Research Square

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Targeted delivery of streptokinase based on fibrin-specific liposomes for in vivo ultrasound catheter thrombolysis

Igor Adzerikho
Belarussian State Medical University
Tatyana Vladimirskaya
Belarussian State Medical University
Irina Lutsik
Belarussian State Medical University
Anatoly Kulak
kulak@igic.bas-net.by

Institute of General and Inorganic Chemistry of National Academy of Sciences of Belarus

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Abstract

Background

Thrombolytic drugs, including streptokinase (SK), are widely used in the treatment of acute thrombosis. A new fibrin-specific immunoliposomal formulation of streptokinase (LSK) for local delivery to the thrombolytic site has demonstrated a significant increase in vascular clearance compared to native SK.

Objectives

To assess the feasibility of improving the efficiency of fibrin-specific liposomes for SK targeted delivery in combination with the intravascular action of catheter ultrasound (US), in acute peripheral arterial thrombosis.

Methods

15 adult male mongrel dogs with arterial thrombosis induced by thrombin were divided into three groups: I) US exposure; II) SC-LSC; III) SC-LSC, followed 30 min after administration by US exposure. US frequency of 25 kHz and an intensity of 48 W/cm² was delivered to the thrombosis zone using a flexible 56 cm waveguide. Assessment of hemostatic parameters included the determination of D-dimer, fibrinogen, plasminogen, and α2-antiplasmin levels. The degree of vessel lumen patency was assessed using histological morphometry.

Results

An *in vivo* experiment demonstrated the potential to significantly enhance the thrombolytic effect of a combined thrombolytic drug comprising 60% native (molecular) SK and 40% LSK, with the additional local application of low-frequency high-intensity ultrasound. The degree of thrombolysis was greatest with the combined action of ultrasound and SK-LSK (86.1%) compared to the individual use of SK-LSK drug (70.2%) and ultrasound alone (12.3%).

Conclusions

The introduction of US into the thrombosis zone in combination with a thrombolytic agent containing free SK and LSK ensured a high degree of thrombolysis without causing a critical increase in fibrinogenolysis, bleeding and other dangerous consequences for animals.

1. Introduction

Thrombolytic drugs, including streptokinase, are widely used in the treatment of acute thrombosis. Using liposomes as carriers for thrombolytic drugs enhances thrombolysis by increasing the penetration of plasminogen activator into the thrombotic mass. Targeted delivery of the drug directly to the thrombus allows for a lower drug dose and a reduced risk of hemorrhagic complications [1, 2]. Fibrin-specific

liposomes for the targeted delivery of streptokinase increased the rate of vascular clearance by an average of 71% in an experimental animal model of thrombosis [3, 4].

The intravascular application of high-intensity, low-frequency ultrasound to thrombi is a promising thrombolysis method. Catheter-delivered ultrasound has been successfully used for intravascular thrombolysis in vitro and in vivo experiments [5–12]. Combining ultrasound with streptokinase enhances the thrombolytic effect, increasing arterial patency and reducing the risk of distal embolism [11, 12].

This study aims to assess the feasibility of improving the efficiency of fibrin-specific liposomes for targeted delivery of streptokinase, in combination with the intravascular action of catheter ultrasound, in acute peripheral arterial thrombosis in animals. The thrombolytic agent used was SK-LSK, containing both free streptokinase (SK) and liposome-bound streptokinase (LSK) in a 0.6/0.4 ratio, a previously developed agent [3] that has been successfully tested *in vivo* in animals [4].

2. Materials and Methods

2.1. Preparation of a targeted streptokinase delivery thrombolytic agent

The liposomal form of streptokinase LSK was prepared by encapsulating it in liposomes conjugated via carboxylated dextran with fibrin-specific monoclonal antibodies FnI-3C (IgG2 class) [3, 4]. For liposome preparation, a mixture of phosphocholine and cholesterol in a 2:1 molar ratio was dissolved in chloroform, and the solvent was evaporated until a homogeneous film formed. A 40 mM aqueous glucose solution was then added, and the mixture was sonicated for 1–2 min. The resulting suspension was lyophilized. Streptokinase was added to the lyophilized liposomes at a concentration of 34,500 U per 1 mg of lipid, followed by three freeze-thaw cycles and final lyophilization. To enhance fibrin specificity, the streptokinase-loaded liposomes were conjugated with monoclonal antibodies to fibrin. For this purpose, a liposomal form of streptokinase containing 3 mol.% hexadecylamine was mixed with a conjugate of carboxylated dextran and fibrin-specific monoclonal antibodies FnI-3C (IgG2 class) and incubated for 1 hour with stirring.

