel times between PSCs and CSCs vary in different parts of the country, usually from 10 to 90 min [10,11].

Time-to-recanalization is an essential parameter. However, how to pre-select patients suitable for EVT in pre-hospital care (i.e., whether to transfer to a PSC with early IVT and secondary transport to a CSC for EVT, or direct transfer of patients with severe neurological impairment to a CSC for IVT and EVT) is not known.

We compared the clinical outcome between patients: 1. indicated for EVT after IVT failure and admitted directly to a CSC and patients transferred from a PSC to CSC after IVT; 2. treated using EVT after failed IVT treatment and 3. patients contraindicated to IVT treated with EVT only. Also, we wished to identify predictors of symptomatic intracerebral hemorrhage (SICH) and good clinical outcome 90 days after EVT. We also compared the safety and efficacy of EVT in patients with different sites of occlusion of cerebral arteries.

Materials and methods

Registry

Czech Registry of Cerebral Mechanical Recanalizations in Acute Ischemic Stroke (CERBERUS) has been established for collection of prospective data in the Czech Republic. Seven stroke centers providing EVT have been inputting data into this registry: University Hospital Ostrava (since January 2006), Vítkovice Hospital Ostrava (September 2013), University Hospital Hradec Králové, Regional Hospital Liberec, Motol University Hospital in Prague, Military University Hospital Prague (January 2014) and University Hospital Plzeň (January 2015).

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008). The study protocol was approved by the local ethics committee (approval number: 169/2013). Patients provided written informed consent. Independent witnesses verified the signatures of patients who experienced technical problems.

Patients, inclusion criteria and organization of EVT treatment

In the Czech Republic, all acute-stroke patients found to be within the time window for IVT and without known contraindication for IVT must be transferred to the nearest stroke center (PSC or CSC) for diagnostics and IVT.

The EVT was indicated in the stroke centers participating in the CERBERUS under five conditions: 1. occlusion of large vessels (middle cerebral artery (MCA), internal carotid artery (ICA) – occlusion of the cervical segment with/without MCA occlusion or T-type occlusion, basilar artery (BA) diagnosed with CTA or MRA); 2. procedure start within 6–8 hours (an 8-hour time window was applied in particular CSCs based upon approval of the local ethics committee) after stroke onset with specific exceptions (e.g., posterior circulation stroke due to BA occlusion); 3. IVT failure (no neurological improvement after IVT start till the start of EVT or during transfer) or contraindication to IVT; 4. neurological deficit upon hospital admission of ≥ 8 points (using the National Institutes of Health Stroke Scale; NIHSS) or fluctuating neurological deficit; 5. self-sufficiency before current stroke (0–2 points in the modified Rankin scale; mRS).

All CT/MRI scans were viewed locally. No standardized imaging-based patient selection system, such as Alberta Stroke Program Early CT (ASPECT) score, was used routinely. Endovascular team was called immediately after major artery occlusion diagnosis and when no contraindication for EVT existed. PSC stroke physician was required to contact a CSC immediately after imaging. Transfer from the PSC to the CSC was performed by regional Emergency Medical Service (EMS) at the highest priority level. CT or MRI scans were transferred using a national picture archiving and communication system (PACS) to the CSC; however, this could not delay the transfer organization. Imaging was not routinely repeated in the CSC after transfer unless neurological deterioration (> 4 NIHSS points) occurred.

All stroke centers that were a part of the CERBERUS collected prospective data on all consecutive EVT-treated stroke patients to the registry. Demographics (age, sex) as well as information on risk factors and medical history (blood pressure, blood glucose, blood cholesterol, smoking status, alcohol consumption, treatment with antithrombotic drugs/statins, body mass index (BMI), pre-event transient ischemic attack (TIA) or stroke, atrial fibrillation) were collected at baseline. The NIHSS was used to assess stroke severity and the mRS to determine self-sufficiency.

Patients were divided into three groups: treatment with IVT in a PSC before transfer to a CSC for EVT (group 1); treatment with IVT directly in a CSC followed by EVT in the same center (group 2); no treatment with IVT before EVT due to a contraindication to IVT or outside the time window (group 3).

