

5 **Thrombolysis and thrombectomy for the treatment of acute** 6 **ischemic stroke in Vietnam** 7

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13 **Abstract.** Over the past four decades age-adjusted population-based stroke incidence rates in low and
14 middle-income countries increased more than 100%, constituting an epidemic. Therefore, initial
15 establishment the results and present situation on the treatment of the acute ischemic stroke in Vietnam
16 is an urgent theme. On the number of some stroke unit in Vietnam treated thrombolysis and
17 thrombectomy. On the 50 of stroke unit, department, stroke center in Vietnam about 640 beds / 93
18 millionaire people (North: 360 beds/23 unit; Middle: 70 beds/7 unit; South: 220 beds / 16 unit). On the
19 1145 patients, treated rt-PA had NIHSS medium score to enter hospital: 14.1; mRS post three months:
20 mRS (0-1) was 52.2%, mRS (6 score) was 6.12 %. Intracranial hemorrhage rate was 4.1 %. On the 269
21 patients treated thromboectomy, the mean age was 62.14 ± 13.3 ; NIHSS medium score to enter
22 hospital: 16.2 ± 7.85 ; complete recanalization after treatment (TICI score 2b-3) was 60.3 %. The rate of
23 functional independence (90 day mRS score of 0 - 2) was 34.6 %; the death rate was 17.9 %; intracranial
24 hemorrhage and symptomatic hemorrhage rate was 22.5 % and 10.1 %. Thrombolysis and
25 thrombectomy are important treatments, it will reduce disability (not mortality) in some patients after
26 acute ischemic stroke, but to take particular by specialize and it is better to take time introducing high
27 quality safe services. For this purpose, a better network approach to stroke care in Vietnam needs to be
28 developed.
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30 **Key words:** acute ischemic stroke; NIHSS score; mRS score; thrombolysis; thrombectomy.

32 INTRODUCTION

33
34 Acute ischemic stroke (AIS) exacts a heavy toll in death and disability
35 worldwide. Nowadays, AIS is one of the most devastating neurological diseases,
36 which imposes an enormous burden on the society (Lengand Xiong, 2019; Brottand
37 Bogousslavsky, 2000; Mukherjee and Patil, 2011). It is resulting in decreased quality
38 of life, mortality, increased burden of informal caregivers and high costs to the society
39 (Dewilde et al., 2014; Henriksson et al., 2010; Van Exel et al., 2005; Dawson et al.,
40 2007). It has enormous clinical, social, and economic implications and demands a
41 significant effort from both basic scientists and clinicians in the quest for
42 understanding the underlying pathogenic mechanisms, and thereby adopting suitable
43 preventive measures and successful therapies (Deb et al., 2010).

44 There are two major types of stroke. The most common one is the ischemic
45 stroke, which accounts for ~ 85% of the total stroke cases. It occurs as a result of an
46 obstruction within a blood vessel leading to or within the brain. Another major type of
47 stroke is the hemorrhagic stroke, which accounts for 10%–15% of the total stroke
48 cases. It results from a weakened blood vessel that ruptures and bleeds in the brain.
49 The blood then accumulates and compresses the surrounding brain tissue, resulting in
50 brain damage. Unfortunately, only about one third of patients who are having a stroke
51 are aware of its symptoms, and most bystanders are not knowledgeable about the
52 signs of stroke. When symptoms or signs are recognized, emergency medical services
53 should be notified (Lengand Xiong, 2019).

