INFLUENCE OF SHORT TERM INTRAVENOUS ANTICOAGULATION THERAPY IN PATIENTS WITH ISCHEMIC CEREBROVASCULAR EVENTS

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Abstract

BACKGROUND: Progressive stroke (PS) and Crescendo Transient Ischemic Attacks (CTIA) is a generally accepted although unproven, indication for urgent intravenous anticoagulation therapy.

METHODS: Consecutive patients with PS and CTIA admitted in Ghaem hospital, Mashhad during 2007 - 2008 enrolled in a prospective clinical study. PS and CTIA patients underwent intravenous heparin therapy with 1000 units per hour without a bolus dose at least for 3 days. PS and CTIA patients who had a contraindication for intravenous heparin therapy, received 80 mg Aspirin per day. Early clinical course including improvement, stabilization, deterioration and development of residual stroke was evaluated in two therapeutic groups of PS and CTIA patients.

RESULTS: 170 PS patients (103 males, 67 females) with mean age of 60.4 ± 12.3 years and 88 CTIA patients (50 males, 38 females) with mean age of 60.1 ± 6.8 years were assessed. 141 PS and 64 CTIA patients received short period intravenous heparinization. Distribution of subtypes of early clinical course between two therapeutic groups of PS and CTIA patients, was significantly different; $X^2 = 10.487$, df = 2, P = 0.005 and $X^2 = 6.72$, df = 2, P = 0.035 respectively. Distribution of residual stroke in two therapeutic groups of PS and CTIA patients, was not significantly different; $X^2 = 1.443$, df = 1, P = 0.23, OR = 0.557 (0.212-1.462) and $X^2 = 1.01$, df = 1, P = 0.315, OR = 0.617 (0.24-1.587) respectively.

CONCLUSION: PS and CTIA patients who underwent short period intravenous heparin therapy have significantly more probability of improvement and less probability of deterioration in their early clinical course than PS and CTIA patients who received Aspirin therapy.

Keywords: Progressive Stroke (PS), Crescendo TransientIschemic Attacks (CTIA), Intravenous anticoagulation therapy, Heparin therapy.

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Introduction

Neurological deficits of ischemic stroke, are frequently unstable during early phase of stroke. Patients my show progressive deterioration with stepwise or nonstepwise fashions or fluctuations with periods of improvement[1]. Stroke in evolution is a non-specific term and is not synonymous with thrombosis in evolution.[1] Almost 30% of stroke patients worsen after entery to the hospital.[1] Common practice considers that heparin followed by warfarin is indicated if observation provides clear evidence of recognizable worsening of an ischemic neurological disability.[2] This practice has been based on incomplete and largely anecdotal data.[2] In progressive stroke (PS), the focal ischemia worsens over several hours, or a day or two.[1,2] Progression of stroke in a stepwise fashion is easier to regard as stroke due to repeated episodes of thromboembolism than indolently PS.[3,4] Patients exhibiting stepwise progression ,may theoretically be considered as likely to benefit from anticoagulation.[3,4] Conversely, patients who develop neurologic deficit in a nonstepwise progressing fashion, probably are not exhibiting progressive thrombus formation and will not be expected to respond to anticoagulation.[3,4] Brain edema accounts for most of the progression in the later situation.[2] Multiple or Crescendo Transient Ischemic Attacks (CTIA) are frequent in clinical practice. The term CTIA defined as occurance of multiple episodes over a few hours or days, often with increasing duration or severity.[5] Some studies suggest that CTIA may represent a condition of impend-

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ing brain infarction.[6] Common medical practice recommends short term anticoagulation in patients with CTIA without proven efficacy.[5] CTIA and major TIA require urgent evaluation and admission of the patient .[4] This observational study compared the clinical course of PS and CTIA patients who received short term intravenous heparin therapy with similar patients who took ultra low dose of Aspirin.

Materials and Methods

Consecutive patients with PS and CTIAs who were admitted in Ghaem hospital, Mashhad during 2007-2008, enrolled in a prospective observational study. The research was approved by ethics committee of Ghaem hospital. A signed informed consent was taken from the patients or their first degree relatives.

