

# Thrombolysis and thrombectomy as an effective treatment for ischemic cerebral circulation disorders

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**ABSTRACT.** The number of stroke cases has more than doubled worldwide over the past four decades, including in low- and middle-income countries. Therefore, understanding the present situation of acute ischemic stroke in Vietnam is an urgent theme. The number of stroke cases in Vietnam is correlated with and reflected in the number of thrombolysis and thrombectomies performed. To increase the effectiveness of stroke treatment, use of thrombolysis and thromboembolism alone are insufficient. New organizational models for emergency care and methodologies for identifying the first signs of stroke need to be developed. We conducted a retrospective study of reports from 29 clinics that used these two types of treatment in 2009-2017. In the 50 stroke units, departments, and stroke centers in Vietnam, about 640 beds are designed to potentially receive and treat a population of 93 million people. Among the 1145 patients who were treated with recombinant tissue plasminogen activator, they had a National Institutes of Health Stroke Score (NIHSS) medium score when admitted to the hospital: 14.1; modified Rankin Scale (mRS) post three months: mRS (0-1) was 52.2%, mRS (6 score) was 6.12%. Intracranial hemorrhage rate was 4.1%. Of the 269 patients treated with thrombectomy, the mean age was  $62.14 \pm 13.3$ ; NIHSS medium

score entreat admission to the hospital:  $16.2 \pm 7.85$ ; complete recanalization after treatment (TICI score 2b-3) was 60.3%. The rate of functional independence (90 day mRS score of 0 - 2) was 34.6%; the death rate was 17.9%; intracranial hemorrhage and symptomatic hemorrhage rate was 22.5% and 10.1%, respectively. Thrombolysis and thrombectomy are important treatments that can reduce disability (not mortality) in some patients after acute ischemic stroke; however, it is necessary to introduce higher quality and safe services. For this purpose, a better integrated approach to stroke care in Vietnam needs to be developed.

**Key words:** Acute ischemic stroke; NIHSS score; mRS score; Thrombolysis; Thrombectomy

## INTRODUCTION

Acute ischemic stroke (AIS) is an urgent problem of modern healthcare at the world level, since it is accompanied by high rates of mortality and disability as a result and complication of this pathology (Brott and Bogousslavsky, 2000; Mukherjee and Patil 2011; Leng and Xiong, 2019). This, in turn, leads to increased economic costs for individual states due to reduced performance or loss of performance in this category of patients (Van Exel et al., 2005; Dawson et al., 2007 Henriksson et al., 2010). Consequently, AIS is accompanied by significant clinical consequences, social and economic losses, which determines the urgency of the problem and justifies the need for significant theoretical and practical efforts and innovations, improvement of therapeutic, diagnostic and preventive measures for this disease (Deb et al., 2010). The share of AIS accounts for the largest number of cases of acute cerebrovascular accident - more than 85%.

Ischemic pathogenetically caused by sudden obstruction of blood vessels in the brain. Hemorrhagic stroke is observed in 10-15% of cases of acute cerebrovascular accident. The blood poured out of the vessel causes compression of the brain tissue, which, as a result, is the cause of subsequent complications. The current problem is the low awareness of the population about the causes of the clinical manifestations of stroke. Only a third of stroke patients are aware of a history of stroke (Leng and Xiong, 2019).

Immediate reperfusion is key to maintaining the integrity and function of the brain. Intravenous infusion of recombinant tissue plasminogen activator (rt-PA) and endovascular thrombectomy significantly improve the chances of recovery without subsequent disability, as proven in various studies (El Tawil and Muir, 2017). Thrombolysis is the first-line therapy if treatment is started within no more than 4.5 hours after the onset of symptoms. It should be borne in mind that the positive effect of alteplase correlates with the time from the onset of the first symptoms, therefore, the need for early use of thrombolytic therapy is obvious. Alteplase should be used even if further mechanical thrombectomy is possible (Molina and Saver, 2005; Prabhakaran et al., 2015). However, the frequency of recanalization with rt-PA is rather low, especially in occlusion of large vessels: 14% for the internal carotid artery and 55% for occlusion of the middle cerebral artery. (Balami et al., 2015). The use of rt-PA is also associated with a significant number of side effects and

contraindications (Wijdicks et al., 2006). In addition, the latter technique necessarily requires early application after the onset of symptoms (Wang et al., 2015).