54 Brain tissue may be rescued if blood flow is restored rapidly after the onset of
55 AIS. Intravenous recombinant tissue plasminogen activator (rt-PA) and, since 2015,
56 endovascular thrombectomy using stent retrievers can significantly improve the odds
57 of disability free recovery (El Tawil and Muir, 2017). For patients with AIS
58 intravenous alteplase (recombinant tissue plasminogen activator or tPA) is first-line
59 therapy, provided that treatment is initiated within 4.5 hours of clearly defined
60 symptom onset. Because the benefit of alteplase is time dependent, it is critical to treat
61 patients as quickly as possible. Eligible patients should receive intravenous alteplase
62 without delay even if mechanical thrombectomy is being considered (Molina and
63 Saver, 2005; Prabhakaran et al., 2015). However, recanalization rates with rt-PA are
64 usually low, particularly for major vessel occlusion. Previous studies has
65 demonstrated recanalization rates as low as 14% for internal carotid artery and 55%
66 for middle cerebral artery occlusions. Similarly, a systematic review reported a
67 recanalization rate of only 10–15% for major artery occlusions and a 20–40% success
68 rate in a cohort of AIS patients treated with rtPA thrombolysis (Balami et al., 2015).
69 In addition, because of various limitations and potentially severe side effects, the use
70 of rt-PA had very strict inclusion criteria (Wijdicks et al., 2006). For example, it
71 needed to be administered early after symptom onset, often failed to break up large
72 clots, and could cause uncontrolled bleeding in the brain (Wang et al., 2015).

73 Besides thrombolysis, for years, scientists have considered mechanical removal
74 of the clot, a procedure termed endovascular thrombectomy, for patients not eligible
75 for tPA treatment, particularly those who came to hospitals beyond the time window
76 for tPA. However, two issues may limit the widespread clinical use of

77 mechanical thrombectomy. First, only an estimated 10% of patients with AIS have a
78 proximal large artery occlusion in the anterior circulation and present early enough to
79 qualify for mechanical thrombectomy within 6 hours, while approximately 9% of
80 patients presenting in the 6 to 24 hour time window may qualify for mechanical
81 thrombectomy. Second, only a few stroke centers have sufficient resources and
82 expertise to deliver this therapy (Alawieh et al., 2018; Palaniswami and Yan, 2015;
83 Watanabe et al., 2019). Simultaneously, previous investigations clearly reveals that
84 that mechanical thrombectomy with a stent retriever in combination with intravenous
85 thrombolysis is superior in patients experiencing AIS caused by large vessel
86 occlusion in the anterior circulation (Coutinho et al., 2017; Guedin et al., 2015).

87 As low and middle-income countries, such as Vietnam, experience the health
88 transition to chronic diseases, the morbidity and mortality from stroke will rise (Victor
89 et al., 2019; Tirschwell et al., 2012; Pham et al., 2016; Nguyen et al., 2010).
90 According to the World Health Organization by 2030, non-communicable diseases
91 will contribute to three quarters of all deaths worldwide (World Health Organization,
92 2005). Over the past four decades, age-adjusted population-based stroke incidence
93 rates in high-income countries decreased by 42% whereas the rates in low and middle-
94 income countries increased more than 100%, constituting an epidemic (Avan et al.,
95 2019). Additionally, of the
96 estimated 5.7 million global stroke deaths in 2005, 87% occurred in low and middle-
97 income countries (Strong et al., 2007). Based on the above consideration, the aim of
98 this study was to review present situation on the treatment of AIS via thrombolysis as
99 well as thrombectomy methods and/or their combination in Vietnam.

100 MATERIAL AND METHODS

101 Subjects

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103 Including 1145 BN given rt-PA (dose 0.9 and 0.6 mg/kg body weight) and 269
104 patients treated with rt-PA then removed thromboectomy in 2009 – 10 October 2017.

105 Methods

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107 According to the meta-analysis of the statistical reports of hospitals using these
108 two treatments, the results obtained are averaged and a percentage.

109 RESULTS AND DISCUSSION

110
111 There are about 50 centers, department and units with about 650 beds in
112 Vietnam for today (Table 1). They spread through the country as: North: 360 beds /
113 23 unit, Middle: 70 beds / 7 unit and South: 220 beds / 16 unit. It is in 2.5 times less
114 comparing with, for example, UK situation (Table 2). In Vietnam only 9 centers that
115 col apply intervene therapy with the total budget from VND 70 - 100 million. I
116 addition, about 1000 - 1100 cases of AIS performed in 2 years, that is in more than 2
117 times more comparing with UK.