The CERBERUS contains data on patients with stroke in the anterior and posterior circulation. However, to compare EVT efficacy (recanalization rate, 90-day clinical outcome) and safety (occurrence of SICH and malignant brain edema) six subgroups based on occlusion site were created: 1. isolated MCA; 2. isolated ICA; 3. ICA + MCA (with patent anterior cerebral artery); 4. T-type ICA; 5. vertebral artery (VA) occlusion with contralateral chronic occlusion or distal embolization to the posterior circulation (VA+); 6. BA occlusion.

Treatment methods

Five methods were used for EVT of occluded cerebral arteries in the participating stroke centers: 1. mechanical thrombectomy with stent retrievers; 2. percutaneous transluminal angioplasty with/without stenting; 3. endovascular sonolysis; 4. intra-arterial thrombolysis; 5. combination of methods. The method was selected by an interventional radiologist.

All logistic data (onset-to-needle time and DNT for IVT; onset-to-groin puncture time, door-to-groin puncture time, procedure time and onset-to-recanalization time for EVT) were assessed in all groups (if applicable).

Recanalization and outcome parameters

Recanalization rate was assessed locally using the Thrombolysis in Cerebral Infarction (TICI) score. Successful recanalization was defined as a score of 2b–3. Neurological status in the NIHSS on day 7 and day 90 and self-sufficiency using the mRS on day 90 were assessed in all patients. Favorable clinical outcome was defined as an mRS score of 0–2. Follow-up CT or MRI was performed in all patients ≤ 24 hours from the stroke onset (and as necessary at any time in case of neurological worsening) to determine SICH. SICH was determined as ICH on the follow-up CT or MRI in combination with deterioration in NIHSS of ≥ 4 points. Malignant brain edema was assessed clinically as deterioration in NIHSS of ≥ 4 points with midline shift on the follow-up CT or MRI.

Statistical analyses

The normality of data distribution was tested using the Shapiro-Wilk test. Categorical variables are reported as frequencies and percentages. Data with normal distribution are reported as a mean ± standard deviation (SD). Parameters not fitting the normal distribution are presented as a median and interquartile range (IQR). Categorical variables in the two arms were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U-test. Univariate and multiple logistic regression analyses with calculation of non-adjusted and adjusted odds ratios (ORs) were used to determine possible predictors of successful arterial recanalization, malignant brain edema, and favorable 90-day clinical outcome, respectively. The following variables were included in the analyses: age, sex, history of arterial hypertension, diabetes mellitus, hyperlipidemia, BMI, smoking, alcohol

Tab. 1. Patients demographic data.

	IVT in CSC Group 1	IVT in PSC Group 2	P value (Group 1 vs. Group 2)	non IVT Group 3	P value (Groups 1+2 vs. Group 3)
number of patients	203	133	NA	232	NA
age, mean ± SD (years)	67.8 ± 12.3	65.4 ± 11.0	0.027	64.9 ± 15.0	0.314
male; n (%)	88 (43.3)	54 (40.6)	0.652	113 (48.7)	0.145
arterial hypertension; n (%)	152 (74.9)	102 (77.9)	0.600	174 (75.0)	0.842
diabetes mellitus; n (%)	42 (20.9)	18 (13.8)	0.110	64 (27.7)	0.010
hyperlipidemia; n (%)	72 (35.8)	58 (44.3)	0.136	86 (37.1)	0.660
smoking; n (%)	35 (22.6)	29 (24.0)	0,886	32 (15.4)	0.038
alcohol abuse; n (%)	0 (0)	1 (0.8)	0.452	7 (3.3)	0.024
statin therapy started before or within 24 h after stroke onset; n (%)	104 (52.3)	46 (35.1)	0.002	80 (35.7)	0.023
atrial fibrillation; n (%)	71 (35.5)	35 (26.7)	0.117	97 (42.0)	0.016
previous TIA; n (%)	6 (3.0)	2 (1.5)	0.488	3 (1.3)	0.538
previous stroke; n (%)	24 (11.9)	8 (6.1)	0.089	29 (12.6)	0.339

CSC – comprehensive stroke center; IVT – intravenous thrombolysis; NA – not applicable; PSC – primary stroke center; SD – standard deviation; TIA – transient ischemic attack.

Tab. 2. Logistic and baseline characteristics.