PS was defined as stepwise or fluctuated worsening of focal neurological deficits over several hours, or a day or two.[1,2,7] These deficits could increase in severity, extent or number.[1,2,7]

CTIA was defined as two transient ischemic attacks(TIAs) within 24 hours, three TIAs within 3 days or 4 TIAs within 2 weeks.[1,7] These crescendo attacks are often increasing in duration and in severity of deficit.[1,5,]

Patients with CTIA were evaluated for presence of motor, sensory, aphasic and amarotic disturbances. Consecutive patients with PS and CTIA underwent intravenous heparin therapy with 1000 units per hour without an initial bolus dose at least for 3 days. PS patients with coma, dense hemiplegia or extensive signs of ischemia in the initial CT (more than one-third of a hemisphere) and PS and CTIA patients with a contraindication for anticoagulation therapy were excluded.[8] Antiplatelet drugs and warfarin were not administered during intravenous heparinization in this 3 days.[8] A brain CT was done for exclusion of intracranial hemorrhage before initiation of heparin therapy in all of these patients.[8,9] Prothromin Time, Partial Thromboplastin Time and International Normalized Ratio were evaluated before anticoagulation therapy and thereafter ,once a day during heparin therapy.[9] PS and CTIA patients who had an initially abnormal coagulation tests were excluded.[9] Short term intravenous heparin therapy in these patients is a routine therapeutic strategy in our instituation.[2,5] PS and CTIA patients with a contraindication of intravenous heparin therapy ,received Aspirin 80 mg per day during hospitalization period.[2,5] The National Institute of Health Stroke Scale (NIHSS) was detected in all of patients with PS and CTIA before heparinization and 3 days later.[10] The clinical course of these patients was categorized as improvement, stabilization and deterioration.[11] Improvement was defined as ≥3 points decrease and deterioration as ≥ 3 points increase in the second NIHSS.[10,11] Other patients were assumed as stabilization group.[10,11] The same NIHSS assessment was perform in PS and CTIA patients who received Aspirin therapy.[10,11] Presence of stroke at 3 days after anticoagulation therapy was evaluated in all of our patients with PS and CTIA. All of these patients had a repeated CT after anticoagulation therapy for investigation of a visible infarct. A residual stroke was defined as the presence of ischemic focal neurological deficit lasting more than 24 hours or observation of a hypodense lesion in the CT corresponding to the manifestations.[11] Demographic and clinical data of the patients recorded in a $SPSS_{11.5}$ software. Pearson Chi-Square and Fisher tests served for statistical anaslysis.

Results

170 patients (103 males, 67 females) with mean age of 60.4 ± 12.3 years developed PS. 141 PS patients (84 males, 57 female) underwent short term intravenous heparin therapy and 29 PS patients (19 males, 10 females) received Aspirin 80 mg per day. Assessment of early stroke course in two therapeutic groups of PS patient**s** is presented in Figure 1. Frequency rate of subtypes of early stroke course was significantly different in our two therapeutic groups of PS patients; $X^2 = 10.487$, df = 2, P = 0.005. The influence of gender on early course of PS was not significant in the heparin and aspirin therapy groups; ($X^2 = 0.063$, df = 2, P = 0.969) and ($X^2 = 0.021$, df = 2, P = 0.990) respectively. 119 PS patients including 68.1% of heparin and 79.3% of Aspirin groups, developed a residual stroke. Distribution of residual stroke was not significantly different in our two groups of PS patients; $X^2 = 1.443$, df = 1, P = 0.23, OR = 0.557 (0.212-1.462). Distribution of residual stroke based on the gender was not significantly different in PS patients who received short term intravenous heparinization; $X^2 = 0.089$, df = 1, P = 0.766, OR = 1.11 (0.543-2.29). Difference in frequency of residual stroke according to the gender, was not significant in PS patients who had on Aspirin; X^2 = df = 1, P = 0.947, OR=0.938 (0.140-6.28). A residual stroke developed in 30% of improvement, 100% of stabilization and 100% of deterioration courses among 170 PS patients. 88 patients (50 males, 38 females) with mean age of 60.1 ± 6.8 years had CTIA. 64 patients (36 males, 28 females) with CTIA, underwent short term intravenous heparinization and 24 CTIA patients (14 males, 10 females) received Aspirin, 80 mg per day. Difference in distribution of residual stroke in

