Surgical Neurology International

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Original Article

Retrospective study of Heparin Administration for Ischemic Stroke when there is an IV-tPA Contraindication

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Received: 14 November 13 Accepted: 11 March 14 Published: 06 May 14

This article may be cited as:
Hakma Z, Stofko DL, Binning MJ, Liebman K, Veznedaroglu E. Retrospective study of Heparin Administration for Ischemic Stroke when there is an IV-tPA Contraindication. Surg Neurol Int 2014;5:62.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/1/62/132032

Abstract

Background: The majority of patients presenting with an ischemic stroke arrive after the 3-4.5 h time window allowed for intravenous tissue plasminogen activator (IV tPA) administration. Most of the literature on heparin use in acute ischemic stroke does not describe dose-adjusted intravenous unfractionated heparin (IV UFH) without bolus, a common method of administration. This study was designed to test whether an anticoagulation regimen of intravenous dose-adjusted UFH with no bolus, in patients with a contraindication to IV TPA, administered within 24 h of an acute ischemic stroke could be effective and safe.

Methods: We conducted a retrospective study of 273 patients over two consecutive years with acute ischemic stroke, who were outside the window for IV tPA. All patients had imaging studies on admission. The primary outcome measure of the study was to evaluate the safety of dose-adjusted IV UFH use in the setting of acute stroke. We looked at duration of heparin infusion, average partial thromboplastin time (PTT) value, and the incidence of new hemorrhagic events.

Results: A total of 273 patients met the inclusion criteria. These patients received heparin infusion within 24 h of symptom onset. The duration of intravenous heparin infusion ranged from 1 to 18 days with a mean of 4 days. Mean PTT value was 72.4. Hemorrhagic complications occurred in 26 patients (9.5%), and included 12 asymptomatic petechial or hemorrhagic conversion (4.3%), 2 symptomatic intracranial hemorrhages (0.7%), 5 gastrointestinal bleeds (2 requiring transfusion and interventions), 2 patients experienced benign hematuria, 4 patients with groin hematomas, and one neck hematoma.

Conclusion: This study suggests that intravenous dose-adjusted UFH with no bolus can be administered to patients with acute ischemic stroke with relative safety.

Key Words: Anticoagulation, hemorrhagic complications, heparin, intravenous tissue plasminogen activator, stroke

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.132032

Quick Response Code:

INTRODUCTION

Acute ischemic stroke is a common problem that carries a significant risk of mortality and morbidity. There are approximately 600,000 new cases of acute ischemic stroke diagnosed each year in the United States, resulting in approximately 150,000 deaths and 300,000 survivors with substantial disabilities.[23] The majority of patients presenting with an ischemic stroke arrive after the time window allowed for IV tPA administration, despite recent guidelines extending the window to 4.5 h.[17] Currently, there are no well-documented immediate treatment options available for patients outside the tPA window who are awaiting transfer to a stroke center, for imaging and/or endovascular intervention.

Current American Stroke Association/American Heart Association recommendations on the management of acute ischemic stroke do not recommend the early use of heparin because of an increased risk of bleeding complications.[2] Most literature on the use of heparin for acute ischemic stroke has not studied heparin use in its commonly administered form; dose-adjusted intravenous unfractionated heparin (IV UFH) with no bolus. The use of heparin in the management of acute ischemic stroke has been the subject of many studies, including a number of randomized controlled trials [Table 1]. However, Low-molecular weight heparin (LMWH) administered subcutaneously was used in most studies, with only a few trials examining the use of IV UFH.[6,11,14,19]

According to our literature review, there is an apparent lack of published data regarding immediate treatments for patients presenting with an IV tPA contraindication. The purpose of this study is to discuss the option of administering weight-based IV heparin to patients presenting within 24 h postischemic stroke, while assessing the safety of this intervention.

MATERIALS AND METHODS

We conducted a retrospective study of 273 consecutive patients, from May of 2009 to June 2011, admitted to Capital Health Regional Medical Center with diagnosis of acute ischemic stroke outside the window for IV tPA. Any patient who received IV Heparin within 24 h of symptom onset was included. The primary goal of this study was to evaluate the safety of dose-adjusted IV UFH in the setting of acute stroke. All patients had imaging studies on admission and at 24 h postheparin infusion. Patients who were converted to oral anticoagulation received a head