	IVT in CSC Group 1 (N = 203)	IVT in PSC Group 2 (N = 133)	P value (Group 1 vs. Group 2)	non IVT Group 3 (N = 232)	P value (Groups 1+2 vs. Group 3)
door-to-needle time for IVT; mean ± SD (minutes)	54.6 ± 26.8	55.8 ± 23.5	0.218	NA	NA
door-to-groin puncture time; mean ± SD (minutes)	116.5 ± 68.9	33.3 ± 48.9	< 0.0001	82.1 ± 173.1	0.445
onset-to-needle time for IVT; mean ± SD (minutes)	139.7 ± 47.2	131.3 ± 48.4	0.075	NA	NA
onset-to-groin puncture time; mean ± SD (minutes)	211.5 ± 75.1	256.9 ± 74.3	< 0.0001	365.6 ± 545.9	0.147
NIHSS baseline; median (IQR)	16.0 (12 – 19)	16.0 (13 – 20)	0.159	15.6 ± 6.9	0.359
body mass index; mean ± SD	28.1 ± 4.2	27.9 ± 4.5	0.61	28.1 ± 5.6	0.437
baseline systolic blood pressure; mean ± SD; (mm Hg)	157.1 ± 23.6	156.0 ± 28.0	0.452	154.2 ± 30.8	0.15
baseline diastolic blood pressure; mean ± SD (mm Hg)	84.4 ± 14.6	86.5 ± 14.5	0.156	85.0 ± 15.7	0.915
baseline blood glucose level; mean ± SD (mmol/l)	7.9 ± 3.1	7.5 ± 1.3	0.407	7.9 ± 3.42	0.937
baseline cholesterol level; mean ± SD (mmol/l)	4.9 ± 1.1	5.3 ± 1.42	0.064	4.8 ± 1.28	0.103

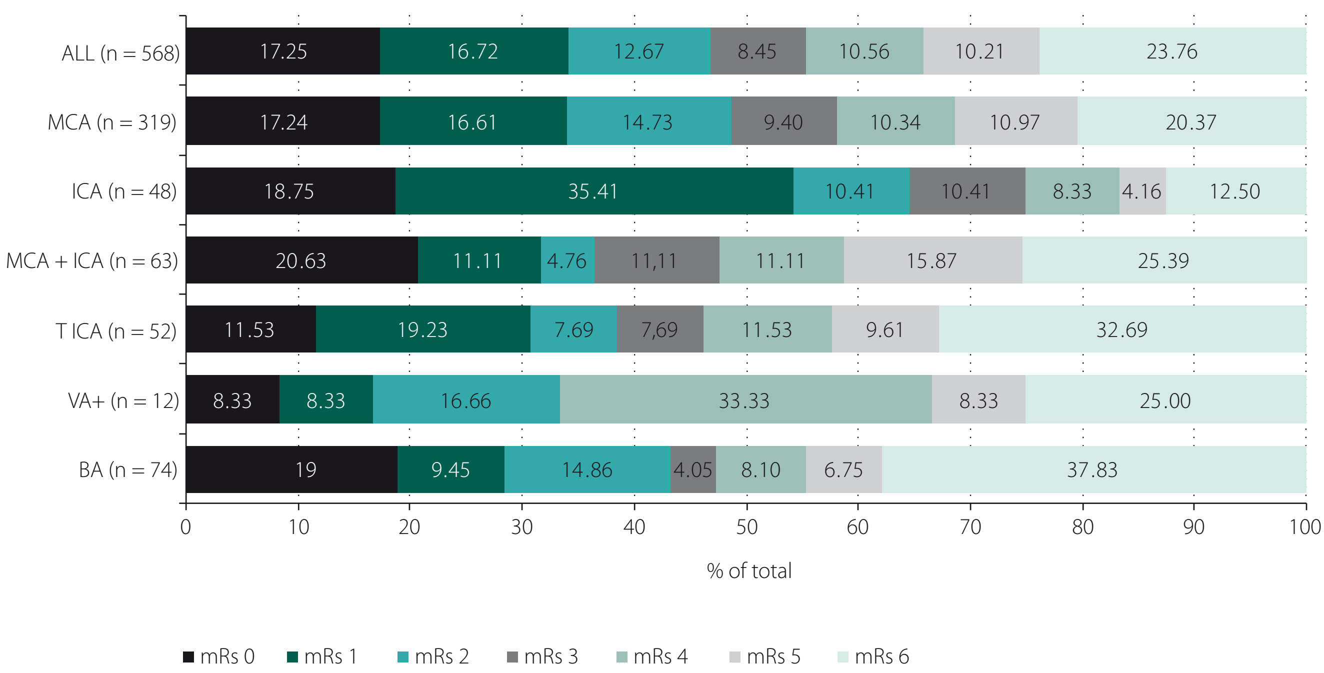
CSC – comprehensive stroke center; IQR – interquartile range; IVT – intravenous thrombolysis; NA – not applicable; NIHSS – National Institutes of Health Stroke Scale; PSC – primary stroke center; SD – standard deviation.