2.2. Ultrasound System

The Pulsar ART-UN1 ultrasonic waveguide-catheter system for intravascular thrombus disruption (Belarusian National Technical University, Minsk, Belarus) was used. The system consists of an ultrasonic generator with adjustable power, a piezoelectric transducer, and a flexible waveguide with a variable cross-section, 560 mm in length, and a spherical end with a 1.8 mm diameter. The ultrasound intensity was 48 W/cm², the frequency was 25 kHz, and the duty cycle 50%.

2.3. Animal Experiments

Experiments were performed on 15 adult mongrel male dogs weighing 15–18 kg in accordance with bioethical principles following the European Convention for the Protection of Vertebrate Animals used

for experimental and other scientific purposes, and the requirements and recommendations, regulatory, scientific, methodological, and reference materials for animal care, feeding, and withdrawal from experiments with subsequent disposal. Experimental protocol was approved by the local Animal Experiment Ethics Committee.

The animals were anesthetized by intramuscular injection of a 5% ketamine solution (6 mg/kg); to maintain anesthesia, 2% sodium thiopental (20 mg/kg), 0.25% droperidol (0.1 mg/kg), 0.005% fentanyl (0.0003 mg/kg), and 1.5% sodium ethaminal (2.0 ml/kg) were administered intramuscularly.

Arterial thrombosis in dogs was simulated for 120 minutes by injecting 0.1 ml of thrombin solution (TECHNOLOGY STANDARD, Barnaul, Russia) into the femoral artery over a 5-cm section bounded by ligatures. The vessel wall was clamped with forceps for 5–10 sec. The presence of a thrombus in the vessel was visually determined by the absence of blood flow in the peripheral areas after the ligatures were removed.

The animals were divided into 3 groups of 5 animals each.

Group I (ultrasound group) underwent catheter ultrasound treatment of a selected vessel fragment (the area of the simulated thrombus) followed by the administration of a heparin solution (Belmedpreparaty, Minsk, Belarus) An introducer sheath (Terumo, Tokyo, Japan) with an outer diameter of 6 Fr and 110 mm length was inserted at the level of the popliteal artery. Immediately before ultrasound treatment, a straight Balton catheter (Balton, Warsaw, Poland) with a diameter of 5 Fr and a length of 500 mm was inserted through the introducer into the internal lumen, into which a waveguide was placed. To prevent thermal and cavitation damage to the vascular wall, the distal end of the waveguide did not exit the catheter lumen. Saline solution was injected through the side port at a rate of 0.1 ml/s. The ultrasound exposure was performed under visual control, moving the waveguide from the proximal to the distal end of the thrombus and back for 3 min at a speed of about 0.6 cm/min.

Group II (SK-LSK group) received SK-LSK diluted in 35 ml of isotonic sodium chloride solution into the femoral vein over 30 min using a 14G peripheral venous catheter (B Braun, Germany) with 2.1 mm outer diameter. Heparin was also administered intravenously by bolus injection at 50 U/kg dose, followed by infusion of the drug at a dose of 22 U/kg/h until the end of the study.

Group III (SK-LSK / US group) received the drug and heparin using the same method and dose as Group II. Thirty minutes after administration, intravascular ultrasound was administered using the same technique as in Group I.

Animals were observed for 180 min from the start of treatment. After this, animals were sacrificed in accordance with GLP standards by administering the maximum dose of 2% sodium thiopental. Arterial sections containing thrombi were excised for histological examination.