122 A total of 1145 patients were enrolled in 8 centers for thrombolysis treatment
 123 and 269 patients in 6 centers for combining therapy (thrombolysis and
 124 thromboectomy) from June 2009 to October 2017 and constitute the study population.
 125 Table 3 shows their baseline demographic characteristics and time-to-treatment.
 126 Patients undergoing thrombectomy in combination with an intravenous thrombolysis,
 127 were, on average, older and they had more often hypertension, hyperlipidemia, and
 128 previous stroke but more often atrial fibrillation.

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Table 1. Amount of 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

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NinhBinh General Hospital	Stroke department	15
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133 The largest differences between groups were observed for stroke severity
 134 (NIHSS score) and location of vessel occlusion. Patients in the thrombectomy groups
 135 had higher symptom severity and more often internal carotid and M1 segment middle
 136 cerebral artery occlusions. Time to intravenous thrombolysis did not differ between
 137 patients with and without an additional thrombectomy.

138 On the 1145 patients, treated rt-PA had NIHSS medium score to enter hospital:
 139 14.1; mRS post three months: mRS (0-1) was 52.2 %, mRS (6 score) was 6.12 %.
 140 Intracranial hemorrhage rate was 4.1 %. On the 269 patients treated thromboectomy,
 141 the mean age was 62.14 ± 13.3 ; NIHSS medium score to enter hospital: 16.2 ± 7.85 ;
 142 complete recanalization after treatment (TICI score 2b-3) was 60.3 %. The rate of
 143 functional independence (90 daymRS score of 0 - 2) was 34.6 %; the death rate was
 144 17.9 %; intracranial hemorrhage and symptomatic hemorrhage rate was 22.5 % and
 145 10.1 %.

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147 Table 2. Actual situation of thrombotic interventions in Vietnam and the UK

Vietnam	UK
About 50 centers, department and units with about 650 beds	About 120 stroke centers
9 hospital 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 interventions nationwide	Total of 82 interventions 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 VND 70 - 100 million)	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; PhuTho: 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		mRS score (after 90 days)				Complications bleeding	
		admission times	after 3 months	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
PhuTho 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	5.3 6	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

Mean	1145	14.1	7.06	52. 2	27. 4	15. 5	6.1 2	4.1 1	7.8
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¹rt-PA: 0.6 - 62 patient; rt-PA: 0.9 - 31 patient; ²rt-PA: 0.6.

In both methods of treatment 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 occurred.

Table 4. Treatment of thrombolytic method combined with thrombolysis

Hospital	No. of patients	The average age	NIHSS score	complete recanalization		mRS (3 months)		Dead, (%)	Complications (%)		
				admission	TICI 2b/3	TICI 0-2	0-2		3-5	A1	B2
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	43	57.5 ± 15.	14.4 ± 4.5	83.7	16.3	55.6	44.4	25.6	34.9		

General Hospital: (6/2016 - 4/2017); rt-PA:43/43 = 100%		4								
Bach Mai Hospital: (6/2015 - 5/2016); rt-PA:25/25 = 100%	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	

158 ¹ complications bleeding; ² recurrent embolism; ³ other

159 CONCLUSION

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161 To improve and facilitate acute stroke treatment new organizational models for
162 acute care should be developed in Vietnam. Only small part of eligible patients
163 receive a thrombolytic therapy, however, 25% may be attained in optimized settings.
164 This reflects considerable under treatment, which is directly related to patient
165 unawareness (e.g. unfamiliarity with stroke symptoms and how to act), delayed
166 hospital arrival, inefficient organizations of hospital stroke services, the narrow
167 therapeutic time window, and skepticism among physicians about the scientific
168 evidence of rt-PA treatment such as emergency physicians. Apparently, integration of
169 individual services into coordinated stroke care systems has proven difficult leading to
170 suboptimal treatment and inefficient use of resources. Implementing all-inclusive
171 organizational models for efficient delivery of acute stroke care requires long term
172 and broad commitment. Typically, they build on the cooperation between various
173 organizations, dedicated staff, and specific resources.

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179 180 CONFLICTS OF INTERESTS

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The authors declare no conflict of interests.

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