Arch Neurosci. 2016 January; 3(1): e30452. doi: 10.5812/archneurosci.30452

Published online 2016 January 16. **Review Article**

Tissue Plasminogen Activator: A Literature Review

Alireza Baratloo,[1] Mohammad Mehdi Forouzanfar,[1,*] Behrooz Hashemi,[1] Saeed Safari,[1] Hosein Delavar Kasmaei,[2] Alaleh Rouhipour,[3] and Ahmed Negida[4]

[1]Department of Emergency Medicine, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[2]Department of Neurology, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[3]Department of Pediatric, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[4]Faculty of Medicine, Zagazig University, Zagazig, Egypt

*Corresponding author: Mohammad Mehdi Forouzanfar, Department of Emergency Medicine, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-9123708649, Fax: +98-2122721155, E-mail: drfrouzanfar@yahoo.com

Received 2015 June 1; **Accepted** 2015 July 13.

Abstract

Context: The production of thrombolytic agents started in 1930s and thrombolytic therapy for stroke began in 1958, on a case by case basis, and, in 1963, a small trial performed.

Evidence Acquisition: Intravenous tissue plasminogen activator (t-PA) was recognized and approved as the thrombolytic agent for acute ischemic stroke that can improve patients' outcome and resolve their neurological deficits. The main reason for the difficulty of stroke treatment is the narrow time window, which leads to a small proportion of eligible patients to be treated with t-PA. The cost-effectiveness and feasibility of intravenous t-PA for treatment of acute stroke in 3 - 4.5 hour time window, after symptom onset, have been confirmed in previous studies.

Results: Data about thrombolytic therapy, at the national level, are scarce in Asia and developing countries, compared to developed world. Thrombolytic therapy using t-PA is used in few low-income countries, including Iran. According to estimations of Iranian stroke patients, eligible for thrombolysis therapy, only 30% of Iranian stroke patients received t-PA.

Conclusions: The high cost of t-PA and lack of appropriate infrastructure are the main barriers for thrombolytic therapy, in developing countries like Iran. On the other hand, most stroke units and centers, which have the infrastructure to deliver thrombolysis, are predominantly available only in large urban areas.

Keywords: Fibrinolytic Agents, Stroke, Iran, Tissue Plasminogen Activator, Thrombolytic Therapy

1. Context

1.1. Brief History of Tissue Plasminogen Activator Production and Use

The production of thrombolytic agents started in 1930s and continued until 1979, when tissue plasminogen activator (t-PA) was purified by Collen and colleagues from the human melanoma cell culture (1-3). Thrombolytic therapy for stroke began in 1958, on a case by case basis, and, in 1963, a small trial was performed. In order to find the appropriate t-PA dose, additional trials were conducted in 1980 (4). In 1983, it became possible to produce recombinant t-PA (rt-PA) by expression of a cloned gene, which opened the door for clinical trials to start, mainly for coronary thrombolysis (5). In 1990, Terashi and coworkers performed the first rt-PA clinical trial, on 364 patients, with acute ischemic stroke (6). In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study claimed that rt-PA was an effective treatment for acute ischemic cerebrovascular accident (CVA), if started in less than 3 hours after symptoms onset (7, 8). In 1996, the food and drug administration (FDA) approved intravenous t-PA. Thereafter, thrombolytic therapy became the worldwide approved treatment option for acute ischemic stroke (9, 10). Nowadays, in addition to acute ischemic stroke, thrombolytic therapy is considered a treatment option for acute myocardial infarction. Furthermore, studies have indicated the use of t-PA in acute renal artery thrombosis (11), cerebral venous thrombosis and other type of venous thromboembolism (12-15).