2.4. Hemostasis studies

Blood samples were collected at baseline, after clot formation, and at 15, 30, 45, 60, 90, 120, and 180 min after drug administration. Hemostasis assessments included D-dimer, fibrinogen, plasminogen, and α2-antiplasmin levels. D-dimer concentrations were determined by turbidimetry, fibrinogen concentrations were measured using a CT 2410 SOLAR hemocoagulometer (Minsk, Belarus), and plasminogen and α2-antiplasmin levels were measured using chromogenic substrates (Instrumentation Laboratory Company-Lexington, USA) on an ACL-200 coagulometer (Instrumentation Laboratory SpA Divisione Commerciale, Italy).

2.5. Histological studies

Arterial samples were formalin-fixed, sectioned in paraffin, and stained with hematoxylin and eosin for survey microscopy. Morphometric assessment of the free lumen of vessels (FL) was performed using Leica QW, version 1.56 (Wetzlar, Germany), a quantitative microscopy software program for image analysis and processing. The thrombus area (S1) and vessel lumen area (S2) were measured, and FL was calculated as the ratio of the vessel lumen area to the sum of the thrombus area and the vessel lumen area (FL = S2/S1 + S2).

2.6. Statistical Analysis

Statistical analysis of the results was performed using the Statistica 10.0 software package (StatSoft, USA). To determine the statistical significance of differences between groups, the Mann–Whitney U test was used for paired comparisons, and for three or more groups, the Kruskal–Wallis rank analysis of variance was used. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. The effect of ultrasound, thrombolytic agent, and their combined action on hemostasis parameters

Ultrasound in the absence of a thrombolytic agent, as expected based on previously obtained results [12], had a minor effect on plasma D-dimer concentrations. Following an initial nearly twofold ($p < 0.01$) elevation in D-dimer concentration upon the US action, the value fluctuated within the range of 0.94 ± 0.4 μg/mL over the subsequent three hours. Administration of SK-LSK without US increased D-dimer concentration, starting at 1.11 ± 0.4 μg/mL after a 30-min induction period and reaching 2.81 ± 0.9 μg/mL ($p < 0.01$) by the 180th min. An even more pronounced increase in D-dimer concentration (3.7 ± 0.6-fold; $p < 0.01$) was observed in the combination of US and SK-LSK (Fig. 1a).

There was a decrease in plasminogen levels, from 114 ± 28 to 50 ± 19% ($p < 0.05$) over 3 hours, indicates activation of the fibrinolytic system by ultrasound, as observed in similar animal experiments [12]. The combined application of ultrasound and SK-LSK exerts an additional, relatively small (up to 51 ± 14%) but statistically significant ($p < 0.05$) effect on this process (Fig. 1b). The marked decrease in plasminogen in

the presence of SK-LSK may be associated with the unbound streptokinase, which activates plasminogen not only bound to a clot but also freely circulating in the blood.

A moderate decrease in blood α2-antiplasmin levels (from 120% to 90%, $p < 0.05$) immediately after ultrasound exposure indicates its minimal consumption in the absence of a thrombolytic agent (Fig. 1c). Ultrasound exposure in the presence of SK-LSK causes a very significant drop in α2-antiplasmin levels – up to 20–30% ($p < 0.05$), indirectly indicating that the drug not only caused local thrombus lysis but also systemic activation of fibrinolysis.

The fibrinogen concentration under the action of ultrasound in the absence of a thrombolytic drug remains within the statistical error limits at a level of 3.2 ± 0.1 g/L throughout the entire 180-min ultrasound exposure cycle (Fig. 1d). In the presence of SK-LSK, thrombosis causes a slight initial increase in fibrinogen, followed by a decrease in its concentration by almost twofold over a period of 30–60 min, followed by a noticeable increase and a return to the initial value by the 120th min of exposure. Characteristically, the action of ultrasound has virtually no effect on this dynamics of temporary changes in fibrinogen concentration (Fig. 1d). Presumably, such a complex temporal dynamics of fibrinogen changes may be associated with the presence of 60% free streptokinase in SK-LSK drug, which is capable of causing systemic fibrinogenolysis, activating the conversion of plasminogen to plasmin throughout the bloodstream, and not only locally within the thrombus. The relatively rapid return of fibrinogen concentration between 60 and 120 min can presumably be associated with the release of fibrinogen adsorbed on the vascular epithelium [13].