Endovascular thrombectomy is considered an alternative to thrombolysis and has a high level of evidence base. However, two issues may limit the widespread clinical use of mechanical thrombectomy. First, only an estimated 10% of patients with AIS have a proximal large artery occlusion in the anterior circulation and present early enough to qualify for mechanical thrombectomy within 6 hours, while approximately 9% of patients presenting in the 6-to-24-hour time window may qualify for mechanical thrombectomy. Second, only a few stroke centers have sufficient resources and expertise to deliver this therapy (Palaniswami and Yan, 2015; Alawieh et al., 2018; Watanabe et al., 2019). The result of a number of studies demonstrates a clear advantage of the combined use of mechanical thrombectomy using a stent retriever in combination with pharmacological thrombolysis, especially in occlusion of large cerebral vessels and their branches (Guedin et al., 2015; Coutinho et al., 2017).

According to statistics, the level of disability and mortality from AIS is steadily increasing in countries with an unstable economic situation, with low and middle income (Nguyen et al., 2010; Tirschwell et al., 2012; Pham et al., 2016). According to data provided by the World Health Organization, by 2030, noncommunicable diseases could be the cause of 75% of total global deaths (World Health Organization, 2005). Over the past 40 years, the incidence and mortality rates from AIS in developed countries have decreased by 42%, while in low- and middle-income countries, the corresponding rates have more than doubled (Avan et al., 2019). Nearly 90% of all AIS deaths occur in low- and middle-income countries (Strong et al., 2007). Considering all of the above, the aim of this study was to analyze the current situation in the treatment of AIS using thrombolysis, as well as thrombectomy methods and / or their combination in Vietnam.

## **MATERIAL AND METHODS**

### **Subjects**

We included 1145 patients given rt-PA (doses 0.9 and 0.6 mg/kg body weight) and 269 patients treated with rt-PA and then had thromboectomy from 2009 –2017. The study was approved by our institutional ethics in human research committee.

### **Methods**

According to the meta-analysis of the statistical reports of hospitals using these two treatments, the results obtained are averaged and a percentage. The data were analyzed using statistical methods, SPSS version 22, EZR version 1.38. To present the typical result for nominal qualitative variables, the mode of indicators, interval estimation of dichotomous variables, were used. When making multiple comparisons between groups, we used the Chi-square test with Bonferroni correction.

## **RESULTS AND DISCUSSION**

Currently, there are about 50 centers, departments and units with about 650 beds in Vietnam for this type of patient (Table 1). By region of the country: North: 360 beds / 23

units, Middle: 70 beds / 7 units, and South: 220 beds / 16 units. This is 2.5 times less than in first-world countries, such as the UK (Table 2). In Vietnam, there are only 9 centers that can apply intervention therapy with the total budget per patient from USD 3000-4300. In addition, about 1000 - 1100 cases of AIS were treated during two years, which is in more than two times higher than in the UK.

