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Incidence of Hemorrhagic Complications among Patients Treated with Thrombolytic in Erbil City, Iraq

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ABSTRACT

Background: Recombinant tissue-type plasminogen activator is an option of treatment for suspected occlusive vascular thrombi and its sequel (transmural myocardial infarction, pulmonary embolism, and ischemic stroke). The most important concern associated with those patients is the fear of hemorrhagic complications.
Objectives: To evaluate the incidence and risk factors of bleeding following the use of recombinant tissue-type plasminogen activator.
Materials and methods: This prospective study was conducted in the Intensive Care Units of Roj-halat Emergency Hospital and Rizgary Teaching Hospital in Erbil city, Iraq. The duration of the study was through the period from 1st of June, 2016 to 1st of March, 2017. A convenient sample of 100 patients was selected. The patients were followed after their admission to Intensive Care Units for 24 hours after their treatment with recombinant tissue-type plasminogen activator to explore their complications.
Results: Bleeding complication represented 10% of patients treated with recombinant tissue-type plasminogen activator (50% for each major and minor bleeding). There was a significant association between increased age of patients treated with recombinant tissue-type plasminogen activator and bleeding (P-value = 0.01). Patients with a history of hypertension, diabetes, and smoking were significantly associated with a bleeding complication of recombinant tissue-type plasminogen activator (P-value <0.05).
Conclusion: The incidence of bleeding among patients after treatment with recombinant tissue-type plasminogen activator in the intensive care unit was acceptable. The age, diabetes, smoking, and hypertension were risk factors for increasing the bleeding complications in subjects treated with recombinant tissue-type plasminogen.

Keywords: Recombinant tissue-type plasminogen; Bleeding; Complications; Incidence.

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INTRODUCTION

Plasminogen is a glycoprotein formed in the liver, and it circulates in the blood, with a half-life of 2.2 days. Plasmin is formed from its precursor plasminogen. It has the ability to lyse fibrin clots to fibrin degradation products (FDP) and D-dimer; the conversion to active protease is mediated by tissue-type (tPA) and urokinase-type (uPA) plasminogen activators. Alpha2-antiplasmin is the main inhibitor of the generated plasmin which quickly inactivated [1, 2].

Myocardial infarction (MI) is a life-threatening condition that results from the reduction of oxygen supplying the cardiac tissue due to coronary artery occlusion. The end result is the death of heart tissue with a reduction of cardiac output and blood pressure.

As a result of low blood pressure, sympathetic stimulation occurs and leads to vasoconstriction which results in a reduction of coronary blood flow hindering even more heart contractility, ultimately leading to cardiogenic shock and death. So, immediate treatment of the MI prevents more tissue death and the development of cardiogenic shock [3].

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The main objective in the treatment of MI is restoring the cardiac blood flow in the shortest possible time. To achieve this aim, there are various ways include minimally invasive operations like percutaneous coronary interventions (PCI), and pharmacological drugs like recombinant tissue-type plasminogen activator (rtPA) [3].

The pre-hospital treatment of MI reduces morbidity and mortality, therefore, it became an essential therapeutic option [4]. Pre-hospital thrombolysis gives certain advantages, such as immediate access, and the possibility to add adjunctive drugs [4]. Thrombi that involve the deep veins of the lower limbs, pelvis, renal, upper limbs, or the right cardiac champers might result in the development of pulmonary embolism (PE). The thrombolytic agent should be used in individuals with acute PE associated with low blood pressure and without a high risk of bleeding [5].

In the USA, the following thrombolytic drugs Alteplase, Reteplase, and Tenecteplase are approved for the treatment of MI. While, Tenecteplase is used in the treatment of MI during the pre-hospital period, before the availability of PCI [6]. Intravenous ACTILYSE is used in adults to lyse suspected occlusive coronary artery thrombi associated with evolving transmural MI. The treatment can be initiated within 12 hours of symptom onset [7]. The following should be considered in management:

1. Ischemic symptoms or equivalent $\leq$ 12 h.
2. ST-elevation ¿1mmin2 contiguous leads.
3. Bundle-branch block presumed to be new.