Table 1: Randomized trials of heparin use in acute ischemic stroke

Study	Study population	Study endpoint	Comments
CESG (1983)[19] UFIVH	Cardioembolic stroke within 48 h	Recurrent stroke	*n*=45. Trend toward reduction in study endpoint among those anticoagulated
Duke (1986)[14] UFIVH	Partial stable stroke within 48 h	Change in neurological status, number of patients with stroke progression and functional outcome at 7 days, 3 months, and 1 year	*n*=225. No differences observed between endpoints among the two treatment groups
FISS (1995)[20] LMWH (fraxiparin)	Acute ischemic stroke within 48 h	Death or dependency at 6 months	*n*=308. Favorable effect of heparin
IST (1997)[25] UFSCH	Acute ischemic stroke within 24 h	Death at day 14, death or dependency at 6 months	Nonblinded; aPTT not monitored; no benefit from heparin
TOAST (1998)[21] LMWH (danaproid)	Acute ischemic stroke within 24 h	Glasgow outcome scale and Barthel index	*n*=281. No difference in treatment groups except for 'large artery stroke' subgroup
TAIST (1998)[4] LMWH (tinzaparin)	Acute ischemic stroke within 48 h	Modified Rankin score at 6 months	*n*=1486 (no placebo group). No differences between treatment groups
TOPAS (2001)[13] LMWH (certoparin)	Acute ischemic stroke	Barthel index	*n*=767. No differences between treatment groups
HAEST (2000)[5] LMWH (dalteparin)	All patients with cardioembolic stroke within 30 h	Recurrent ischemic stroke within 14 days, functional outcome, death	*n*=404; no placebo group. No difference between treatment groups
IV heparin within the first 3 h (2005)[6] UFIVH	Acute nonlacunar hemispheric infarctions	Modified Rankin score at 90 days	*n*=418, more self independent patients and fewer death in heparin group
RAPID (2005)[11] UFIVH, Bolus followed by 12 IU/kg/h infusion	Nonlacunar ischemic stroke, less than 12 h	Modified Rankin score at 90 days	*n*=67, UFH was at least as safe as ASA

aPTT: Average partial thromboplastin time, UFH: Unfractionated heparin, ASA: Adjusted UFH or aspirin CESG: Cerebral embolism study group, UFIVH: Intravenous unfractionated heparin, LMWH: Low-molecular weight heparin, IST: The international stroke trial, TOAST: Trial of ORG 10172 in acute stroke treatment, TAIST: Tinzaparin in acute ischaemic stroke, TOPAS: Therapy of patients with acute stroke, HAEST: Heparin in acute embolic stroke trial, RAPID: The rapid anticoagulation prevents ischemic damage

computed tomography (CT) prior to starting therapy. Intracranial and extracranial hemorrhages (ECH) were recorded, with symptomatic intracranial hemorrhages being characterized based on the National Institute for Neurological Disorders and Stroke (NINDS) criteria and severe ECH based on the need for blood transfusion. Heparin was discontinued depending on the severity of the hemorrhage and actively reversed with protamine if needed. Heparin was infused at a rate to keep the activated partial thromboplastin time (aPTT) between 60 and 80 with no initial bolus.

We looked at patients' age, gender, length of stay, duration of heparin infusion, average aPTT value, necessity of endovascular or cranial procedures, use of aspirin, clopidogrel or warfarin on admission and during hospitalization, incidence of new hemorrhage, admission and discharge Glasgow Coma Score (GCS) as well as National Institute of Health Stroke Scale (NIHSS).

Approval from Capital Health Regional Medical Centers Institutional review board (IRB) was obtained and informed consent was waived since it was a retrospective study of prospectively collected data.

Patients were included if they met the following criteria: Aged between 18 and 90 years with a clinical diagnosis of acute ischemic stroke, known time of onset, and the patient was outside IV tPA time window or with a contraindication to IV tPA. We excluded patients who received IV tPA for this ischemic stroke, any evidence of intracranial hemorrhage on CT or known bleeding diathesis.

RESULTS

A total of 273 patients met the inclusion criteria, 149 males and 124 females. Patient ages ranged from 20 to 91, with an average age of 65 years. All patients had imaging studies on admission as part of the stroke protocol to rule out intracerebral hemorrhage. These patients received heparin infusion within 24 h of the onset, with the duration of intravenous heparin infusion ranging from 1 to 18 days, and a mean of 4 days. Mean PTT value was 72.47. Length of stay ranged from 1 to 36 days (with one outlier staying 77 days) and median length of stay was 6 days. The mean GCS and NIHSS on admission were 13.3 and 8.13, respectively. Both GCS and NIHSS improved on discharge to 14 and 6.41, respectively.