3.2. Evaluation of the effectiveness of thrombolysis based on histological examination

According to survey microscopy, occlusive and subocclusive red thrombi with fibrin fields (primarily in the head area) tightly adhered to the intima were visualized in arterial slides from animals with simulated thromboses (Fig. 2a).

All arterial samples from the ultrasound-treated group of animals showed a mixed thrombus with multiple large and small slit-like cavities (Fig. 2b). Along the arterial periphery, the thrombotic mass had a loose, reticular appearance with small, rounded lumens. Mural fibrin was visible in all samples. After SK-LSK administration in the absence of ultrasound action, the vessel lumen was clear in three arterial samples, with small thrombus fragments located along the arterial periphery (Fig. 2c). In two samples, small thrombus fragments with foci of loosening were observed in the center of the vessel lumen; mural fibrin was observed in one sample. With the combined action of ultrasound and SK-LSK, almost complete thrombolysis was achieved in four (80%) animals (Fig. 2d). In one animal, polymorphic, mostly small, thrombus fragments containing fibrin were visualized. Quantitative assessment of the degree of thrombolysis shows that the best results were obtained with the combined effect of SK-LSK and ultrasound compared to the individual use of SK-LSK and individual ultrasound (86.1%; 70.2%; 12.3%, respectively (Fig. 3).

4. Discussion

The study demonstrates the high efficacy of thrombolysis induced by intravascular low-frequency ultrasound on a femoral artery thrombus 30 min after intravenous administration of a thrombolytic agent containing 60% free streptokinase and 40% bound to immunoliposomes. The targeted streptokinase delivery system demonstrated not only increased efficacy compared to the molecular (native) streptokinase [3, 4] but also the potential to enhance this efficacy with ultrasound significantly.

It has previously been established that the use of molecular (native) streptokinase in combination with low-frequency ultrasound not only increases the effectiveness of arterial thrombolysis but also reduces the risk of distal embolism [11, 12]. Importantly, ultrasound treatment during the therapy period (3 min) did not alter the structure or functional properties of streptokinase molecules, and did not cause noticeable damage to the hemostatic system [14]. This study utilized a targeted streptokinase delivery system in combination with free molecular streptokinase, which acts at the initial stage of thrombolysis. It is likely that the 60% free streptokinase in the combined thrombolytic drug ensures preliminary saturation of the thrombus with streptokinase molecules for 30 min before the ultrasound is turned on, facilitating the effective initiation of ultrasound-induced thrombolysis. Further, until the thrombus is destroyed, the liposomal form of streptokinase becomes active, localizing to thrombotic fragments via the immunoactive component.

The study suggests that sequential ultrasound application, not immediately but after a certain time, specifically 30 min after administration of a thrombolytic drug, is consistent with modern algorithms for providing care to patients with acute coronary and peripheral artery thrombosis. In the absence of rapid thrombus destruction using interventional technologies, a thrombolytic drug is administered, and only then are percutaneous interventions performed [15, 16]. Currently, high-frequency ultrasound is predominantly used in clinical practice in the treatment of diseases such as pulmonary embolism, stroke, and peripheral arterial disease [17–19]. While low-frequency ultrasound is known to have a more pronounced thrombolytic effect, its clinical application is limited by the length and flexibility of the waveguide. In the presented study, we used a specially designed flexible waveguide system with a variable cross-section, enabling transmission of low-frequency ultrasound to the thrombus over a distance of at least 50 cm with sufficiently high intensity [20].

Streptokinase is known to cause fibrinogenolysis, which can increase the risk of hemorrhagic complications. This study demonstrated that additional ultrasound exposure had virtually no effect on the streptokinase-induced reduction in fibrinogen levels and did not cause hemorrhagic complications in animals of any experimental group. To minimize other complications, particularly those caused by the relatively powerful low-frequency ultrasound applied to the vascular wall, the flexible waveguide within the catheter was positioned so that the waveguide tip, which concentrates acoustic energy, did not protrude beyond the catheter's distal end. Given that the thrombus itself acted as an acoustic damper for the ultrasound, damage to the intima was minimal.

