INCIDENCE OF DEEP VENOUS THROMBOSIS IN STROKE PATIENTS IN MEDICAL INTENSIVE CARE UNIT ZAGAZIG UNIVERSITY HOSPITALS, EGYPT.

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ABSTRACT

Background and Purpose: Venous thromboembolism(VTE) is a leading cause of morbidity and mortality during the acute recovery period after stroke. This study was designed to study the incidence of deep venous thrombosis (DVT) in acute stroke patients & determine the risk factors contributing to development of DVT in these patients.

***Patients &Methods*:** 280 patients, admitted because of acute stroke, were enrolled in this study. All patients were examined by Doppler ultrasonography (DUS) of the four limbs at one and two weeks after admission for possibility of DVT . If the patients was suspected to have DVT before or after this time (limb swelling, local pain or tenderness) DUS of the affected limb was done. We performed D-dimer assay level and considered it as an important marker for DVT suspicion. Other co-morbidities, type of stroke and their relation to DVT development were investigated. Data were collected, entered and checked using SPSS software version 17. Univariate and multivariate analysis of data were done to determine important predictor risk factors for DVT development in stroke patient

***Results*:** 25 out of 280 patients(8.93%) developed DVT during their stay in intensive care unit (ICU) as a complication of acute stroke. DVT affected mainly the paralyzed limb and was mainly distal and occurred mostly after 2 weeks of admission. Patients complicated with DVT were characterized by being older and having higher percentage of smokers with no impact of gender. Multivariate regression analysis identified atrial fibrillation (AF) and intracerebral hemorrhage (ICH) as independent risk factors for early stroke related DVT (p=0.002 & p=0.025 respectively).

Conclusions: Incidence of DVT as a complication of stroke was 8.93 %. AF and ICH were determined as predictors and independent risk factors for development of DVT poststroke.

We recommend to follow the international guidelines for DVT prophylaxis .

INTRODUCTION

Stroke is a devastating public health problem worldwide, considered as the third leading cause of death in developed countries, and the leading cause of disability among adults **[1].** Stroke is also a major cause of long-term disability and has potentially enormous emotional and socioeconomic results for patients, their families, and health services**[2].** The occurrence of medical complications has been shown to contribute to poor outcome because these complications may hinder optimum rehabilitation, increase the length of hospital stay and resource use. Furthermore, medical complications have been associated with increased mortality.**[3].** Deep vein thrombosis (DVT), including pulmonary embolism (PE) as a sequel, is a serious complication of stroke. It is considered to develop mostly within 2 weeks post-stroke. **[4].**

The diagnosis of DVT in the critically ill patients presents specific challenges because many patients are not able to communicate their symptoms (such as leg pain or shortness of breath), **[5].**The aim of this study was to establish the incidence of early stroke-related DVT and identify risk factors for its development. The present work was a prospective study conducted from January to June 2012 at the stroke unit of Medical ICU at Zagazig University Hospitals,Egypt.

SUBJECTS AND METHODS

This study was an observational longitudinal prospective one. It included patients admitted to stroke unit of medical ICU at Zagazig University Hospitals with diagnosis of stroke in the period from January to June 2012. 280 patients were enrolled in this study. Patients with current DVT before admission were excluded. Patients with ischemic stroke received prophylactic anticoagulation unless contraindicated while for those with hemorrhagic stroke, no anticoagulant prophylaxis was used. Informed consents to participate in the study were obtained from patients or their relatives.

Methods: All subjects of this study were subjected to the following:

a - History of the present illness and past history of any medical disorder with particular attention to HTN, DM, atrial fibrillation and smoking.

b - Full general examination with special attention to ; blood pressure measurement, pulse, temperature and cardiac examination. During their hospital stay, all patients were examined for possibility of DVT (if the circumference of the an extremity was more than 1 cm larger than the other side, it was

considered as swollen. Also we searched for local pain or tenderness).

c - Full neurological examination.

d - Routine investigations including complete blood picture, renal and liver function tests, bleeding profile (PT, PTT, INR), random blood glucose levels, electrolytes, serum, C-reactive protein,, ECG,

e - D- dimer, a suspected marker for DVT were done for all patients.

