Review Article

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Conversion of Fibrinolysis Reserves into Thrombolysis Resources. Bolus Compositions of Plasminogen Activators

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ABSTRACT

Analysis of research and clinical data demonstrated the efficacy and ponderability of thrombolysis as the method of choice. Significant reserve of thrombolytic therapy beetles conjunctive application of tissue and urokinase plasminogen activators in decreased doses. The perspective of this combined approach consists in forming of bolus thrombolytic compositions on the base of plasminogen activators due to burly science-medical cooperation of researchers and clinical coworkers.

Keywords

Cardiology research, Thrombolytic therapy, Fibrinolysis, Tissue plasminogen activator, Urokinase plasminogen activator, Conjunctive administration, Bolus thrombolytic composition.

Abbreviations

pro-u-PA: pro-urokinase, STEMI: ST-segment elevation myocardial infarction, t-PA: Tissue plasminogen activator, u-PA: Urokinase plasminogen activator.

Introduction

The bold and brilliant statements concerning thrombolytic era in medical aid gradually lost their shine and clinical position in comparison with high-tech medicine. Primary/emergent percutaneous coronary intervention (PCI) has gained well-deserved significance. An opinion has shaped that the use of thrombolysis will steadily decrease in megapolices with sufficient number of high-tech cardiological aid centers (catheter laboratories). However, the situation in developing Asian, African and Latin American countries with an average delay in hospitalization of patients with acute ST-segment elevation myocardial infarction (STEMI) of 4 hours is different [1]. Accumulated data demonstrate limited availability of primary angioplasty and stenting, implying the necessity of using thrombolytics as therapy of choice. Sudden and fast-developing COVID-19 pandemic caused by SARS-CoV-2 infection has notably changed global agenda of clinical research. Conventional clinical picture has changed considerably under the conditions of pandemic and combination of pathologies. A secondary role of PCI was defined in association with unexpected sudden COVID-19 manifestations in STEMI patients [2]. Fibrinolysis was a better choice than PCI. An objection rapidly raised that there is excessive risk of thrombolysis in these patients and a notable proportion of unsuccessful outcomes [3]. On the basis of this and other documented and approved reports thrombolysis was not recommended as the first-choice method (primary approach). Nevertheless, even in COVID-19 situation diagnostic strategy in STEMI patients is based on coronary angiography [3].

Perpetual Clinical Importance of Thrombolysis

Solution to the PCI-vs-thrombolysis problem can be found by improving both approaches. Are the resources of thrombolysis exhausted? Even superficial analysis of available research results

reveals certain reserves. Fibrinolysis with the use of a single agent (tissue plasminogen activator, t-PA) seems a longstanding mistake [4]. The reason for it is ignoring a complementary effect produced by t-PA and prourokinase (pro-u-PA) in fibrinolysis in vivo and their synergic effect upon lysis of fibrin clot in vitro. Presumably, combination of t-PA bolus with pro-u-PA infusion provides higher safety compared with t-PA alone and allows a considerable decrease in effective doses of both agents. These arguments support fibrinolysis as the simplest and fastest method for restoration of blood flow/circulation with subsequent normalization of its function [4].

Combination of Plasminogen Activators

The development of combined thrombolytic therapy (5 mg bolus t-PA followed by 90-min infusion pro-u-PA, 40 mg/h, PATENT study) was interrupted due to change in the ownership of the company producing pro-u-PA [4]. This approach, nevertheless, was not alone in combined administration of the fibrinolytic agents t-PA and u-PA (urokinase plasminogen activator). Considerable effort was made to increase effectiveness and safety of fibrinolysis by chemical and biological modification of plasminogen activators [5-7], the use of external and internal fibrinolysis [8] and maintaining the thrombolysis-initiating effect of t-PA by prolonged activity of stable u-PA derivatives [9].

Bolus Thrombolytic Compositions

The prospectiveness of these research approaches consists in developing combined compositions based on t-PA and u-PA for bolus administration at markedly reduced doses of both components [5,9]. Combined application of clinical t-PA preparations with modified u-PA is experimentally confirmed [5–7], clinically important [10-12] and requires serious, long organizational and financial efforts for productive activity of highly qualified clinicians and scientists.

Conclusion

After current epidemiological threats are overcome, clinical research into mental health, oncology, cardiology, chronic pain, and telemedical technologies will hopefully regain prepandemic level, the study and therapeutic use of bolus thrombolytic compositions will be given the attention it deserves. Together with the development of arsenal and technologies of catheter laboratories, this approach broadens the prospects for global improvements in health care system and therapy of cardiovascular patients.

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