Based on the experimental and literature data from this study, it is likely that the enhancement of ultrasound-induced fibrinolysis via targeted delivery using immunoliposomes is primarily due to cavitation, which is most pronounced with high-power low-frequency ultrasound. Such ultrasound is likely capable of stimulating the release of streptokinase molecules from liposomes by destabilizing their membranes, including due to the thermal effect of acoustic energy. Thus, the combined thermal and cavitation effects of ultrasound are the main reason for the release of streptokinase from its liposomal form [21–23]. The use of a targeted streptokinase delivery system ensures high affinity for fibrin across the entire surface of the thrombus, including its marginal part, leading to earlier and more complete restoration of the vessel lumen compared to native streptokinase.

5. Conclusions

An *in vivo* experiment demonstrated the potential to significantly enhance the thrombolytic effect of a combined thrombolytic drug comprising 60% native (molecular) streptokinase and 40% immunoliposomal streptokinase, with the additional local application of low-frequency (25 kHz) high-intensity ultrasound. Introduction of catheter-based ultrasound via a flexible waveguide 30 min after thrombolytic drug administration ensured virtually complete thrombolysis in 4 of 5 animals, and small thrombus fragments were visualized in 1 animal. The degree of thrombolysis was greatest with the combined action of ultrasound and SK-LSK (86.1%) compared to the individual use of SK-LSK drug (70.2%) and ultrasound alone (12.3%). Importantly, although the combined action of ultrasound and the SK-LSK drug did result in some changes in hemostasis, it did not cause a critical increase in fibrinogenolysis or lead to bleeding or other dangerous consequences for the animals. Therefore, the combined use of ultrasound and a thrombolytic agent based on free and liposomal streptokinase can be considered a truly effective way to improve thrombolytic therapy.

Declarations

Ethics approval This study was performed in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes, as well as the requirements and recommendations, regulatory, scientific, methodological, and reference materials for animal care, feeding, and withdrawal from experiments with subsequent disposal.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contribution

All authors contributed to the study conception and design, material preparation, data collection and analysis. All authors read and approved the final manuscript.

Data Availability

The datasets obtained during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AI disclosure

During the preparation of this work, the authors used ChatGPT for technical editing of the graphic abstract.

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Consent for publication

Not applicable.

