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

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Abstract

Introduction: Progressing stroke (PS) and Crescendo Transient Ischemic Attacks (CTIA) are generally accepted, though unproven, indications for urgent anticoagulation and there remains evidence-free practice of intravenous heparin therapy in these patients.

Methods and Materials: Consecutive PS and CTIA patients admitted in Mashhad Ghaem hospital 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 heparin therapy received 80 mg Aspirin per day. Early clinical courses including improvement, stabilization, deterioration and development of residual stroke were 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 a short period of intravenous heparinization. The distribution of subtypes of early clinical course into 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 a short period of intravenous heparin therapy have significantly more probability of improvement and less probability of deterioration in their early clinical course.

Key Words: Progressive Stroke, Transient, Ischemic, Attacks, Heparin

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Introduction

Neurological deficits of ischemic stroke are frequently unstable during the early phase of stroke. Patients may 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' condition worsened after being admitted in 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 a set of 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 be regarded 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 are probably 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 is defined as the 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 a short term intravenous heparin therapy with similar patients who take ultra low dose of Aspirin.

Methods and Materials

Consecutive patients with PS and CTIAs, admitted in Mashhad's Ghaem hospital during 2007- 2008 enrolled in a prospective observational study. PS was defined as the stepwise or fluctuated worsening of focal neurologic deficits over several hours, or a day or two[1,2,7]. These deficits could grow 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 increase in duration and 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 once per day during heparin therapy.[9] PS and CTIA patients who had an initially abnormal coagulation test 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 the 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 the stabilization group.[10,11] The same NIHSS assessment was performed for 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 the presence of ischemic focal neurological deficit lastingfor 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 form was filled by the patients or their first degree relatives. Pearson Chi-Square and Fisher tests were performed 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 a 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 patients is presented in Figure 1.

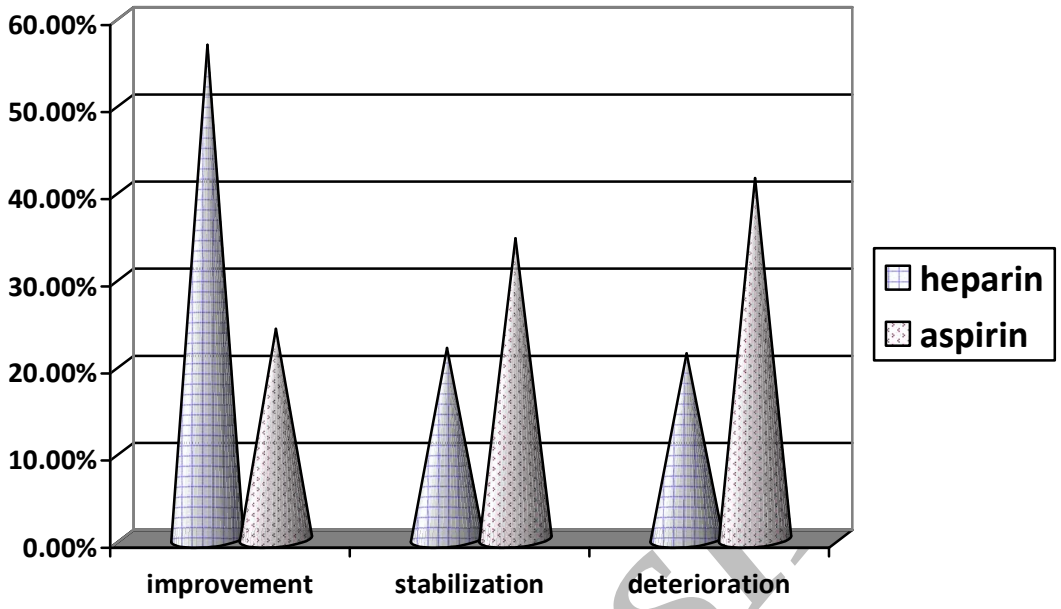

Figure 1: Frequency rate of stroke course in two therapeutic groups of PS patients. Data are presented in percentage in each group separately.

The 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. The 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). The 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 was 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 the 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). The frequency of early clinical course in two therapeutic groups of CTIA patients was significantly different; X2=6.72, df=2 , p=0.035. The 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.