2. Evidence Acquisition

2.1. Tissue Plasminogen Activator in Stroke: Dosage and Time Window

Intravenous t-PA was recognized as the approved thrombolytic agent for acute ischemic stroke that can

improve patients' outcome and resolve their neurological deficits. The main reason for the difficulty of stroke treatment is the narrow time window, which leads to a small proportion of eligible patients to be treated with t-PA (16). The first clinical application of t-PA, with the aim of dose verification, mechanism of action, and safety profile, in stroke thrombolysis, began in early 1990s. Then, large randomized, placebo-controlled, double-blinded trials tested the safety and efficacy of t-PA, in acute ischemic stroke. Studies like ATLANTIS A and B (Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke), and ECASS-1 and -2 (European Cooperative Acute Stroke Study) are several of the famous studies that have challenged the proper dose, efficacy, side effects and cost-effectiveness of intravenous t-PA, for treatment of acute stroke (Table 1) (17-20).

Results of the literature review on 15 articles, regarding t-PA and stroke, published in 2012, suggested that intravenous thrombolysis using t-PA can be applied, as an effective treatment, by using 0.9 mg/kg up to 4.5 hours from stroke onset, when infused under good conditions, and emergency medicine physicians play a crucial role in this process (26-29).

3. Results

3.1. Profits and Possible Side Effects of Tissue Plasminogen Activator

The cost-effectiveness and feasibility of intravenous t-PA, for the treatment of acute stroke in 3 - 4.5 hour time window, after symptom onset, have been proved in previous studies (17-19, 30-32). A published systematic review and meta-analysis have found an overall 46% recanalization rate, with intravenous t-PA (33). In a cost effectiveness study, thrombolytic therapy was compared with medical therapy, without t-PA; the quality-adjusted life-years (QALYs), as a measurement for health benefits, was balanced with the cost of intravenous t-PA in 3 to 4.5 hour time window (17). The budget impact analysis, based on stroke incidence rates and the impact of thrombolysis on society's health, showed that thrombolysis improve society's health, although the quality of life may have a stronger association with age, sex, level of education and post-stroke duration (34-36). The most serious complication of rt-PA thrombolytic therapy is intracranial hemorrhage (ICH) (16). Based on NINDS trials, ICH could be categorized in two groups: 1) symptomatic ICH, documented with computed tomography (CT) and associated with clinical deterioration; 2) ICH with CT finding and no clinical deterioration (9). To decrease the risk of ICH, t-PA protocols have been developed by the American Heart Association, American Stroke Association (ASA), American Academy of Neurology, NINDS and recently by the American College of Emergency Physicians (37). According to previously published reports, racial differences in blood coagulation and fibrinolytic factors are the main causes of ICH among Asians, which affects the cost and advantages of thrombolysis therapy (38). Monitoring the administrated t-PA plays a critical role in appropriate treatment of patient with ischemic stroke. The American Academy of Neurology and the Stroke Council of the American Heart Association recommend neurological assessments and blood pressure monitoring. It is also suggested that the monitoring should be performed every 15 minutes, for 2 hours, every 30 minutes, for 6 hours, and every 60 minutes, until 24 hours after beginning the t-PA treatment (39).

3.2. Tissue Plasminogen Activator in Developing Countries

Data about thrombolytic therapy, at the national level, are scarce in Asia and developing countries, compared to the developed world. The Indian Stroke Epidemiology Study reported that intravenous and intra-arterial thrombolysis is commonly used in India; also, according to the ongoing Indo-USA national stroke registry, the rate of intravenous thrombolysis is 11% (40). In the study performed in south India, they reported that from the 30% of patients, who were referred within 3 hours after stroke onset, only 16% were eligible for intravenous thrombolysis with t-PA. However, they could not afford to pay the cost. More importantly, stroke rehabilitation services are only available in the private hospitals of the cities (40, 41). Findings of a cross-sectional study in Taiwan, regarding thrombolytic therapy for acute CVA, from 2003 through 2010, showed that of the 394988 patients with CVA, 2385 (0.60%) had received thrombolytic therapy, and that the utilization of t-PA increased from 0.03%, in 2003, to 1.51%, in 2010 (40).