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Figures

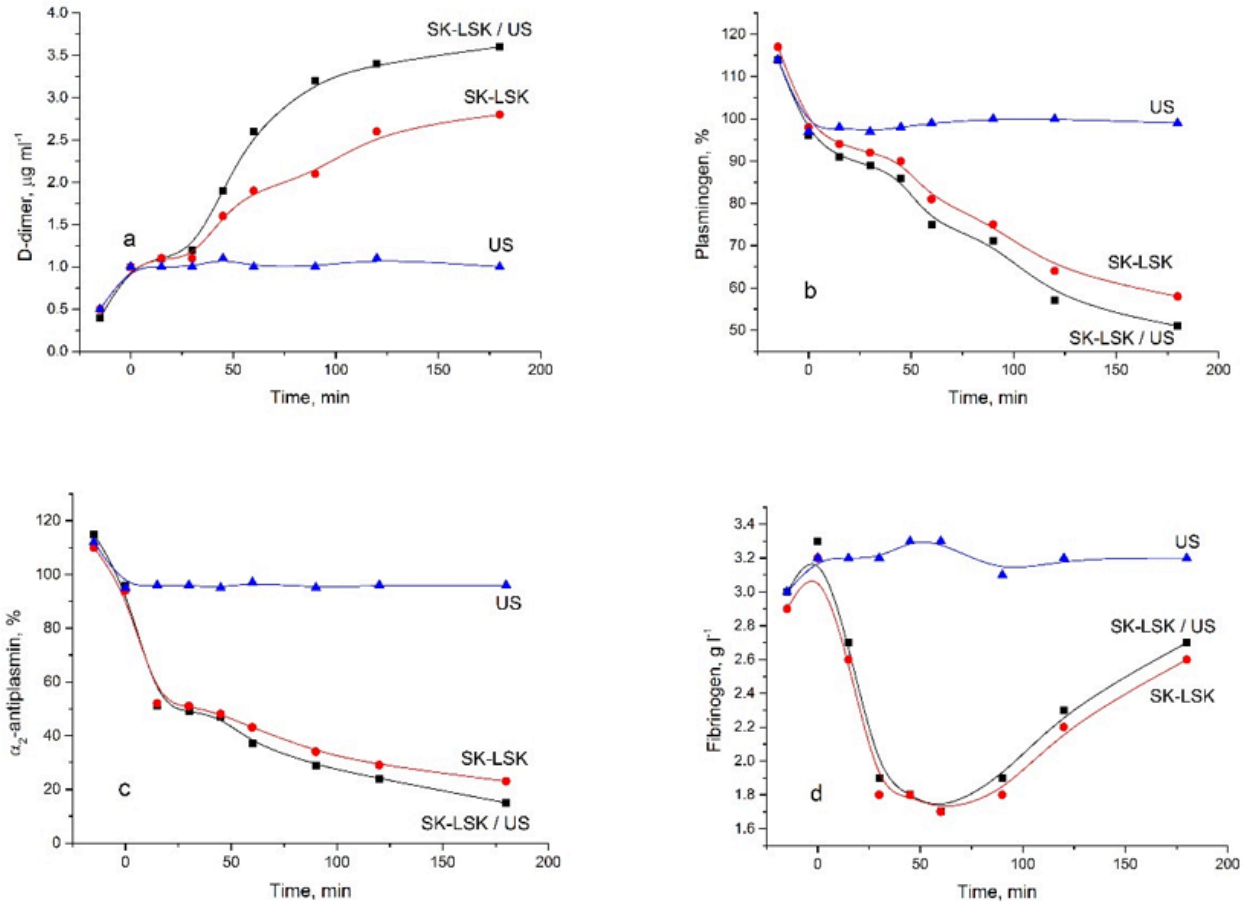


Figure 1

The effect of ultrasound (US), liposomal thrombolytic drug (SK-LSK), and combination of liposomal thrombolytic drug with ultrasound (SK-LSK / US) on the dynamics of D-dimer (a), plasminogen (b), alpha-2-antiplasmin (c), and fibrinogen (d) concentration. The data represent the means ± SD, (n = 5, *P < 0,05 and **P < 0,01 compared with SK-LSK).

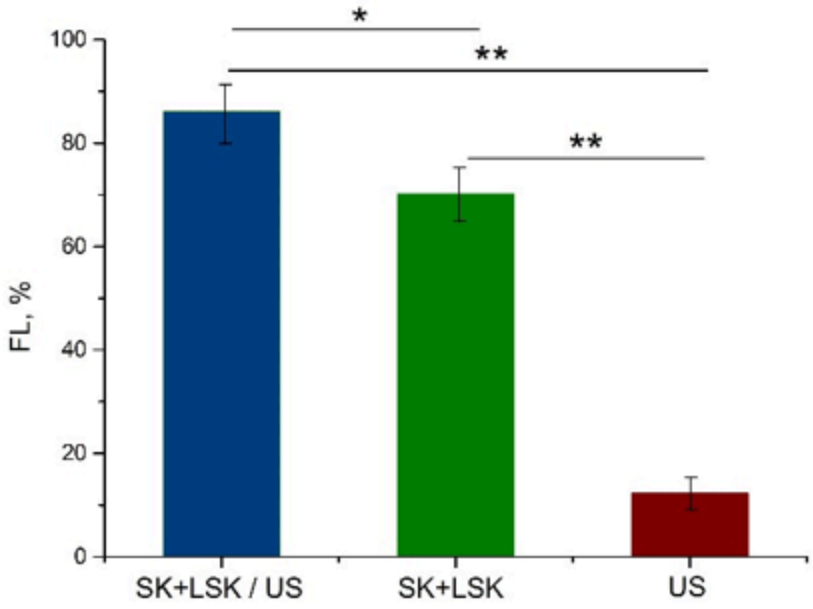


Figure 3

Histogram of quantitative analysis of the degree of free lumen of the vessel 180 minutes after thrombolysis. The data represent the means ± SEM. Relevant significant differences are indicated with a black bar and asterisk, n = 5, *P < 0,05 and **P < 0,01).

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