Also, ACTILYSE is used in subjects with acute massive PE and acute ischemic stroke in whom the thrombolytic agent is considered appropriate [8, 9]. Early initiation of thrombolytic agents has a more favorable result [10, 11]. We aimed to assess the incidence and risk factors of hemorrhage after the use of a rtPA.

MATERIALS AND METHODS

This study is a prospective study conducted in the Intensive Care Unit (ICU) of Roj-halat Emergency Hospital and ICU of Rizgary Teaching Hospital in Erbil. The duration of the study was through the period from 1st of February 2016 to 1st of March, 2017. Patients with cardiovascular diseases admitted to ICU of Roj-halat Emergency Hospital and ICU of Rizgary Teaching Hospital and treated with rtPAs were the study population.

Inclusion criteria were all patients who were indicated for treatment via rtPA and stay at ICU for at least 24 hours after drug infusion. The exclusion criteria were patients left the hospital before 24 hours and the patient died before 24 hours due to causes other than hemorrhage (cardiac complications mostly). A convenient sample of 100 patients treated with rtPAs in ICU was selected after eligibility for inclusion and exclusion criteria. Informed consent was taken from every subject. The study was approved by the Arab Board Committee.

Detailed information was taken from every patient regarding the age, gender, occupation, history of smoking, diabetes mellitus, hypertension, heart failure, coronary artery disease, and other chronic diseases, and evidence of bleeding after treatment with rtPAs. Bleeding from the gum was considered minor form, while, intracranial hemorrhage (ICH) was considered a major type.

The number of Platelets, PT, APTT, serum creatinine, and blood urea were recorded for every subject. The data were analyzed using version 22 SPSS for quantitating and qualitative variables. P Value < 0.05 considered a statistically significant difference.

RESULTS

A total of 100 patients admitted to ICU and treated with rtPA were included in this study with a mean age of 62.1±11.2 years; 60% of them were affecting the age groups ¡50 and 60-69 years (30% for each group). Males were more than females with male to female ratio as 1.3:1. Most occupation of our patients was retired (43%). All these findings were shown in Table 1.

Most of our patients with a history of hypertension (66%), smoking (62%). While, the majority without a history of heart failure (93%), coronary heart diseases (84%) and other chronic diseases (91%) Table 2.

The results of investigations (Platelets, PT, APTT, serum creatinine, and blood urea) in the majority of the studied patients were normal Table 3.

Only 10% (5% for each minor and major bleeding) of the patients were suffered from bleeding following rtPA treatment as in Table 4.

There was a statistically significant difference between patients with or without a history of hypertension, diabetes, and smoking regarding the bleeding complication P-value <0.05 Table 5.

There was a high statistically significant difference between the 2 groups (bleeding vs non-bleeding) regarding the number of platelets, PT, and APTT P-value 0.001 Table 6.

DISCUSSION

The biochemical and cellular changes of blood represented in balance referring to hemostasis which working in two ways; fibrinolysis aiming in maintaining blood in fluid state and coagulation aiming in preventing blood loss [1]. The most commonly used fibrinolytic nowadays is the rtPAs which are the results of genetic engineering techniques DNA sequence mutations of tissue-type plasminogen activators. The new ver-

Table 1. Sociodemographic characteristics of patients treated with rtPA.

Variable	No.	%
Age		
<50 years	30	30.0
50−59 years	26	26.0
60−69 years	30	30.0
≥70 years	14	14.0
Total	100	100.0
Gender		
Male	56	56.0
Female	44	44.0
Total	100	100.0
Occupation		
Housewife	32	32.0
Public servant	8	8.0
Self-employed	17	17.0
Retired	43	43.0
Total	100	100.0

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Table 2. Sociodemographic characteristics of patients treated with rtPA.

Variable	No.	%
Hypertension		
Yes	66	66.0
No	34	34.0
Total	100	100.0
DM		
Yes	48	48.0
No	52	52.0
Total	100	100.0
Heart failure		
Yes	7	7.0
No	93	93.0
Total	100	100.0
Coronary heart diseases		
Yes	16	16.0
No	84	84.0
Total	100	100.0
Smoking		
Yes	62	62.0
No	38	38.0
Total	100	100.0
Other chronic diseases		
Yes	9	9.0
No	91	91.0
Total	100	100.0

Table 3. Investigation results of patients treated with rtPA.