f - Radiological investigation including; brain CT on admission to clarify wether the stroke was of an ischemic or hemorrhagic etiology, and Doppler ultrasonography (DUS) at one and two weeks after admission or when DVT was clinically suspected before or after this time. DUS was done to the upper and lower limbs (paralyzed and healthy).

g - Severity assessment was done using the commonly used scoring systems in ICU for critically ill patients, Glasgow coma scale. (GCS)

Glasgow coma scale **[6]:**

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Open eyes in response to voice	Open eyes Spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensive sounds	Utters inappropriate words	Confused, disoriented	Oriented converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli(decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Generally, impairment of level of conciousness is classified as: Severe with GCS ≤8, Moderate GCS 9-12, Minor GCS ≥13

Statistical analysis : All data were coded, checked, entered and analyzed using SPSS software version 17.

RESULTS

Table (1): Incidence of DVT in stroke patients and its relation to the etiology.

Type of stroke	Total number of patients =280	Patients complicated by DVT Number =25 (8.93 %)	Percentage(%)
ICH	28	7 cases	25%
Infarction	213	16 cases	7.5%
SAH	39	2 cases	5.1%

Table (2): Radiological distribution of the DVT (n=25).

	Lower limb (n=22)	Upper limb (n=3)	Total (n=25)
Right / left	9/14	0/2	10/15
Proximal / Distal	7 / 16	2	8 / 17
Paralytic / Healthy	17 / 6	2 / 0	19 / 6

Of the 25 DVT cases, 23 occurred in the lower limbs and 2 in the upper limbs. The weak limb was affected in 23 patients.

Table (3): Socio-demographic characteristics of the study group.

	Mean age ± SD	Number of patients	Percentage
Age ranged from 38-79 yrs	60.5 ± 7.6		
S e x : M a l e / Females		1 3 0 / 150	4 6.4 % / 53.6 %
Smoking : Smokers		32	11 .4 %
Nonsmkers		248	88 .6 %

The mean age for the patients was 60.5 years, 130 were males and 11. 4 % of the all were smokers.

Table (4): Clinical characteristics of the study group.

Comorbidity	**Number of the patients**	**Percentage %**
Diabetes (DM)	85	30.1 %
Hypertention (HTN)	110	39.2 %
Atrial Fibrillation (AF)	50	18.2 %
DM & HTN	35	12.5 %
Glasgow coma scale (GCS) (X ± SD)	10.28 ± 2.52	
Type of stroke : Intracerebral hemorrhage (ICH)	28	10 %
Cerebral infarction	213	76.1 %
Subarachnoid hemorrhage (SAH)	39	13.9 &

Table (5); Special characteristics of the complicated patients.
The mean duration of onset of DVT was 13.96 days ranging from 4 to 32 days.

	Mean value (x) ± SD	**Minimum**	**Maximum**
Period of recumbency before DVT in days	13.96 ± 7.54	4	32
D – dimer	3891.56 ± 1095.56	1280	5880
GCS	9.64 ± 3.19	4	14

Table (6): Univariate analysis of the data regarding social characteristics:

	DVT group	**Non DVT group**	**Test of significance**	**p- value**
	n = 25	n = 255		
Age (yrs) ,(X ± SD)	64.04 ± 11.53	60.13 ± 7.04	2.47	0.01
Age >65 (n = 70)	11 (15.7 %)	59 (84.3 %)	5.285	0.022
Age <65 (n = 210)	14 (6.7 %)	196 (93.3 %)		
Sex : Male	13 (10 %)	117 (90 %)	0.343	0.558
Female	12 (8 %)	138 (92 %)		
Smoking: Smokers	7 (21.9 %)	25 (78.1 %)	7.447	0.006
Nonsmokers	18 (7.3 %)	230 (92.5 %)		

Univariate analysis of data of complicated group compared to uncomplicated group from the socio-demographic point of view showed that the mean age of patients complicated with DVT was 64.04 from which 15.7% were elder than 65 years old. Patients complicated with DVT were elder in age , had significantly higher percentage of smokers and comparable gender distribution.