**Table 1.** Stroke specialized units in Vietnam.

Hospital	Type of center	Number of beds per center
Bach Mai Hospital; 103 Army Hospital (stroke department)	Stroke unit	40
108 Military Central Hospital	Stroke center	55
Thai Nguyen National Hospital; Cho Ray Hospital; Phu Tho General Hospital	Stroke center	20
115 People's Hospital	Stroke department	70
Bac Ninh General Hospital; Quang Ninh General Hospital; An Binh Hospital; Cao Bang General Hospital; Gia Dinh People Hospital; Ha Giang General Hospital; Thong Nhat Hospital; Tuyen Quang General Hospital; Nguyen Tri Phuong Hospital; Vinh Phuc General Hospital; Trieu An Hospital; Nghe An General Hospital; Ninh Binh General Hospital; 105 Army Hospital; Trung Vuong Hospital; Thanh Hoa General Hospital; Friendship Hospital; 175 Army Hospital; Ngoc Lac General Hospital; Hue Central Hospital; Thu Duc General Hospital; Ha Nam General Hospital; Da Nang General Hospital; Dong Nai General Hospital; Hung Yen General Hospital; National hospital of obstetrics and gynecology; Tien Giang General Hospital; Viet Tiep General Hospital; 17 Army Hospital; Can Tho General Hospital; Thai Binh General Hospital; Quang Nam General Hospital; Ho Chi Minh City University of Medicine and Pharmacy; Bac Giang General Hospital; Quy Nhon General Hospital; An Giang General Hospital; Lang Son General Hospital	Stroke unit	10
Ninh Binh General Hospital		

A total of 1145 patients were enrolled in eight centers for thrombolysis treatment and 269 patients in six centers for combining therapy (thrombolysis and thromboectomy) from June 2009 to October 2017 and constitute the study population. Table 3 shows their baseline demographic characteristics and time-to-treatment. Patients undergoing thrombectomy in combination with an intravenous thrombolysis, were, on average, older and they had more often hypertension, hyperlipidemia, and previous stroke, and more often atrial fibrillation.

The largest differences between groups involved stroke severity (NIHSS score) and vessel occlusion location. Patients in the thrombectomy groups had greater symptom severity and had internal carotid and M1 segment middle cerebral artery occlusions more frequently. Time to intravenous thrombolysis was not different between patients with an additional thrombectomy compared to those without.

On the 1145 patients, treated rt-PA had NIHSS medium score to enter hospital: 14.1; mRS post three months: mRS (0-1) was 52.2 %, mRS (6 score) was 6.12 %.

**Table 2.** Current situation of thrombotic interventions in Vietnam and the United Kingdom (UK) National Institute for Health and Care Excellence Guideline (2016).

Vietnam	UK
About 50 centers, departments and units with about 650 beds	About 120 stroke centers
Nine hospitals that can intervene (108 Military Central Hospital, Bach Mai Hospital, 103 Army Hospital, Phu Tho General Hospital, Hue Central Hospital, 115 People's Hospital, Cho Ray hospital, Ho Chi Minh City University of Medicine and Pharmacy, Can Tho General Hospital)	24 centers that can intervene
Total of 20 intervention centers nationwide	Total of 82 intervention centers across the UK (2 in Scotland and 1 in Wales)
Budget for intervention has not been set yet, depending on the patient, on average each case (from USD 3000-4300)	Budget for interventions through the Ministry of Health has been agreed since April 2017 - around £ 12,000 per case (VND 350 million)
About 1000 - 1100 cases performed in 2 years (V115: 500; BV108: 200, Bach Mai: 200; DRH: 34; Cho Ray: 40; V103: 10; Phu Tho: 6)	500 cases were performed in 2016 - 2017