Variable	No.	%
Platelets mean±SD (156.7±25.5×10^9/L)		
Normal	90	90.0
Low	10	10.0
Total	100	100.0
PT mean±SD (13.2±1.4 seconds)		
Normal	95	95.0
Prolonged	5	5.0
Total	100	100.0
APTT mean±SD (34.9±5.3 seconds)		
Normal	95	95.0
Prolonged	5	5.0
Total	100	100.0
Serum creatinine mean±SD (1.3±0.8 mg/dl)		
Normal	77	77.0
High	23	23.0
Total	100	100.0
Blood urea mean±SD (45±18.9 mg/dl)		
Normal	75	75.0
High	25	25.0
Total	100	100.0

sions of rtPAs were characterized by convenient bolus dosing, longer half-life, enhanced brin specicity and higher resistance [2].

Bleeding complications after the use of rtPA in the present study were detected in the incidence rate of 10% of patients. This finding is lower than the bleeding rate of 12% reported by Al-Kubaisi & Al-Rikabi study in Iraq [12] on 50 patients with myocardial infarction in ICU. Our results are also lower

Table 4. Bleeding complication following rtPA treatment.

Variable	No.	%
Bleeding		
Yes	10	10.0
No	90	90.0
Total	100	100.0
Bleeding types		
Major (ICH)	5	50.0
Minor (gums)	5	50.0
Total	10	100.0

Table 5. Distribution of co-morbidities of patients treated with rtPA according to bleeding.*

Variable	Bleeding		No bleeding		X^2	P
	No.	%	No.	%		
Hypertension					5.7*	0.01
Yes	10	100.0	56	62.3		
No	0	–	34	37.7		
Diabetes Mellitus					4.5*	0.04
Yes	8	80.0	40	44.5		
No	2	20.0	50	55.5		
Heart failure					2.8*	0.1
Yes	2	20.0	5	5.6		
No	8	80.0	85	94.4		
Coronary heart diseases					0.6	0.4
Yes		3 30.0	13	14.4		
No	7	70.0	77	85.6		
Smoking					3.7*	0.08
Yes	9	90.0	53	58.9		
No	1	10.0	37	41.1		
Other chronic diseases					1.1*	0.6
Yes	0	–	9	10.0		
No	10	100.0	81	90.0		

* Fisher's exact test.

than the results of Muhamad et al [13] study in Malaysia which was a retrospective study on MI patients admitted to the emergency unit from 2009-2011 and found that 12% of MI patients treated with rtPAs had bleeding complications. However, the bleeding rate of 10% in the present study is higher than the bleeding rate of 6.5% found by Erlemeier et al [14] study in Germany. These differences between studies are not wide and might be due to differences in study designs and inclusion criteria. The rtPAs are regarded as novel drugs for the treatment of myocardial infarction, acute ischemic stroke, and pulmonary embolism. Although the advantages of rtPAs use, many contraindications, and serious disadvantages were discovered in multiple studies [2]. Berkowitz et al [15] study in Canada showed that the use of rtPAs for MI patients was associated with much co-morbidity like bleeding (12.6%), long hospital stay (22%) and mortality (1.1%).

Our study found that 5% of cases after rtPAs had intracranial hemorrhage (ICH) and the other 5% had minor (gums) bleeding. This finding is higher than the results of Pheerawong et al [16] study in Thailand which reported a rate of ICH as 1%. In another study carried out in the USA by Brass et al [17], the ICH rate among MI patients in ICU after treatment with rtPA was 1.43%. However, it was documented that

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Table 6. Distribution of investigations findings of patients treated with rtPA according to bleeding.*