Table (7) Comparison between DVT & non DVT group as regarding other co-morbidities & Glasgow coma scale

	Complicated group		uncomplicated group		Test of significance	p - value
Number	**25**		**255**			
Co-morbidity						
- Diabetes	**11**	**(12.6 %)**	**76**	**(87.4 %)**	**2.142**	**0.143**
(n=87)	**12**	**(10.4 %)**	**103**	**(89.6 %)**	**0.455**	**0.461**
- Hypertension	**11**	**(21.6 %)**	**40**	**(78.4 %)**	**12.253**	**0.000**
(=115)	**4**	**(9.8 %)**	**37**	**(90.2 %)**	**0.04**	**0.841**
- Atrial fibrillation (n=51)						
- DM & HTN (n=41)						
GCS (x ± SD)	**9.46 ± 3.19**		**10.34 ± 2.44**		**1.33**	**0.18**

There was a statistically significant difference regarding presence of AF as a predictor of DVT , but statistically non significant difference regarding co morbidity with diabetes and hypertension or regarding Glasgow coma scale.

Table (8), Univariate analysis of the data as regarding type of stroke.

Type of stroke	Total number of patients	Complicated patients	Test of significance	p- value
ICH	28	7 cases = 25 %	Fisher (corrected chi square)	0.006
Infarction	213	16 cases = 7.5 %	2.2	0.13
SAH	39	2 cases = 5.1 %	Fisher	0.54

Patients having ICH appear to have a risk of developing DVT more than cerebral infarction and SAH as 25% of hemorrhagic stroke patients were complicated by DVT.

Table (9) Backward Step wise regression analysis of the factors predicting DVT among study group.

		B	S.E.	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
						Lower	Upper
Step 3(a)	**AF**	1.423	.460	.002	4.150	1.685	10.221
	ICH	1.947	.870	.025	7.010	1.274	38.573
	Infarction	.781	.795	.326	2.184	.460	10.377
	Constant	-3.608	.792	.000	.027		

This table showed that AF and ICH were the most predicors of DVT among acute stroke patients.

DISCUSSION

Deep vein thrombosis (DVT), including pulmonary embolism (PE) as a sequel, is a serious complication of various medical conditions including stroke. It is considered to develop mostly within 2 weeks post-stroke. The diagnosis of DVT in the critically ill patients presents specific challenges because many patients are not able to communicate their symptoms **[5]** . The aim of our study was to establish the occurrence of early stroke-related DVT and to identify risk factors for its development. This work was a prospective study conducted from January to June 2012 at the stroke unit of Medical ICU at Zagazig University Hospitals. 280 patients were enrolled in this study.

Our findings showed that the frequency of DVT in acute stroke patients admitted to medical ICU was 8.93%. Out of 280 patient admitted to ICU having acute cerebrovascular accident; 25 got DVT during their stay in ICU.These results are consistent with a study performed by **Bembenek et al.[7],**at Poland in which 10.7% of stroke patients were complicated by DVT

In a study carried out in four critical care unites in Assuit Main University Hospital at 2008, 6.66 **%** of the study group (critically ill medical patients) developed DVT during hospital stay **[8] .** In a study carried out to identify importance of prophylaxis against Venous Thromboembolism in "Anaesthesia ICU of Zagazig University Hospitals" at 2002 , 6 cases out of 92 were recorded to have DVT with an overall incidence of 6.5 % **[9].**