abuse, atrial fibrillation, previous TIA, previous stroke, previous use of antithrombotic agents, statin therapy started before or within 24 h after stroke onset, baseline NIHSS, baseline systolic blood pressure, baseline diastolic blood pressure, baseline glucose level, baseline cholesterol level, IVT administration, location of arterial occlusion, procedure time and onset-to-recanalization time. All tests

Tab. 3. Results.

	IVT in CSC Group 1 (N = 203)	IVT in PSC Group 2 (N = 133)	P value (Group 1 vs. Group 2)	non IVT Group 3 (N = 232)	P value (Groups 1+2 vs. Group 3)
procedure time; mean ± SD (minutes)	67.1 ± 38.6	60.5 ± 36.5	0.172	63.0 ± 34.5	0.813
onset-to-recanalization time; mean ± SD (minutes)	274.8 ± 79.5	340.2 ± 79.5	0.002	354.1 ± 352.8	0.606
successful recanalization (TICI 2b-3); n (%)	160 (78.61)	103 (77.50)	0.766	168 (72.34)	0.0545
NIHSS day 7; median (IQR)	6.0 (2–12)	8.0 (3–16)	0.140	6.0 (2–15)	0.610
mRS day 90; median (IQR)	2.0 (1–5)	3.0 (1–5)	0.512	3.0 (1–6)	0.663
SICH occurrence; n (%)	16 (8.0)	6 (4.6)	0.163	9 (4.0)	0.194

CSC – comprehensive stroke center; IQR – interquartile range; IVT – intravenous thrombolysis; mRS – modified Rankin Scale; NIHSS – National Institutes of Health Stroke Scale; PSC – primary stroke center; SD – standard deviation; SICH – symptomatic intracerebral hemorrhage; TICI – Thrombolysis in Cerebral Infarction.



Graph 1. Comparison of 90-day clinical outcome (modified Rankin scale) between different arterial territory occlusions.

were carried out at an alpha significance level of 0.05. Data were analyzed using SPSS v22.0 (IBM, Armonk, NY, USA).

Results

Data on 568 patients (313 males; mean age 66.1 ± 13.2 years) who underwent EVT were collected from January 2006 until the end of July 2015. Out of the 568 patients, 133 underwent EVT after IVT failure in a CSC (79 males; mean age 65.4 ± 11.0 years), 203 underwent EVT in a CSC after IVT carried out in a PSC (115 males; mean age 67.8 ± 12.3 years) and 232 patients contraindicated to IVT underwent EVT in a CSC (119 males; mean age 64.9 ± 15.0 years).

The three groups of patients did not differ in baseline characteristics except for the time to start of EVT. Time from a CSC admission to the start of EVT (door-to-groin puncture time) was significantly shorter in patients diagnosed and treated primarily with IVT in a PSC, whereas the diagnosis was made already in the PSC. On the contrary, time from stroke onset to the start of the EVT procedure was significantly shorter in patients treated with IVT followed by EVT in the same CSC. Procedure length did not differ significantly between groups regardless of previous IVT. The time-to-recanalization also did not differ significantly between the IVT (groups 1 and 2) and non-IVT (group 3) patients but was significantly shorter in patients treated with IVT in a CSC (group 1) compared to those treated with IVT in a PSC (group 2). Onset-to-hospital arrival time

Tab. 4. Comparison of outcomes between different arterial territory occlusions.