In South Africa, the stroke services and units are available at hospitals of both the public and private sectors (42). Evaluation of all stroke patients receiving t-PA for thrombolysis in South Africa, between January 2000 and February 2011, showed that there were similar safety and early efficacy outcomes, compared to the developed and other developing countries (43).

3.3. Specific Obstacles of Tissue Plasminogen Activator Use in Iran

Thrombolytic therapy, using t-PA, is used in few low-income countries, including Iran (38). Based on the studies performed by Ghandehari et al. the resources and infrastructure for thrombolysis of stroke patients exist in approximately 14 hospitals, in Iran, which cover less than one third of Iranian stroke patients (38, 44). According to estimations of Iranian stroke patients, eligible for thrombolysis therapy, only 30% of Iranian stroke patients received t-PA (44). There are several obstacles towards t-PA use, such as prehospital barriers,

financial constraints, lack of infrastructure and low levels of public information (38). The high cost of t-PA and lack of appropriate infrastructure are the main barriers for thrombolytic therapy, in developing countries like Iran. On the other hand, most stroke units and centers, which have the infrastructure to deliver thrombolysis, are predominantly available in urban areas of big cities (38, 45). Lack of coverage for t-PA treatment of stroke patients, in the Iranian health insurance system, has been supposed as one of the most important barrier of thrombolytic therapy (44). Several of the Iranian centers that use intravenous t-PA in stroke patients are the Neurology Department of Firoozgar Hospital, Tehran, Iran and the Emergency Department of Shohadaye Tajrish Hospital, Tehran, Iran.

Results of a pilot study (Part I in 2009) of intravenous t-PA, in CVA Iranian patients, showed that only 30% of eligible patients were capable of paying the t-PA vial, by themselves, and 86% of eligible patients missed thrombolytic therapy, due to delay in diagnosis, if t-PA was free of charge (44, 46). In part II of the same study (2010 - 2013), in which eligible patients were treated with intravenous t-PA, based on the ASA guidelines and using the established stroke code to prevent delay in diagnosis and triage, there was a 62% recovery rate for patients treated with t-PA (47). Part III of the study (2013) investigated the problems and limitations of intravenous t-PA (38, 44, 46).

Table 1. Summary of the Early Large Randomized Controlled Trials of Tissue Plasminogen Activator[a]

Study	Reference	Year	Number of Patients	Dose, mg/kg IV	Time Window, h	Findings
ATLANTIS-A	(21)	1993	142	0.9	(0 - 6)	This trial stopped due to increased rate of symptomatic ICH in the 5 - 6 hour time window from stroke onset.
ATLANTIS-B	(22)	1996	613	0.9	(0 - 5)	There was no significant rt-PA benefit on the 90-day efficacy end points in patients treated between 3 and 5 hours. The risk of symptomatic ICH increased with rt-PA treatment.
NINDS t-PA	(23)	1995	P.1 = 291, P.2 = 333	0.9	(0 - 3)	Treatment with intravenous t-PA, within 3 hours of the onset of ischemic stroke, improved clinical outcome at 3 months.
ECASS-I	(24)	1995	620	1.1	(0 - 6)	In this trial, 1.1 mg/kg dose was effective for the subgroup of stroke patients, with moderate to severe neurologic deficit and without extended infarct signs, on the initial CT scan. The risk of treating ineligible patients is associated with increase of hemorrhagic complications and death.
ECASS-II	(25)	1998	800	0.9	(0 - 6)	This trial should set a trend towards efficacy, although ICH up to 7 days was observed.
ECASS-III	(26)	2000	821	0.9	(3 - 4.5)	In this trial, rt-PA improved clinical outcomes, in patients with acute ischemic stroke, treated between 3 and 4.5 hours.

[a]Abbreviations: ATLANTIS: alteplase thrombolysis for acute non-interventional therapy in ischemic stroke; CT, computed tomography; ECASS: European cooperative acute stroke study; ICH, intracerebral hemorrhage; NINDS: National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator.

4. Conclusions

Understanding these obstacles will help in finding solutions to meet them and provide the necessary infrastructures in this regard. Solving these problems will certainly help to improve the quality of life, in patients with stroke.