Variable	Bleeding		No bleeding		X^2	P
	No.	%	No.	%		
Platelets					100*	<0.001
Normal	0	–	90	100.0		
Low	10	100.0	0	–		
PT					47.4*	<0.001
Normal	5	50.0	90	100.0		
Prolonged	5	50.0	0	–		
APTT					47.4*	<0.001
Normal	5	50.0	90	100.0		
Prolonged	5	50.0	0	–		
Serum creatinine					0.03	0.8
Normal	2	20.0	21	23.3		
High	8	80.0	69	76.7		
Blood urea					2.3	0.1
Yes	5	50.0	70	77.8		
No	5	50.0	20	22.2		

* Fisher's exact test.

the risk of ICH is ranging from 5-6% among MI and stroke patients managed by rtPAs. Balami et al study in the UK stated that causes of ICH were vessel wall breakdown, low fibrinogen, platelet disruption in addition to disruption of the blood-brain barrier [18]. Minor bleeding rate of 5% is lower than the results of Pheerawong et al [16] study in Thailand which reported a rate of 15.5%. Periodontitis was the common risk factor that influences minor gums bleeding especially for elderly age patients [19].

The current study showed a highly significant relationship between elderly age MI patients and increased incidence of bleeding after rtPAs treatment (P-value<0.001). This is similar to the results of De Jaegere et al [20] study in the Netherlands which stated that the ICH rate was increased among MI patients in ICU after rtPAs treatment. On the other hand, Soumerai et al [21] study in the USA found many advantages of rtPA use among elderly patients (>75 years) as compared to disadvantages. Although the high bleeding risk of rtPAs for elderly patients with MI, the outcome of MI patients not treated with rtPAs in ICU remains very high, especially if weighted against mortality outcome. Previous two American observational studies documented that advantages of rtPAs among younger age patients did not include elderly age MI patients (>80 years) [22, 23]. Previous Spanish study on 500 elderly patients with STEMI treated with rtPAs in ICU found after treatment; the mortality rate was 44% which was attributed to myocardial rupture [24]. Finally, the decision regarding rtPAs use for elderly patients is dependable on weighing benefits versus complications [25].

The gender in the present study was not significantly related to the bleeding risk of rtPAs therapy. This finding is inconsistent with the results of Brass et al [17] study in the USA which revealed that female gender MI patients are significantly associated with bleeding after rtPA treatment. This inconsistency might be due to the difference in gender relationships with MI between different countries.

In conclusion, the incidence of bleeding among patients after treatment with rtPA in ICU was 10%. The increasing age, diabetes mellitus, smoking, and hypertension were risk factors for increased bleeding complications in individuals treated with rtPA.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

[1] R. Mehta and A. D. Shapiro. Plasminogen deficiency. *Haemophilia*, 14(6):1261–1268, 2008.

[2] P. Gurman, O. R. Miranda, A. Nathan, C. Washington, Y. Rosen, and N. M. Elman. Recombinant tissue plasminogen activators (rtpa): a review. *Clin Pharmacol Ther*, 97(3):274–285, 2015.

[3] D. Kireyev, H. C. Tan, and K. K. Poh. Management of acute st-elevation myocardial infarction: reperfusion options. *Ann Acad Med Singapore*, 39:927–933, 2010.

[4] P. Goldstein and E. Wiel. Management of prehospital thrombolytic therapy in st-segment elevation acute coronary syndrome (< 12 hours). *Minerva Anestesiol*, 71(6):297–302, 2005.

[5] G. H. Guyatt, E. A. Akl, M. Crowther, D. D. Gutterman, and H. J. Schunemann. Executive summary: antithrombotic therapy and prevention of thrombosis: American college of chest physicians evidence-based clinical practice guidelines. *Chest*, 141(2):7S, 2012.

[6] G. Melandri, F. Vagnarelli, D. Calabrese, F. Semprini, S. Nanni, and A. Branzi. Review of tenecteplase (tnkase) in the treatment of acute myocardial infarction. *Vasc. Health Risk Manag*, 5:249, 2009.

[7] S. G. Goodman and W. J. Cantor. Dripandship for acute stsegment myocardial infarction. *Pol. Arch. Med. WEWNTRZNEJ*, 119(11):726–730, 2009.

[8] J. Rther, G. A. Ford, and V. N. S. Thijs. Thrombolytics in acute ischaemic stroke: historical perspective and future opportunities. *Cerebrovasc. Dis.*, 35(4):313–319, 2013.