	MCA N = 319	ICA N = 48	ICA + MCA N = 63	T-type ICA N = 52	VA+ N = 12	BA N = 74
procedure time; mean ± SD (minutes)	59.0 ± 30.5	70.5 ± 40.7	69.5 ± 42.7	64.9 ± 40.5	69.25 ± 27.8	78.5 ± 38.0
onset-to-recanalization time; mean ± SD (minutes)	288.6 ± 115.3	371.1 ± 162.2	267.4 ± 100.9	267.4 ± 89.8	304.1 ± 162.9	372.3 ± 174.0
successful recanalization (TICI 2b-3); n (%)	251 (78.6)	31 (64.1)	41 (65.5)	36 (68.6)	7 (54.5)	53 (71.4)
NIHSS day 7; median (IQR)	7 (2–15)	3.5 (1–9)	7.5 (1–15)	5.5 (3–15)	3 (2–6)	6.5 (2–19.75)
mRS day 90; median (IQR)	3 (1–5)	1 (1–3.25)	4 (1–6)	4 (1–6)	3 (2–4.5)	4 (1–6)
SICH occurrence; n (%)	19 (6.0)	4 (8.1)	3 (4.8)	4 (7.7)	0 (0)	1 (1.7)

BA – basilar artery; ICA – internal carotid artery; IQR – interquartile range; MCA – middle cerebral artery; mRS – modified Rankin Scale; NIHSS – National Institutes of Health Stroke Scale; SD – standard deviation; SICH – symptomatic intracerebral hemorrhage; TICI – Thrombolysis in Cerebral Infarction; VA – vertebral artery.

Tab. 5. Independent predictors of malignant cerebral edema development in anterior circulation.

	Adjusted OR	95% CI		P Value
baseline NIHSS	1.114	1.114	1.171	< 0.0001
baseline blood glucose level	1.135	1.053	1.223	0.001
left hemisphere	0.495	0.286	0.856	0.012
ICA + MCA vs. MCA occlusion	2.200	1.039	4.657	0.039
T-type ICA vs. MCA occlusion	4.580	2.282	9.193	< 0.0001

CI – confidence interval; ICA – internal carotid artery; MCA – middle cerebral artery; NIHSS – National Institutes of Health Stroke Scale; OR – odds ratio

(68 vs. 75 min, respectively) and DNT did not differ significantly between PSCs and CSCs. The average delay of EVT start in transferred patients was 45 min and varied depending on the availability of EMS transfer, duration of transfer, and work-up time in a PSC. Unfortunately, the time of transfer and time spent in a PSC before transfer was not measured (Tab. 1, 2).

Patients were treated using: 1. mechanical thrombectomy with stent retrievers (254 subjects); 2. percutaneous transluminal angioplasty with/without stenting (157 subjects); 3. endovascular sonolysis (3 subjects); 4. intra-arterial thrombolysis (24 subjects) or 5. combination of methods (130 subjects).

Overall prevalence of SICH was 5.5%. On day 90, 46.7% of patients achieved favorable clinical outcome (mRS 0–2) and further 8.5% of patients achieved clinical outcome of mRS 3. Subgroups did not differ significantly with regard to the prevalence of SICH or clinical outcome (Tab. 3, Graph 1). No difference was found in patients who were treated with intra-arterial thrombolysis alone or in combination with another method. Favorable clinical outcome was achieved in 55.4% of patients who had successful recanalization (TICI 2b–3) vs. 22.1% of patients with the TICI score of 0–2a ($p < 0.0001$).

The only independent negative predictor of successful recanalization in all patients was the duration of the procedure (adjusted OR 0.985; 95% confidence interval (CI): 0.976–0.993; $p = 0.0002$) and, in patients with occlusion in the anterior circulation, also IVT DNT (adjusted OR 0.986; 95% CI 0.974–0.998, $p = 0.027$). There was no significant difference in the likelihood of achieving recanalization between subgroups with regard to occlusion site (Tab. 4).

Higher blood glucose level at baseline and longer DNT were identified as independent predictors of the risk of SICH in all patients (adjusted OR 1.016; 95% CI 1.002–1.029; $p = 0.024$; and adjusted OR 1.145; 95% CI 1.018–1.288; $p = 0.024$, respectively).