Acknowledgments

We would like to express our special thanks to the Emergency Department Shohadaye Tajrish Hospital staff.

Footnote

Authors' Contributions: All the authors have contributed to drafting/revising the manuscript, study concept, or design, as well as data interpretation.

References

1. Rother J, Ford GA, Thijs VN. Thrombolytics in acute ischaemic stroke: historical perspective and future opportunities. *Cerebrovasc Dis.* 2013;**35**(4):313–9. doi: 10.1159/000348705. [PubMed: 23615379]
2. Collen D, Lijnen HR. Tissue-type plasminogen activator: a historical perspective and personal account. *J Thromb Haemost.* 2004;**2**(4):541–6. doi: 10.1111/j.1538-7933.2004.00645.x. [PubMed: 15102005]
3. Rijken DC, Collen D. Purification and characterization of the plasminogen activator secreted by human melanoma cells in culture. *J Biol Chem.* 1981;**256**(13):7035–41. [PubMed: 6787058]
4. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study I. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ.* 2005;**172**(10):1307–12. doi: 10.1503/cmaj.1041561. [PubMed: 15883405]
5. Van de Werf F, Ludbrook PA, Bergmann SR, Tiefenbrunn AJ, Fox KA, de Geest H, et al. Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction. *N Engl J Med.* 1984;**310**(10):609–13. doi: 10.1056/NEJM198403083101001. [PubMed: 6537987]
6. Terashi A, Kobayashi Y, Katayama Y, Inamura K, Kazama M, Abe T, editors. Clinical effects and basic studies of thrombolytic therapy on cerebral thrombosis.; Seminars in thrombosis and hemostasis.; 1990; Thieme; pp. 236–41.
7. Mullen MT, Pisapia JM, Tilwa S, Messé SR, Stein SC. Systematic review of outcome after ischemic stroke due to anterior circulation occlusion treated with intravenous, intra-arterial, or combined intravenous+ intra-arterial thrombolysis. *Stroke.* 2012;**43**(9):2350–5. [PubMed: 22811451]
8. Benedict CR, Refino CJ, Keyt BA, Pakala R, Paoni NF, Thomas GR, et al. New variant of human tissue plasminogen activator (TPA) with enhanced efficacy and lower incidence of bleeding compared with recombinant human TPA. *Circulation.* 1995;**92**(10):3032–40. [PubMed: 7586274]
9. Mehrpour M, Aghaei M, Motamed MR. Safety and feasibility of intravenous thrombolytic therapy in Iranian patients with acute ischemic stroke. *Med J Islam Repub Iran.* 2013;**27**(3):113–8. [PubMed: 24791120]
10. Davami F, Sardari S, Majidzadeh AK, Hemayatkar M, Barkhordari F, Enayati S, et al. A novel variant of t-PA resistant to plasminogen activator inhibitor-1; expression in CHO cells based on in silico experiments. *BMB Rep.* 2011;**44**(1):34–9. doi: 10.5483/BMBRep.2011.44.1.34. [PubMed: 21266104]
11. Syed MI, Shaikh A, Ullah A, Akhter TS, Ranginwala S, Mohammed MI, et al. Acute renal artery thrombosis treated with t-PA power-pulse spray rheolytic thrombectomy. *Cardiovasc Revasc Med.* 2010;**11**(4):264. e1–7. [PubMed: 20934664]
12. Niwa J, Ohyama H, Matumura S, Maeda Y, Shimizu T. Treatment of acute superior sagittal sinus thrombosis by t-PA infusion via venography–direct thrombolytic therapy in the acute phase. *Surg Neurol.* 1998;**49**(4):425–9. [PubMed: 9537662]