two groups of CTIA patients was not significant; $X^2 = 1.01$, df = 1, P = 0.315, OR = 0.612 (0.24-1.587). The effect of gender on frequency of residual stroke in CTIA patients who received short term intravenous heparinization was not significant; $X^2 = 0.367$, df = 1, P = 0.545, OR, 0.734 (0.27-1.997). Distribution of residual stroke was not significantly different according to the gender in CTIA patients who received aspirin therapy; $X^2=0.12$, df = 1, P = 0.729, OR = 1.33 (0.261-6.801). Frequency of early clinical course in two therapeutic groups of CTIA patients, was significantly different; X2 = 6.72, df = 2, P = 0.035. Distribution of early clinical course was not significantly different based on the gender in CTIA patients who received short period intravenous heparinization and aspirin therapy ($X^2 = 0.12$, df = 2, P = 0.941 and $X^2 = 0.171$, df = 2, P = 0.918) respectively. Figure 2 illustrates early clinical course of 88 CTIA patients in our two therapeutic groups. Motor, sensory, aphasic and amarotic manifestations were found in 48%, 19%, 15% and 2% of our CTIA cases respectively. Two PS and one CTIA cases had minor hemorrhagic complications of intravenous anticoagulation including echymosis and hematuria

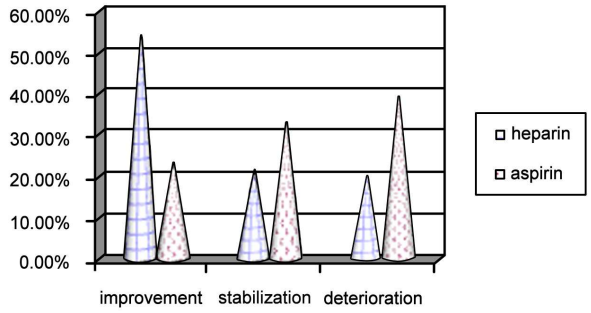

Figure 1. Frequency rate of stroke course in two therapeutic groups of PS patients.
Data are presented in percentage in each group separately

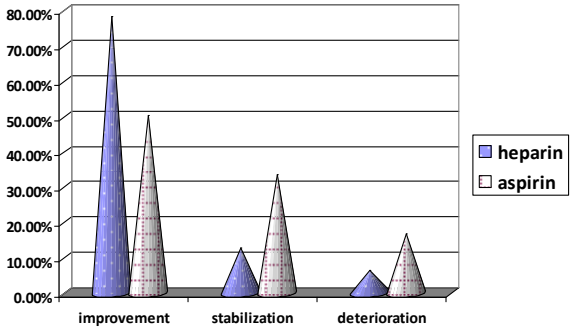

Figure 2. Frequency rate of early clinical course in two therapeutic groups of CTIA patients
Data are presented in percentage in each group separately.

Discussion

Clinical trials suggested a beneficial effect of anticoagulation therapy in PS patients. [3,4]Based on the results of these trials, the indication for heparin therapy in this condition, became widely accepted.[2,5] Other studies have not been conclusive in indication of anticoagulation therapy for PS patients, however overview of whole related studies suggested that, heparin therapy reduces the risk of PS.[1,2,12] Meanwhile, lack of precise criteria for entry and outcome, non-blinded observation and small number of patients ,makes these studies inadequate by current methodological standards.[2,5,13] The main reason that 72 hours was selected as cut off point in assessment of our patients, is that progression period is usually completed in 72 hours.[1] At the other side some of these patients are practically discharged in 3-4 days after anticoagulation therapy and extention of hospitalization time only for research is not possible ethically. Use of intravenous heparin therapy in PS patients, is still a matter of controversity in recent years.[14] Although short term intravenous heparinization, demonstrated no significant influence on development of residual stroke in our PS patients, however it has confirmed a significant influence on early stroke course in PS patients. PS patients on short period intravenous heparinization, had significantly more probability for improvement and less probability for deterioration. Heparin therapy is widely used for clustering or CTIA.[2] This therapeutic strategy for TIA derived by extrapolating results of intravenous anticoagulation therapy for PS.[2,5] Although intravenous heparin therapy is recommended for CTIA, the data supporting its efficacy, derived from old and limited studies.[15] However, intravenous heparinization has been shown to be a safe therapeutic method in these cases.[15] Despite reports of safety in administration of bolus of intravenous heparin administration, bolus dose of heparin was not adminstered in our PS and CTIA patients and none of them developed major hemorrhagic complications.[16] There remains relatively evidence-free practice of using heparin in patients with CTIAs.[14] Although short period intravenous heparin therapy was associated with a non significant decrease on frequency of residual stroke in our CTIA patients, however patients who underwent this therapy had better clinical course. Common practice of neurologists, about using intravenous heparin therapy in patients with PS and CTIA is different. Neurologists of United States more frequently use intravenous heparin therapy in PS and CTIA patients than Canadian neurologists (51% versus 33%) and (47% versus 9%) respectively.[17] The main reason of this difference is the effect of medicolegal factors on the neurologists.[17] Up to date therapeutic guidelines of American