Higher baseline NIHSS score and blood glucose level, right-hemisphere stroke, ICA-MCA, and T-type ICA occlusion were independent negative predictors of malignant brain edema in patients who had a stroke in the anterior circulation (Tab. 5). No predictor of malignant brain edema was identified for patients who had a stroke in the posterior circulation.

Older age, history of arterial hypertension and diabetes mellitus, baseline NIHSS, systolic blood pressure, blood glucose level, BMI and procedure duration were negative predictors of favorable clinical outcome at 90 days. Isolated ICA occlusion, history of hyperlipidemia and statin treatment were positive predictors of favorable 90-day clinical outcome (Tab. 6). Of these parameters, only older age, baseline NIHSS, baseline blood glucose level and procedure duration were independent negative predictors of good clinical outcome. A history of statin treatment was an independent positive predictor of good clinical outcome (Tab. 7).

Discussion

This is the first study comparing two systems of organization of stroke care. Patients treated with EVT after IVT failure admitted directly to a CSC had significantly shorter onset-to-start of EVT time and onset-to-recanalization time than patients treated with IVT in a PSC and transferred subsequently to a CSC. However, this difference could have been even greater should the endovascular team be in-house in a “24/7” regimen. At present, CSC endovascular teams in the Czech Republic are contacted mostly by telephone [10,11]. When an occlusion of a major artery is diagnosed, CSC members are telephoned first; subsequently, it takes (on average) additional 40 min to start the procedure. This delay is eliminated in patients transferred from PSCs as the endovascular team arrives during the patient's transfer to a CSC. Clinical outcome was not significantly different between these two groups and a trend towards better results was observed in patients treated directly in a CSC only. Further shortening of the door-to-puncture time in a CSC seems to be essential and can show statistical significance but is limited mainly by human and economic resources. Nevertheless, the current two-level system in the Czech Republic shows that both ways, if well organized, are fully comparable, showing similar results in terms of reaching favorable clinical outcomes. Thus, the most suitable strategy (primary transport to a CSC or primary transport to a PSC with secondary transport to a CSC) should be chosen for a particular region depending on local conditions and ensuring that IVT does not delay EVT and vice versa.

Successful recanalization (TICI 2b–3) in different arterial territories was achieved in 54.5–78.6% of subjects in the CERBERUS, with the lowest prevalence being in VA+ occlusions and the highest being in MCA occlusions. Prevalence of reperfusion (TICI 2b–3) in the anterior circulation was achieved in 74% of patients, similarly to the results of randomized trials (72.4–88.0% [2–6]) and almost identically to a similar retrospective study using data from a Belgian registry (73%). Prevalence of recanalization achieved in strokes in the posterior circulation in the CERBERUS was lower than that achieved in the Belgian registry (71 vs. 100%) [12].

Patients who underwent EVT after IVT failure and patients contraindicated to IVT treated with EVT only did not differ significantly in terms of clinical outcome (mRS 0–2 in 46.3 vs. 47.0%) and SICH (6.5 vs. 4.0%). These percentages are similar to comparable groups in randomized clinical trials [2–6].

Prevalence of SICH was not significantly higher in patients treated directly in a CSC and varied in different regions from 0% (VA+) to 8.1% (ICA). In our study, SICH was more prevalent in the anterior circulation (6.2%) than in the posterior circulation (1.1%). These results differed from those obtained in the Belgian study (3 vs. 13%) [12]. Nevertheless, our finding is similar to that reported by Dornak et al., who found that in patients treated with IVT alone (not with EVT), prevalence of ICH was 17.2% in patients with stroke in the anterior circulation and 5.1% only in patients with a stroke in the posterior circulation. These findings could be due to: 1. lower lesion volume in infratentorial strokes and better collateral circulation in comparison to the MCA; 2. the brainstem is nourished with small-ended arteries [13].

Higher baseline blood glucose levels and longer DNT were identified as independent

Tab. 6. Predictors of good 90-day clinical outcome (modified Rankin scale 0–2).