In three large randomised study groups, the prevalence ranged from 3.4 % to 6.6%.**[10]. Vergouwen et al. [11],** in his study, reported clinically relevant DVT in 1% to 5% of the patients. In our study, newly developed early stroke-related DVT was predominantly distal (17 of 25 cases), which is consistent with other studies **[12].**We found that 19 out of the 25 complicated cases affected the paralyzed limb . This is in agreement with previous studies such as **Brandstater et al.[13],** who found an incidence of DVT of approximately 50% within 2 weeks in the absence of heparin prophylaxis; the majority of these affected the paralyzed limbs and were asymptomatic. The risk of DVT correlated with the degree of paralysis**.** Based on this and previous studies, it can be concluded that patients with severe stroke have a higher propensity for developing DVT. Predilection for the paralyzed limb is probably explained by a combination of loss of the calf muscle pump and repeated minor trauma **[14].** Our results revealed that older patients were more vulnerable to the emergence of DVT post stroke. The mean age for complicated group in our study was 64.04 years and age above 65 yrs was significantly complicated by DVT using univariate analysis of data (p=0.022).This is in agreement with **Sun et al.[15]** who found DVT more frequent (28.0%) in the patients ranging 70 approximately 79 years. In our study, there was no difference regarding gender in complicated cases (p=**0.558**) in ageement with most of the previous studies as **Kong** et **al.[16].** who found DVT was not related to gender, race or ambulatory status**.** However**, Sun et al.[15],** found a higher incidence of DVT observed in female more than in male (29.4% vs 18.0%, P = 0.004) from 488 cases he examined . In this study, Patients complicated with DVT had significantly higher percentage of smokers (21.9 % p=0.006) by univariate analysis of the data. Although it seems possible that elevated levels of fibrinogen may contribute to an increased rate of venous thromboembolism(VTE), the nature of the relationship between smoking and elevated fibrinogen levels appears much clearer. Indeed, it would appear that cigarette smoking is the strongest known environmental influence on plasma fibrinogen concentration and has consistently been linked to elevated plasma fibrinogen levels **[17].** Tobacco smoke reduces the amount of oxygen carried in the blood and may damage vessel walls, potentially leading to clot formation **[18].** As for co-morbid diseases, we found no significant difference regarding hypertension (p=0.461) , diabetes (p=0.143) or both together (p=0.841) upon predicting DVT occurrence . This was in correlation with previous studies in which no significant difference was mentioned regarding DM or HTN .

In our study , we found a high significance regarding atrial fibrillation using univariate analysis (11 out of 25 ; 21.6% , p=0.000) and multivariate regression analysis (p=0.002) . **Noel et al. [19],**found that the frequency of thromboembolic events in patients with AF far exceeded that in those without (P=0.001). Patients with AF were significantly older and had higher frequencies of cardiomegaly and history of cardiac failure, both conditions probably being linked. In view of these data, a possible pathophysiologic role of a poor hemodynamic situation as the main risk factor for deep venous thrombosis with an indirect effect of AF was considered. Therefore, it seems that AF is an independent risk factor for deep venous

thrombosis or pulmonary embolism in stroke patients.

Our results revealed that 25 % of intracerebral hemorrhage cases were complicated with DVT (p= 0.006) while 7.5% of patients with ischemic stroke were complicated with DVT which is in line with the results of a study suggesting that patients with ICH may, in fact, be at higher risk for DVT than ischaemic stroke patients **[20].**

Gregory and Kuhlemeier [21], investigated the prevalence of DVT in both hemorrhagic and thromboembolic stroke patients hospitalized acutely. They found that the presence of hemorrhagic stroke was an independent risk factor for DVT (p<0.0007). An additional risk factor for DVT included increased length of hospital stay (p<0.00001) Also, **Skaf et al.[22],**observed a surprisingly increased rate of DVT and VTE in hemorrhagic stroke patients in comparison to ischemic stroke patients. Although, they noted that the ischemic stroke patients use antithrombrotic prophylaxis more frequently which could account for the rate difference in hemorrhagic patients.

The incidence of clinically apparent DVT was studied in a large cohort of hospitalized patients with stroke from 1979 to 2003 determined from the National Hospital Discharge Survey. DVT was reported in 0.74% of 1,4109,000 patients with ischemic stroke and in 1.37% of 1,606,000 patients with hemorrhagic stroke. The difference between patients with ischemic and hemorrhagic stroke probably is the result of less rigid preventive management and of a generally more severe focal deficit in the second group. In the CLOTS-2 (Clots in Legs or stockings after Stroke), DVT also occurred about twice as often after hemorrhagic stroke than after ischemic stroke **(Clots in Legs or stockings after Stroke) Trial Collaboration 2010).**

From our study we can conclude**:** Incidence of DVT among patients with stroke during ICU stay was 8.93% being higher in hemorrhagic than ischemic strokes (25% vs. 7.5%). Patients complicated with DVT were characterized by being older and having higher percentage of smokers and presence of AF and higher presentation with ICH. Gender, co morbid diseases (DM, HTN) and GCS had no differences between complicated and uncomplicated patients. Using multivariate regression analysis; presentation with AF and intracerebral hemorrhage were found to be the most important predictors of DVT occurrence.