13. Baratloo A, Safari S, Rouhipour A, Hashemi B, Rahmati F, Motamedi M, et al. The Risk of Venous Thromboembolism with Different Generation of Oral Contraceptives; a Systematic Review and Meta-Analysis. *Emergency.* 2014;**2**(1):1–11.
14. Kasmaei HD, Baratloo A, Nasiri Z, Soleymani M, Shirafkan A, Hamedi ZS. Report of Nineteen Cerebral Vein Thrombosis Referrals to an Emergency Department: a Case Series and Literature Review. *Arch Neurosci.* 2015;**2**(2)
15. Delavar Kasmaei H, Baratloo A, Soleymani M. A 33-year-old woman with severe postpartum headache. *Emergency.* 2013;**1**(1):27–9.
16. Briosa ED, Almeida A, Monteiro N, Paiva Nunes A, Ferreira P, Mendonca N, et al. Successful Thrombolysis despite Having an Incidental Unruptured Cerebral Aneurysm. *Case Rep Neurol Med.* 2014;**2014**:323049. doi: 10.1155/2014/323049. [PubMed: 25525532]
17. Tung CE, Win SS, Lansberg MG. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. *Stroke.* 2011;**42**(8):2257–62. doi: 10.1161/STROKEAHA.111.615682. [PubMed: 21719767]
18. Fagan SC, Morgenstern LB, Petitta A, Ward RE, Tilley BC, Marler JR, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology.* 1998;**50**(4):883–90. [PubMed: 9566367]
19. Ehlers L, Andersen G, Clausen LB, Bech M, Kjolby M. Cost-effectiveness of intravenous thrombolysis with alteplase within a 3-hour window after acute ischemic stroke. *Stroke.* 2007;**38**(1):85–9. doi: 10.1161/01.STR.0000251790.19419.a8. [PubMed: 17122430]
20. Delavar Kasmaei H, Baratloo A, Nasiri Z, Soleymani M, Oraee Yazdani M. Recombinant Tissue Plasminogen Activator Administration in Patients With Cerebrovascular Accident; A Case Series. *Arch Neurosci.* 2015;**2**(2)
21. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g) : results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. *Stroke.* 2000;**31**(4):811–6. [PubMed: 10753980]
22. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA.* 1999;**282**(21):2019–26. [PubMed: 10591384]
23. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology.* 2000;**55**(11):1649–55. [PubMed: 11113218]
24. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;**274**(13):1017–25. [PubMed: 7563451]
25. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet.* 1998;**352**(9136):1245–51. [PubMed: 9788453]
26. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;**359**(13):1317–29. doi: 10.1056/NEJMoa0804656. [PubMed: 18815396]
27. DeMers G, Meurer WJ, Shih R, Rosenbaum S, Vilke GM. Tissue plasminogen activator and stroke: review of the literature for the clinician. *J Emerg Med.* 2012;**43**(6):1149–54. doi: 10.1016/j.jemermed.2012.05.005. [PubMed: 22818644]
28. del Zoppo GJ, Saver JL, Jauch EC, Adams HP. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator a science advisory from the American Heart Association/American Stroke Association. *Stroke.* 2009;**40**(8):2945–8. [PubMed: 19478221]
29. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from