Of the 273 patients, 96 (35%) were discharged on long-term anticoagulation (warfarin), 156 (57%) on aspirin and 162 (59%) on clopidogrel [Table 2]. Hemorrhagic complications occurred in 26 patients (9.5%) [Table 3]. No patient with petechial hemorrhagic conversion had clinical worsening of their exam; mortality in three patients was related to fusiform aneurysm rupture, basilar thrombosis, and pontine hemorrhage.

DISCUSSION

Stroke remains a frequent and costly problem worldwide, but with the substantial advances made in the understanding of stroke mechanisms, risk factors, treatment options and advanced imaging modalities, new therapies are rapidly emerging. Currently, drugs that interfere with hemostasis and clot formation, such as anticoagulants and antiplatelet agents, are becoming the primary management of patients with cerebrovascular disease.[12]

The use of heparin in the management of acute ischemic stroke has been the subject of many studies, although few trials examined the use of IV UFH. For the most part, these studies have shown no benefit from heparin, with small decrease in the risk of stroke progression or recurrence being offset by an increase in hemorrhagic complications.[14] Nonetheless, heparin is still frequently prescribed in the hope of maintaining collateral flow, preventing thrombus propagation, and attenuating early recurrence of stroke, especially in patients with cardioembolism and large-artery atherosclerosis.[1] When US neurologists were presented with a brief vignettes for the following five scenarios: Stroke in evolution, atrial fibrillation (Afib)-related stroke, vertebrobasilar stroke, carotid territory stroke, and multiple transient ischemic attacks, they frequently used intravenous heparin for patients with acute stroke with Afib (88%), stroke in evolution (51%), vertebrobasilar

Table 2: Anticoagulation regimen

Medication	Admission (%)	Discharge (%)
Warfarin	27 (9)	96 (35)
Aspirin	105 (38)	156 (57)
Clopidogrel	43 (16)	162 (59)

Table 3: Hemorrhagic complications

Complication	*N*	Percentage	Comments
Hematuria	2	0.7	Did not require any intervention
Neck hematoma, after CEA	1	0.3	CEA Complicated by intraoperative thrombosis, transferred to our hospital on heparin drip for possible endovascular intervention
GI Bleed	5	1.8	2/5 required transfusions, endoscopy and/or embolization
SAH	1	0.3	Ruptured fusiform basilar aneurysm
Symptomatic ICH	1	0.3	Pontine hemorrhage
Groin hematoma	4	1.4	None required surgical interventions
Petechial hemorrhage or asymptomatic hemorrhagic conversion	12	4.3	Asymptomatic, found on follow up imaging
Total	26	9.5	

CEA: Carotid endarterectomy, SAH: Subarachnoid hemorrhage, ICH: Intracerebral hemorrhage, GI: Gastrointestinal

stroke (30%), carotid territory stroke (31%), and multiple transient ischemic attacks (47%).[3]

The theoretical benefit of heparin is that it reduces the development of erythrocyte-fibrin thrombi, which form in regions of vascular stasis by activating antithrombin III, thereby preventing clot propagation. Several other studies suggested that in addition to its antithrombotic effects, UFH also modulates inflammation, thus the effect of early anticoagulation may be attributed to modulation of the inflammatory pathway that appears to be most relevant in the first few hours of ischemia.[10,22,27]

Some published data exists on IV heparin administration but tends to look at other time frames or a longer heparin administration.[6,11,14,19] Other studies focus on heparin dosing following IV tPA administration and analyze important patient data such as co-morbidities, early bleeding complications, and patient outcomes. Again, this information does not account for the large patient group that is not eligible to receive IV tPA. Literature also supports prevention of further thromboembolism after stroke by administering heparin.

Since the publication of the International Stroke Trial (IST), treatment of acute ischemic stroke using heparin has become controversial.[25] Even though the IST showed that the rate of recurrent ischemic stroke at 14 days in the group of patients receiving heparin independent of dose was significantly reduced (2.95% versus 3.8%), it also demonstrated an equivalent rate of hemorrhagic stroke (1.2% versus 0.4%). However, the IST used a high dose of twice daily subcutaneously (SC) administered heparin, but did not monitor aPTT. Without monitoring aPTT it remains unclear if heparin led to systemic anticoagulation in a subset of patients. Furthermore, the IST did not require mandatory CT scanning of the head before treatment, thus only 69% of the patients had a CT before randomization, a major criticism of the study. Since the IST used twice daily SC heparin without aPTT monitoring and did not mandate pretreatment imaging, it is difficult to make any conclusions regarding the efficacy and safety of closely monitored full dose IV heparin with pretreatment CT of the head.