and Europian stroke associations, do not recommend short term intravenous anticoagulation in PS and CTIA patients.[18,19] This management is recommended in textbooks of cerebrovascular disease and is the routine therapeutic strategy in our department.[2,5,8] Since low dose Aspirin therapy is recommended as a standard management for PS and CTIA patients, it is not ethically possible to compare intravenous heparin therapy with placebo in these patients. Thus we compared intravenous heparin therapy with ultra low dose of Aspirin. Although our clinical study suggests intravenous heparinization in PS and CTIA patients, however randomized and double blind clinical trials is recommended in this concept.

References

1. Miller VT, Hart RG. Heparin anticoagulation in acute brain ischemia. Stroke 1988; 19(3): 403-6.
2. Barnett HJM, Meldrum HE, Eliasziw M. Antithrombotic therapy in disease of the cerebral vasculature. In: Barnett HJ, Mohr JP, Stein BM, Yatsu FM, Editors. Stroke: Pathophysiology, Diagnosis & Management. Philadelphia: Churchill Livingstone; 1998. p. 1602.
3. Baker RN. Anticoagulant therapy in cerebral infarction. Report on cooperative study. Neurology 1962; 12: 823-35.
4. Carter AB. Use of anticoagulants in patients with progressive cerebral infarction. Neurology 1961; 11: 601-9.
5. Moulin T, Bougousslavsky J. Anticoagulation in stroke. In: Ginsberg MD, Bogousslavsky J, Editors. Cerebrovascular Disease; Pathophysiology, Diagnosis and Management. London: Blackwell Scientific Publications Ltd; 1998. p. 1854.
6. Crespo M, Melo TP, Oliveira V, Ferro JM. Clustering Transient Ischemic Attacks. Cerebrovasc Dis 1993; 3(4): 213-20.
7. Johnston SC. Clinical practice. Transient ischemic attack. N Engl J Med 2002; 347(21): 1687-92.
8. Warlow CP, Dennis MS, Gijn JV, Hankey GJ, Sandercock PAG, Bamford JM. Stroke: A Practical Guide to Management. 2nd ed. London: Wiley-Blackwell; 2001. p. 267-8.
9. Feen ES, Zaidat OO, Suarez JI. Principles of neurointensive care. In: Bradley WG, Daroff RB, Fenichel G, Jankovic J, Editors. Neurology in Clinical Practice. 6th ed. Philadelphia: Butterworth-Heinemann; 2008. p. 979.
10. Wahlgren NG. Stroke Scales. In: Ginsberg MD, Bogousslavsky J, Editors. Cerebrovascular Disease: Pathophysiology, Diagnosis and Management. London: Blackwell Scientific Publications Ltd; 1998. p. 1213.
11. Ghandehari K, Izadi Z. The Khorasan Stroke Registry: results of a five-year hospital-based study. Cerebrovasc Dis 2007; 23(2-3): 132-9.
12. Millikan CH, McDowell FH. Treatment of progressing stroke. Stroke 1981; 12(4): 397-409.
13. Zeevi N, Chhabra J, Silverman IE, Lee NS, McCullough LD. Acute stroke management in the elderly. Cerebrovasc Dis 2007; 23(4): 304-8.
14. Donnan GA, Davis SM. Controversy: the essence of medical debate. Stroke 2003; 34(2): 372-3.
15. Byer JA, Easton JD. Therapy of ischemic cerebrovascular disease. Ann Intern Med 1980; 93(5): 742-56.
16. Toth C. The use of a bolus of intravenous heparin while initiating heparin therapy in anticoagulation following transient ischemic attack or stroke does not lead to increased morbidity or mortality. Blood Coagul Fibrinolysis 2003; 14(5): 463-8.
17. Al Sadat A, Sunbulli M, Chaturvedi S. Use of intravenous heparin by North American neurologists: do the data matter? Stroke 2002; 33(6): 1574-7.
18. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007; 38(5): 1655-711.
19. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008; 25(5): 457-507.