	OR	95% CI		P value
age	0.977	0.964	0.989	**0.0004**
gender	1.139	0.813	1.596	0.450
arterial hypertension	0.651	0.440	0.964	**0.032**
diabetes mellitus	0.620	0.409	0.940	**0.024**
hyperlipidemia	1.660	1.174	2.349	**0.004**
body mass index	0.950	0.915	0.987	**0.009**
smoking	1.094	0.696	1.720	0.696
alcohol abuse	0.681	0.161	2.885	0.602
atrial fibrillation	0.619	0.433	0.884	0.008
previous TIA	1.723	0.481	6.175	0.404
previous stroke	0.926	0.540	1.588	0.781
previous use of antithrombotics	0.886	0.625	1.255	0.496
statin therapy started before or within 24 h after stroke onset	1.638	1.157	2.317	**0.005**
NIHSS baseline	0.865	0.835	0.896	**< 0.0001**
baseline systolic pressure	0.993	0.986	0.999	**0.018**
baseline diastolic pressure	0.992	0.980	1.003	0.140
baseline glucose level	0.882	0.825	0.942	**0.0002**
baseline cholesterol level	0.960	0.794	1.161	0.674
IVT administration	1.044	0.743	1.468	0.802
isolated ICA occlusion	1.921	1.021	3.617	**0.043**
procedure time	0.994	0.988	1.000	**0.045**
onset-to-recanalization time	1.000	0.999	1.001	0.964

CI – confidence interval; ICA – internal carotid artery; IVT – intravenous thrombolysis; NIHSS – National Institutes of Health Stroke Scale; OR – odds ratio; TIA – transient ischemic attack.

Tab. 7. Independent predictors of good 90-day clinical outcome (modified Rankin scale 0–2).

	OR	95% CI		P value
age	0.968	0.949	0.987	**0.001**
statin therapy started before or within 24 h after stroke onset	2.018	1.221	3.334	**0.006**
NIHSS baseline	0.873	0.831	0.916	**< 0.0001**
baseline glucose level	0.914	0.836	0.998	**0.045**
procedure time	0.992	0.985	1.000	**0.047**

CI – confidence interval; NIHSS – National Institutes of Health Stroke Scale; OR – odds ratio.

predictors of the risk of SICH in all patients in our study. In the study performed by Nogueira et al., independent predictors of hemorrhagic infarction included diabetes mellitus, pre-procedure IVT, MERCI thrombectomy and longer time-to-groin puncture [14]. Higher baseline NIHSS score and blood glucose level, right hemisphere stroke, ICA-MCA and T-type ICA occlusion were identified as independent negative predictors of malignant brain edema in our anterior circulation stroke patients. In comparison, concurrent involvement of the anterior cerebral artery, i.e. T-type ICA occlusion, was the only predictor of mortality in severe MCA stroke in the study by Walcott et al. [15]. No predictor of malignant brain edema was identified for posterior circulation stroke patients in our cohort.

In our study, older age, baseline NIHSS, baseline blood glucose level, and EVT duration were identified as independent negative predictors; a history of statin treatment was identified as an independent positive predictor of favorable clinical outcome. Ozdemir et al. found older age, blood glucose level, a higher Alberta Stroke Program Early CT (ASPECT) score, and longer onset-to-recanalization time to be negative predictors of favorable clinical outcome in anterior-circulation strokes [16]. These findings are consistent with our previous study in posterior-circulation strokes due to BA occlusion; higher NIHSS at the time of treatment, longer time to treatment and arterial hypertension were identified as independent negative predictors of favorable clinical outcome [17]. Likewise, the ASPECT score [18], older age, stroke severity and a history of diabetes mellitus were identified as negative predictors of good clinical outcome in posterior-circulation strokes [19].

Favorable clinical outcome (mRS 0–2) was identified in 33.3 (65.0%) of patients; the lowest proportion of patients with a positive outcome was observed in VA+ occlusions and the highest in isolated ICA siphon occlusions. In the CERBERUS, favorable clinical outcome in anterior-circulation strokes was achieved in 47.7% of patients compared to the results of randomized trials: 32% in MR CLEAN [3], 44% in REVASCAT [4], 53% in ESCAPE [5] and 60% in SWIFT PRIME [6]. Only patients with occlusions in large vessels were included but selection based on computed tomography perfusion (CTP) was not used routinely in the CERBERUS centers. Therefore, our results are almost identical with studies that did not use perfusion methods [3,12]. The EXTEND-IA trial, in which CTA/CTP was used for patient selection, showed higher prevalence of favorable clinical outcome (71%) [2].