The European Rapid Anticoagulation Prevents Ischemic Damage (RAPID) Trial aimed to randomize 1400 patients with acute ischemic stroke to intravenous weight-adjusted UFH or aspirin (ASA) within 12 h of symptom onset.[6] Even though the study was closed after the enrollment of only 67 patients due to funding, it demonstrated that UFH was at least as safe as ASA contrary to previous trials. The RAPID study was not adequately powered but suggested that the hemorrhagic risk can be minimized by close monitoring and adjustment of the aPTT.

In the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial (acute stroke treatment), there was no benefit for heparinoid-treated patients, although in subgroup analysis, there was a trend toward increased benefit in patients with large strokes.[21]

Camerlingo *et al.*[6] looked at the use of intravenous heparin started within 3 h of stroke as a treatment for acute nonlacunar hemispheric cerebral infarctions. The study was an outcome evaluator-blind design trial looking at 418 patients randomized to receive intravenous heparin sodium or saline. Heparin was infused at a rate to maintain aPTT ratio between 2.0-2.5 × control for 5 days. The primary end point was recovery of a modified Rankin score (mRS) zero to two at 90 days of stroke onset. Safety end points were death, symptomatic intracranial hemorrhages, or major ECH within 90 days of stroke. In the heparin group, there were more independent patients (38.9% versus 28.6%; $P = 0.025$) and fewer deaths (16.8% versus 21.9%; $P = 0.189$), more symptomatic brain hemorrhages (6.2% versus 1.4%; $P = 0.008$), and more major extracerebral bleeds (2.9% versus 1.4%; $P = 0.491$). They concluded that intravenous heparin could be useful in the earliest treatment of acute nonlacunar hemispheric cerebral infarction despite an increase in symptomatic intracranial brain hemorrhages. This study was performed prior to IV tPA gaining approval for acute stoke in Italy. These results should be interpreted with caution as other studies did subgroup analysis in hyperacute anticoagulation and showed neutral results.

Our study has several limitations, the most important being the lack of a control group, which is common in retrospective review. Furthermore, since departmental protocol only required CT imaging at two time points, before the initiation of heparin therapy and 24 h after the initiation of therapy, the number of asymptomatic hemorrhages may be underestimated.

The present study aimed to evaluate the safety of heparin infusion in the setting of acute ischemic stroke when administered intravenously, without bolus and with rigorous monitoring using aPTT. We reviewed the charts of 273 patients and found an overall complication rate of 9%. However, most of these complications were asymptomatic petechial or hemorrhagic conversions found on follow up imaging. Our incidence of petechial and hemorrhagic events without a parenchymal hematoma is well within the accepted range of spontaneous conversion described in the literature for prospective double-blinded placebo-controlled studies.[9,15,26] Several reports revealed that 6-30% of presumed cardioembolic strokes underwent spontaneous hemorrhagic conversion.[8] These hemorrhages were largely asymptomatic, as suggested by series that demonstrated the occurrence of hemorrhagic conversion in most cases was not clinically significant.[18] The incidence of hemorrhagic events in another magnetic resonance imaging (MRI) series was even higher at 50-60%.[26]

Our data included only two serious intracranial hemorrhages (0.7%), one from a ruptured fusiform partially

thrombosed basilar aneurysm that was causing an embolic stroke and the other a pontine hemorrhagic conversion. Both patients expired as a result of these complications. In comparison, the incidence of symptomatic spontaneous hemorrhage in the placebo arm of the IST, CAST, and TOAST ranged from 0.3% to 0.9%.

Acute anticoagulation with parenteral unfractionated intravenous heparin for acute ischemic stroke remains an area of ongoing controversy with strong proponents and critics.[7,16,24] Its use should be restricted to highly selected patients based on proper screening, risk assessment, and radiographic studies.

CONCLUSION

The use of early anticoagulation in ischemic stroke has been a matter of much debate. This study suggests that intravenous dose-adjusted UFH with no bolus can be administered to patients with acute ischemic stroke with relative safety. Further studies will be necessary in patients who present with acute CVA who do not qualify for IV tPA regarding the use of heparin infusion. While intravenous heparin continues to be widely used around the world in the management of acute ischemic stoke, guidelines regarding its use cannot be formalized until there is an adequately powered study demonstrating the safety and efficacy of monitored intravenous heparin.

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