SITS-ISTR. *Lancet Neurol.* 2010;**9**(9):866–74. doi: 10.1016/S1474-4422(10)70165-4. [PubMed: 20667790]
30. Xu ZP, Li HH, Li YH, Zhang Y, Wu Q, Lin L. Feasibility and outcomes of intravenous thrombolysis 3-4.5 hours after stroke in Chinese patients. *J Clin Neurosci.* 2014;**21**(5):822–6. doi: 10.1016/j.jocn.2013.08.014. [PubMed: 24444672]
31. Tekle WG, Chaudhry SA, Hassan AE, Peacock JM, Lakshminarayan K, Tsai A, et al. Utilization of intravenous thrombolysis in 3-4.5 hours: analysis of the Minnesota stroke registry. *Cerebrovasc Dis.* 2012;**34**(5-6):400–5. doi: 10.1159/000343504. [PubMed: 23221276]
32. Shobha N, Buchan AM, Hill MD, Canadian Alteplase for Stroke Effectiveness S. Thrombolysis at 3-4.5 hours after acute ischemic stroke onset–evidence from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry. *Cerebrovasc Dis.* 2011;**31**(3):223–8. doi: 10.1159/000321893. [PubMed: 21178345]
33. Burnette WC, Nesbit GM. Intra-arterial thrombolysis for acute ischemic stroke. *Eur Radiol.* 2001;**11**(4):626–34. doi: 10.1007/s003300000610. [PubMed: 11354758]
34. Mar J, Arrospide A, Comas M. Budget impact analysis of thrombolysis for stroke in Spain: a discrete event simulation model. *Value Health.* 2010;**13**(1):69–76. doi: 10.1111/j.1524-4733.2009.00655.x. [PubMed: 19818059]
35. Fattahi A, Azad A, Montazeri A. Quality of life among stroke patients in kermanshah city. *Mod Rehabil.* 2008;**2**(1):1–8.
36. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. *Stroke.* 2005;**36**(1):62–5. doi: 10.1161/01.STR.0000150515.15576.29. [PubMed: 15569865]
37. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA.* 2000;**283**(9):1151–8. [PubMed: 10703777]
38. Ghandehari K. Barriers of thrombolysis therapy in developing countries. *Stroke Res Treat.* 2011;**2011**:686797. doi: 10.4061/2011/686797. [PubMed: 21603174]
39. Aiyagari V, Gujjar A, Zazulia AR, Diringer MN. Hourly blood pressure monitoring after intravenous tissue plasminogen activator for ischemic stroke: does everyone need it? *Stroke.* 2004;**35**(10):2326–30. doi: 10.1161/01.STR.0000141937.80760.10. [PubMed: 15331797]
40. Hsieh CY, Chen CH, Chen YC, Kao Yang YH. National survey of thrombolytic therapy for acute ischemic stroke in Taiwan 2003-2010. *J Stroke Cerebrovasc Dis.* 2013;**22**(8):e620–7. doi: 10.1016/j.jstrokecerebrovasdis.2013.07.043. [PubMed: 24126287]
41. Nandigam K, Narayan SK, Elangovan S, Dutta TK, Sethuraman KR, Das AK. Feasibility of acute thrombolytic therapy for stroke. *Neurol India.* 2003;**51**(4):470–3. [PubMed: 14742924]
42. de Villiers L, Kalula SZ, Burch VC. Does multidisciplinary stroke care improve outcome in a secondary-level hospital in South Africa? *Int J Stroke.* 2009;**4**(2):89–93. doi: 10.1111/j.1747-4949.2009.00254.x. [PubMed: 19383048]
43. Bryer A, Wasserman S. Thrombolysis for acute ischemic stroke in South Africa. *Int J Stroke.* 2013;**8 Suppl A100**:112–3. doi: 10.1111/ijs.12059. [PubMed: 23692573]
44. Ghandehari K, Zahed AP, Taheri M, Abbasi M, Gorjestani S, Ahmadi AM, et al. Estimation of Iranian stroke patients eligible for intravenous thrombolysis with tPA. *Int J Stroke.* 2009;**4**(4):236. doi: 10.1111/j.1747-4949.2009.00273.x. [PubMed: 19689746]
45. Durai Pandian J, Padma V, Vijaya P, Sylaja PN, Murthy JM. Stroke and thrombolysis in developing countries. *Int J Stroke.* 2007;**2**(1):17–26. doi: 10.1111/j.1747-4949.2007.00089.x. [PubMed: 18705983]
46. Ghandehari K, Foroughipour M, Pourzahed A, Taheri M, Abbasi M, Gorjestani S, et al. Thrombolysis in stroke patients; problems and limitations. *Iran J Med Sci.* 2015;**35**(2):145–8.
47. Ghandehari K. Design of a standard Iranian protocol of Intravenous thrombolysis with tissue plasminogen activator: A national project. *Iran J Neurol.* 2013;**12**(2):72–4. [PubMed: 24250907]