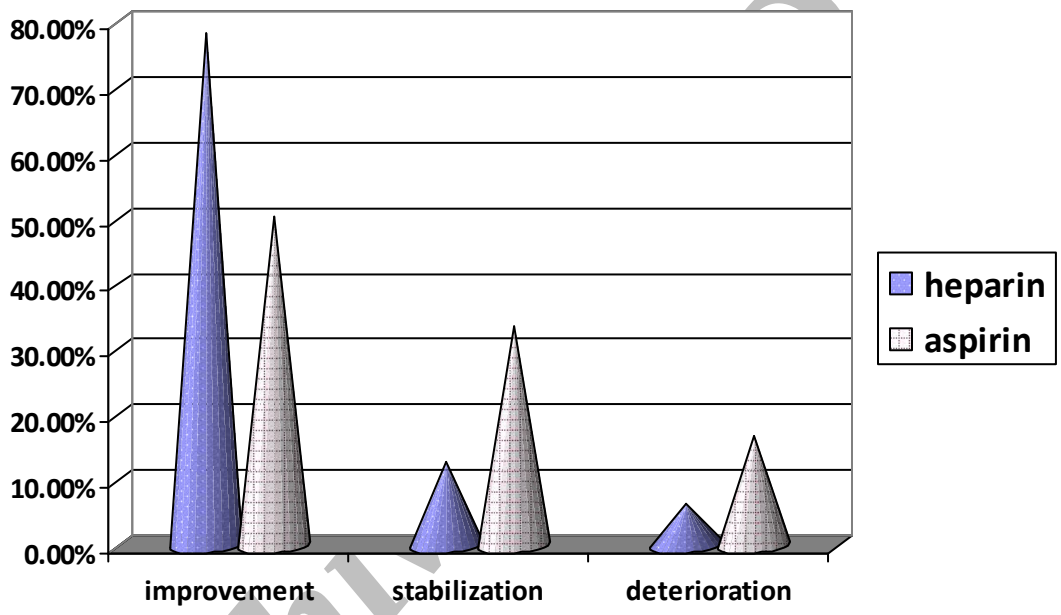

Figure 2: Frequency rate of early clinical course in two therapeutic groups of CTIA patients. Data are presented in percentage in each group separately.

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.

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; on the other hand some of these patients are practically discharged in 3-4 days after anticoagulation therapy and the extention of hospitalization time just for research is not possible ethically. The use of heparin in PS patients has still been a matter of controversy in recent years.[14] Although short term intravenous heparinization demonstrated non significant influence on the development of residual stroke in our PS patients, 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 due to the 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 is meager and comes from old and limited studies.[15]. However, intravenous heparinization has proved to be a safe therapy in these cases.[15] Despite the presence of 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. The useof heparin in patients with CTIA[14] remains a relatively evidence-free practice. Although a short period intravenous heparnization was associated with a non significant effect on the development of residual stroke in our CTIA patients, 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. The 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 diseases 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 the use of intravenous heparinization in PS and CTIA patients, randomized and double blind clinical trials is recommended in this concept.

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تاثیر درمان به هپارین وریدی بر بیماران سکته مغزی در حال پیشرفت و حملات گذرای ایسکمی مغزی افزایش یابنده

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چکیده

سابقه و هدف: سکته مغزی درحال پیشرفت و حملات گذرای ایسکمی افزایش یابنده به عنوان اندیکاسیون‌های ثابت نشده درمان ضدانعقادی فوریتی پذیرفته شده‌اند. در طبابت روزمره نیز درمان با هپارین وریدی در این بیماران بدون اثبات قطعی فایده آن ادامه دارد.

روش بررسی: بیماران پی در پی با سکته مغزی پیشرونده و حملات گذرای ایسکمی مغزی افزایش یابنده که در بیمارستان قائم مشهد در سالهای ۲۰۰۸- ۲۰۰۷ بستری شده‌اند در یک مطالعه مشاهده‌ای آینده‌نگر قرار گرفتند. بیماران فوق تحت درمان با ۱۰۰۰ واحد در ساعت هپارین وریدی بدون دوز اولیه به مدت حداقل سه روز قرار گرفتند. بیمارانی که کونتراندیکاسیون درمان وریدی با هپارین را داشتند نیز ۸۰ میلیگرم آسپرین روزانه دریافت کردند. سیر بالینی زودرس پس از سه روز شامل بهبودی تثبیت و وخامت و ایجاد سکته مغزی برجای مانده در دو گروه درمانی از بیماران فوق بررسی شد.

یافته‌ها: ۱۷۰ بیمار (۱۰۳ مرد و ۶۷ زن) با سکته مغزی در حال پیشرفت و میانگین سنی ۱۲/۳± ۶۰/۴ سال و ۸۸ بیمار (۵۰ مرد و ۳۸ زن) با حملات گذرای ایسکمی مغزی افزایش یابنده و میانگین سنی ۶/۸ ± ۶۰/۱ سال بررسی شدند. ۱۴۱ بیمار با سکته مغزی در حال پیشرفت و ۶۴ بیمار با حملات گذرای ایسکمی مغزی افزایش یابنده درمان کوتاه مدت با هپارین وریدی را دریافت نمودند. توزیع فراوانی انواع سیر بالینی زودرس بین دو گروه درمانی از بیماران با سکته مغزی در حال پیشرفت و حملات گذرای ایسکمی مغزی افزایش یابنده تفاوت معنی‌دار داشت بترتیب $X^2=10.487, df=2 , p=0.005$ و $X^2=6.72, df=2 , p=0.035$. توزیع فراوانی سکته مغزی برجای مانده در دو گروه درمانی از بیماران با سکته مغزی در حال پیشرفت و حملات‌گذرای ایسکمی مغزی افزایش یابنده تفاوت معنی‌داری نداشت بترتیب $X^2=1.443, df= 1, p=0.23, OR=0.557$ (0.212-1.462) و $X^2=1.01, df=1, p=0.315, OR=0.617$ (0.24-1.587).

نتیجه گیری: بیماران با سکته مغزی در حال پیشرفت و حملات گـذرای ایـسکمی مغـزی افـزایش یابنده که تحت درمان با هپارین وریدی هستند احتمال بیشتری از بهبود و احتمال کمتری از بـدتر شدن در سیر زودرس خود را دارند.

واژه های کلیدی: سکته مغزی- پیشرونده- حمله- ایسکمی- هپارین