**Table 3.** The results of treatment of venous thromboembolism (via rt-PA).

Hospital	No. Of patients	NIHSS score admission times after 3 months		mRS score (after 90 days)				Complications bleeding	
				0 - 1	2 - 3	4 - 5	6	Yes	No
115 People's Hospital: (6/2009 - 3/2011) (1/2011 - 4/2012)*	152 /96*	12.8	8.02	56.2			6.3	4.6 /3.1	2.6 /12.5
108 Military Central Hospital: (2016 - 2017)	50	14.5± 5	6.0±4	57.0				4.3	3.0
103 Army Hospital: (6/2016 - 6/2017)1	316	15.4 ± 6	6.1 ± 3	46.1	29.5	18.1	6.4	6.7/5.7	10.2
Phu Tho General Hospital: (9/2015 - 10/2017) (the first 6 months of 2017)*	220/58*			57.4			3.2	3.8	10.0
Thanh Hoa General Hospital: (5/2011 - 9/2017)	110			52.0	24.0	14.0	10.0	2.0	2.0
Viet Tiep Hospital: (1/2012 - 6/2016)	112			41.9	26.8	25.9	5.36	5.3	
Thai Nguyen National Hospital: (1 - 7/2017)	18			61.0	22.2	11.3	5.6		
Bach Mai Hospital: (1/2015- 9/2016)2	61			50.9	34.4	8.2	6.0	3.3	11.5

<sup>1</sup>rt-PA: 0.6 - 62 patient; rt-PA: 0.9 - 31 patient; <sup>2</sup>rt-PA: 0.6.

Intracranial hemorrhage rate was 4.1 %. On the 269 patients treated thromboectomy, the mean age was  $62.14 \pm 13.3$ ; NIHSS medium score to enter hospital:  $16.2 \pm 7.85$ ; complete recanalization after treatment (TICI score 2b-3) was 60.3 %. The rate of functional independence (90 day mRS score of 0 - 2) was 34.6 %; the death rate was 17.9 %; intracranial hemorrhage and symptomatic hemorrhage rate was 22.5 % and 10.1 %.

In both methods of treatment (thrombolysis treatment and combining therapy - thrombolysis and thromboectomy) complications bleeding was observed. In case of thrombolysis this factor was 4.6%, where at combining therapy – 22.5%. In addition, at rt-PA + thromboectomy therapy other complications such as recurrent embolism was ocured.

**Table 4.** Treatment of thrombolytic method combined with thrombolysis.

Hospital	No. Of patie	The average	NIHSS score admission	complete recanalization		mRS (3 months)		Died, (%)	Complications (%)		
				TIC 1 2b/3	TIC 1 0-2	0 - 2	3 - 5		A1	B2	C3
108 Military Central Hospital (7/2016 - 6/2017); rt-PA:6/138=18.9 %	138	61.7 ± 12.7	46.7 discharge: 55.8	79.7	20.3	58.7	41.3	18.1	18.8 (10.1)	5.1	7.9
108 Military Central Hospital (1/2014 - 8/2017); rt-PA:4/27 = 14.8 %	27/ 341	64.7 ±13.2	16.6 ± 4.9	88.9	12.1	58.7	41.3	11.1	0	0	0
115 People's Hospital(4/2012 - 3/2013); rt-PA: 21/36 = 58.3%	36	61.5± 13.8	17.8±5.5	33.3 TI MI:3	55.6 TI MI > 2	55.6	44.4	16.7	36.1(11.1)		
115 People's Hospital and Nghe An General Hospital: (6/2016 - 4/2017); rt-PA:43/43 = 10 0%	43	57. 5 ± 15. 4	14.4±4.5	83.7	16.3	55.6	44.4	25.6	34.9		
Bach Mai Hospital: (6/2015 - 5/2016); rt-PA:25/25 = 10 0%	25	62.3 ± 114	16.0 (10-23)	16.0	84.0	44.2	55.8	N			
Mean	269	62.14 ± 133	16.2 ± 7.85	60.3	37.7	34.6	45.4	17.9	22.5		

## CONCLUSIONS

To optimize the diagnosis and treatment of acute cerebrovascular accidents in Vietnam, it will be necessary to develop and improve algorithms for providing emergency care. Only a small proportion of patients with appropriate indications receive thrombolytic therapy in a timely manner, which is due, among other things, to a low level of patient awareness of the symptoms of stroke and imperfect algorithms for first aid. The use of various innovative approaches to the diagnosis and treatment of strokes turned out to be ineffective, which shows the relevance of research and the need for new techniques in this area.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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