*** Recommendations:**

Efforts should be made to improve nursing via integrated system that involves the cooperation of physician, physiotherapists, and radiologists to provide early and specific diagnosis, maintain limb function and joint mobility, avoid complications and moreover to qualify the patient at later stage to live near normal life.

DVT prophylaxis should be given according to protocols or standardized practice , not according to discretion of the physicians. Patients proven to have AF should start anti- coagulation therapy unless contraindicated.

American Heart Association (AHA) Stroke Council Recommendations for patients with acute primary ICH [23].

Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful andeffective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of aprocedure or treatment

Class IIa**:** The weight of evidence or opinion is in favor of the procedure or treatment

Class IIb: Usefulness/efficacy is less well established by evidence or opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful

Therapeutic recommendation

Level of Evidence A: Data derived from multiple randomized clinical trials

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies

Level of Evidence C**:** Consensus opinion of experts

Recommendations for Prevention of Deep Vein Thrombosis and Pulmonary Embolism

1. Patients with acute primary ICH and hemiparesis/hemiplegia should have intermittent pneumatic compression

for prevention of venous thromboembolism(*Class I, Level of Evidence B*).

2. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 3 to 4 days from onset *(Class IIb, Levelof Evidence B).*

3. Patients with an ICH who develop an acute proximal venous thrombosis, particularly those with clinical or subclinical pulmonary emboli, should be

considered for acute placement of a vena cava filter *(Class IIb, Level of Evidence C)*.

4. The decision to add long-term antithrombotic therapy several weeks or more after placement of a vena cava

filter must take into consideration the likely cause of the hemorrhage (amyloid [higher risk of recurrent

ICH] versus hypertension), associated conditions with increased arterial thrombotic risk (eg, atrial fibrillation

[AF]), and the overall health and mobility of the patient *(Class IIb, Level of Evidence B)*.

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الملخص العربي

المقدمة:
تعتبر السكتة الدماغية من أهم أسباب العجز الجسدى لدى كبار السن حيث يترتب عليها قلة النشاط الحركى وملازمة الفراش لمدة طويلة والتى قد تؤدى الى حدوث مضاعفات كثيرة من أهمها حدوث جلطات وريدية عميقة والانسداد الرئوى. وقد أظهرت الدراسات المختلفة فى مرحلة ما بعد السكتة الدماغية أن معدلات الاصابة بجلطات الساقين العميقة تتراوح ما بين ٢,٥% الى ٥٠% وذلك يعتمد على طريقة وتوقيت الفحص وغالبا ما تحدث ما بين أسبوع الى أسبوعين من الاصابة بالسكتة الدماغية، بينما نسبة حدوث الانسداد الرئوي تتراوح ما بين ٠.٨% الي ٣٩% .

الهدف من البحث:
تقييم نسبة الاصابة بجلطات الاطراف الوريدية العميقة في مرضي السكتة الدماغية في وحدة الرعاية المركزة بقسم الباطنة بمستشفيات جامعة الزقازيق وتقييم العوامل المساعدة والمؤثرة في حدوثها .

الدراسة والوسائل:
تم اختيار مرضي السكتة الدماغية من وحدة الرعاية المركزة بقسم الباطنة بمستشفيات جامعة الزقازيق في الفترة من يناير الي يونيو ٢٠١٢ ، وقد تم أخذ التاريخ المرضي كاملا لكل مريض وتم اجراء الفحص السريري العام وفحص الاطراف للبحث عن اعراض الجلطات العميقة كما تم عمل اشعة صوتية لاوردة الساقين والذراعين وكذلك الفحص المعملي لنسبة دي- دايمر .
اظهرت نتائج البحث اصابة ٢٥ حالة بجلطة الاطراف الوريدية العميقة من اجمالي ٢٨٠ حالة سكتة دماغية (ما يعادل ٩%) وتزداد نسبة حدوث هذه المضاعفات في حالات النزيف الداخلي بالمخ وكذلك المرضي الذين يعانون من الاضطراب الاذيني.

التوصيات :
-العناية الطبية الكاملة بمريض السكتة الدماغية وتشجيع الحركة مبكرا .
-استخدام المراتب الهوائية والشرابات الهوائية الضاغطة في حالات نزيف المخ .
-استخدام مضادات التجلط بجرعات وقائية ما لم تكن محظورة وحسب البروتوكولات المعترف بها .