Influence of Intravenous Heparin Therapy in Patients with Progressive Stroke and Crescendo Transient Ischemic Attacks

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Citation

K Ghandehari, K Nikkhah, A Boroumand, S Javad, H Nejad, S Derakhshan, A Ardakani, G Fatahzadeh. *Influence of Intravenous Heparin Therapy in Patients with Progressive Stroke and Crescendo Transient Ischemic Attacks*. The Internet Journal of Neurology. 2008 Volume 11 Number 2.

Abstract

Background: Progressing stroke (PS) and Crescendo Transient Iachemic Attacks (CTIA) are generally accepted although unproven, indication for urgent anticoagulation and there remains evidence-free practice of intravenous heparin therapy in these patientMethods
: Consecutive patients PS and CTIA admitted in Ghaem hospital, Mashhad during 2007- 2008 enrolled in a prospective observational study. PS and CTIA patients underwent intravenous heparin therapy 1000 units per hour for 3 days without bolus dose. PS and CTIA patients who had a contraindication of intravenous hepain 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 60.4±12.3 years and 88 CTIA patients (50 males, 38 females) with mean age 60.1± 6.8 years were investigated. 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 received short period intravenous heparin therapy have significantly more probability of improvement and less probability of deterioration in their early clinical course.

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 neurology disability [2] . This practice has been based on incomplete and largely anectodal 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 is an indolently PS [3,4] . Patients exhibiting stepwise progression may speculatively be considered as likely to benefit from anticoagulation [3,4] . Conversely, patients who are adding to their 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 impending brain infarction [6] . Common practice of medicine recommends short term anticoagulation in patients with CTIA without proven efficacy [5,6] . CTIA and major TIA require urgent evaluation

and admission of the patient [4]. This observational study compares the clinical course of PS and CTIA patients who receive short term intravenous heparin therapy with similar patients who take ultra low dose of Aspirin.

MATERIALS AND METHODS

Consecutive patients with PS and CTIAs admitted in Ghaem hospital, Mashhad during 2007- 2008 enrolled in a prospective observational study. PS was defined as stepwise or fluctuated worsening of focal neurologic 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 TIAs within 24 hours, three TIAs within 3 days or 4 TIAs within 2 weeks [1,6,7]. These crescendo attacks often are increasing in duration and in severity of deficit [1,5,6,7]. Patients with CTIA were evaluated for presence of motor, sensory, aphasic and amarotic disturbances. Consecutive patients with PS and CTIA underwent intravenous heparin therapy 1000 units per hour for 3 days without an initial bolus dose. PS Patients with coma, dense hemiplegia or extensive signs of ischemia in the initial CT (more than one-third of a hemisphere) were excluded [8]. PS and CTIA patients with a contraindication of 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]. Prothrombin Time, Partial Thromboplastin Time and International Normalized Ratio were evaluated before anticoagulation therapy and thereafter one time per 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 administered 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 have taken 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 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]. The research was approved by ethics committee of Ghaem hospital. A signed informed consent was taken by the patients or their first degree relatives. Pearson Chi-Square and Fisher tests served for statistical anaslysis.

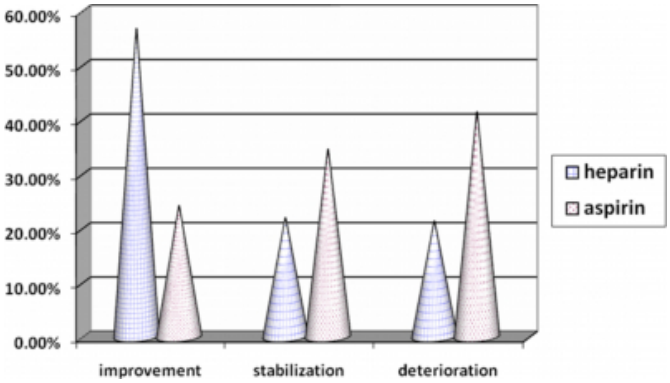
RESULTS

170 patients (103 males, 67 females) with mean age 60.4±12.3 years developed PS. 141 PS patients (84 males, 57 female) underwent short term intravenous heparin therapy and 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 patients 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 therapeutic 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 therapeutic 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 based on the gender was not significant in PS patients who underwent Aspirin therapy; 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 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 therapeutic 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 based on 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 nanifestations 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

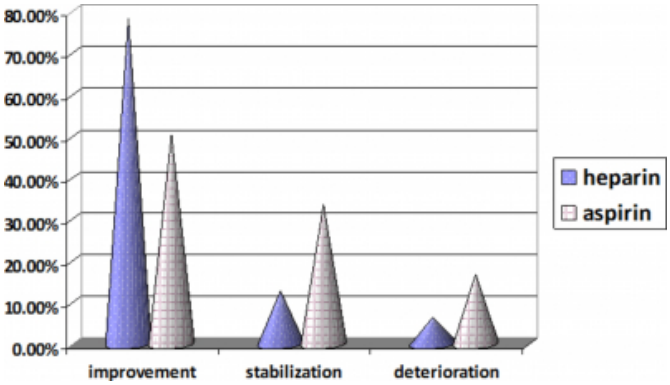
Figure 1: Frequency rate of stroke course in two therapeutic groups of PS patients.



Data are presented in percentage in each group separately.

Figure 2

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

Controlled clinical trials performed more than 30 yeats ago 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 randomized and observational studies have not been conclusive in regard to the indication of anticoagulation in PS [12] . The data in aggregate suggested that heparin reduces the risk of PS [1,2,12] . The 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 in 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 heparin in PS patients is still a matter of controversy in recent years [14] . Although short term intravenous heparinization demonstrated non 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 who have been on short period intravenous heparinization had significantly more probability for improvement and less probability for deterioration. Heparin is widely used for clustering or CTIA [2] . This therapeutic strategy for CTIA has been largely for theoretical reasons and by extrapolation from the results of studies of anticoagulation for PS [2,5] . Although heparin appears to be the prefered treatment for CTIA, the data supporting its efficacy are meager and come from old and limited studies [15] . However, intravenous heparinization has been shown to be

a safe therapy in these cases [15] . Despite reports of safety in administration of bolus of intravenous heparin while initiating heparin therapy [16] , bolus dose of heparin was not adminstered in our PS and CTIA patients and none of them developed major hemorrhagic complications. There remains relatively evidence-free practice of using heparin in patients with CTIA [14] . Although short period intravenous heparnization was associated with a non significant effect on development of residual stroke in our CTIA patients, however our CTIA patients who have been on this therapy had significantly more probability of improvement and less probability of deterioration in their early clinical course evaluation. Common practice of neurologists in regard to using heparin in patients with PS and CTIA is different. United States neurologists are significantly more likely than Canadian neurologists to use intravenous heparin in PS and CTIA patients (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] . It is not ethicaly possible to compare heparin with placebo in the PS and CTIA patients. Thus we compared 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.

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