[9] A. Baratloo *et al.* Tissue plasminogen activator: A literature review. *Arch Neurosci*, 3(1):e30452, 2016.

[10] M. T. Mullen, J. M. Pisapia, S. Tilwa, S. R. Mess, and S. C. Stein. Systematic review of outcome after ischemic stroke due to anterior circulation occlusion treated with intravenous, intra-arterial, or combined intravenous+ intra-arterial thrombolysis. *Stroke*, 43(9):2350–2355, 2012.

[11] B. T. Bateman *et al.* Factors associated with in-hospital mortality after administration of thrombolysis in acute ischemic stroke patients: an analysis of the nationwide inpatient sample 1999 to 2002. *Stroke*, 37(2):440–446, 2006.

[12] K. B. Al-Kubaisi and M. B. Al-Rikabi. The effect of tissue plasminogen activator on the management of acute myocardial infarction. *IRAQI J. Med. Sci.*, page 278, 2000.

[13] N. A. N. Muhamad, Mm. E. MbBcHBAO, M. S. Azizan, N. A. Masani, T. S. Ling, and O. T. Siang. Asscoci-

http://doi.org/10.33091/amj.2020.170955

ation of risk factors and its bleeding complication for tenecteplase administered in acute myocardial infarction (AMI). *Med J Malaysia*, 68(5):381, 2013.

[14] H.-H. ERLEMEIER, W. Zangemeister, L. Burmester, J. Schofer, D.-G. MATHEY, and W. Bleifeld. Bleeding after thrombolysis in acute myocardial infarction. *Eur. Heart J.*, 10(1):16–23, 1989.

[15] S. D. Berkowitz *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation*, 95(11):2508–2516, 1997.

[16] P. Pheerawong and B. Plienthaisong. Outcome of recombinant tissue plasminogen activator in st-segment elevation myocardial infarction in buriram hospital. *J Med Assoc Thail Chotmaihet Thangphaet*, 97(8):804–811, 2014.

[17] L. M. Brass, J. H. Lichtman, Y. Wang, J. H. Gurwitz, M. J. Radford, and H. M. Krumholz. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the cooperative cardiovascular project. *Stroke*, 31(8):1802–1811, 2000.

[18] J. S. Balami, B. A. Sutherland, and A. M. Buchan. Complications associated with recombinant tissue plasminogen activator therapy for acute ischaemic stroke. *CNS Neurol. Disord. Targets (Formerly Curr. Drug Targets-CNS Neurol. Disord*, 12(2):155–169, 2013.

[19] M. G. Lansberg, G. W. Albers, and C. A. C. Wijman. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. *Cerebrovasc. Dis.*, 24(1):1–10, 2007.

[20] P. P. De Jaegere, A. A. Arnold, A. H. Balk, and M. L. Simoons. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. *J. Am. Coll. Cardiol.*, 19(2):289–294, 1992.

[21] S. B. Soumerai, T. J. McLaughlin, D. Ross-Degnan, C. L. Christiansen, and J. H. Gurwitz. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. *Arch. Intern. Med.*, 162(5):561–568, 2002.

[22] A. K. BERGER *et al.* Primary coronary angioplasty vs thrombolysis for the management of acute myocardial infarction in elderly patients. *Surv. Anesthesiol*, 44(3):136–137, 2000.

[23] B. G. Angeja, A. C. Rundle, J. H. Gurwitz, J. M. Gore, and H. V Barron. Death or nonfatal stroke in patients with acute myocardial infarction treated with tissue plasminogen activator. *Am. J. Cardiol.*, 87(5):627–630, 2001.

[24] M. Martnez-Sells, T. Datino, and H. Bueno. Influence of reperfusion therapy on prognosis in patients aged 89 years with acute myocardial infarction. *Am. J. Cardiol.*, 95(10):12321234, 2005.

[25] A. Carro and J. C. Kaski. Myocardial infarction in the elderly. *ging Dis.*, 2(2):116, 2011.

http://doi.org/10.33091/amj.2020.170955