Our study had several main limitations. First, there was no control group and thus the effect of EVT vs. IVT alone could not be assessed. Second, since the participating centers used individual EVT protocols, selection bias cannot be excluded. Third, unified imaging-based selection system was not used and no blinded evaluation of recanalization grade was performed. Fourth, there was no control CT scan performed immediately before EVT in patients transferred from a PSC to a CSC. Fifth, all data were collected prospectively but data on some predictive variables could have been missed. Sixth, no central evaluation of recanalization and outcome rates was performed. Finally, various methods or their combination (mostly percutaneous transluminal angioplasty with/without stenting) were used during the early years of EVT in the founding CERBERUS center (Ostrava), though results were fully comparable with those from clinical trials using stent retrievers exclusively [20].

Our study also had strengths. It was a multicenter assessment of clinical experience with EVT that elicited similar results to those from large randomized clinical trials. Hence, EVT can be considered to be efficient and safe in daily routine use in selected patients. Only patients with IVT failure and patients contraindicated to IVT were included. Thus, inclusion of patients with a favorable response to IVT (that could have influenced the results) was minimized.

Conclusion

We showed that EVT is effective and safe. It can be used routinely in selected patients with acute stroke and large-vessel occlusion and especially in those with IVT failure or a contraindication to IVT. The benefit of direct transfer to a CSC merits further investigation. The trend for better clinical outcome observed in patients treated directly in a CSC suggests that treatment should be in specialised centers with availability of all treatment options. However, this strategy could be region-specific depending on the density of PSCs and CSCs and the distances between them. Our study showed that in the Czech Republic both approaches are comparably effective and safe.

CERBERUS Study Group: Martin Kuliha, Michal Bar (Comprehensive Stroke Center, Department of Neurology, Faculty of Medicine, Ostrava University and University Hospital Ostrava, Czech Republic), Václav Procházka, Tomáš Jonszta, Daniel Czerný, Jan Krajča (Comprehensive Stroke Center, Department of Radiology, University Hospital Ostrava, Czech Republic), Eva Vítková, Jan Waishaupt (Comprehensive Stroke Center, Department of Neurology, Charles University Faculty of Medicine and University Hospital Hradec Králové, Czech Republic), Antonín Krajina, Miroslav Lojík, Jan Raupach, Ondřej Renc, Vendelín Chovanec (Comprehensive Stroke Center, Department of Radiology, Charles University Faculty of Medicine and University Hospital Hradec Králové, Czech Republic), Jiří Polívka, Petr Ševčík, Vladimir Rohan (Comprehensive Stroke Center, Department of Neurology, Faculty of Medicine Charles University and University Hospital Plzeň, Czech Republic), Vladimir Přibáň, Jan Mraček (Comprehensive Stroke Center, Department of Neurosurgery, Faculty of Medicine Charles University and University Hospital Plzeň, Czech Republic), Frantisek Šlauf, Vít Buriánek, Petr Duras (Comprehensive Stroke Center, Department of Radiology, Faculty of Medicine Charles University and University Hospital Plzeň, Czech Republic), Ivana Šarbochová, Aleš Tomek (Comprehensive Stroke Center, Department of Neurology, Faculty of Medicine Charles University and University Hospital Motol, Praha, Czech Republic), Miloslav Roček, Radek Pádr, Michal Polovinčák (Comprehensive Stroke Center, Department of Radiology, Faculty of Medicine Charles University and University Hospital Motol, Praha, Czech Republic), Daniel Václavík, Michal Kusyn (Stroke Center, Department of Neurology, Vítkovice Hospital, Ostrava, Czech Republic), Dušan Kučera (Stroke Center, Vascular Department, Vítkovice Hospital, Ostrava, Czech Republic), Jaroslav Krátký (Stroke Center, Department of Radiology, Vítkovice Hospital, Ostrava, Czech Republic), Roman Havlíček (Comprehensive Stroke Center, Department of Neurology, Military University Hospital, Prague, Czech Republic), Kateřina Langová (Department of Biophysics, Faculty of Medicine and Dentistry, Institute of Molecular and Translational Medicine, Palacký University Olomouc, Olomouc, Czech Republic).

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