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Pharmaco-mechanical technique for selective thrombolysis in peripheral vessels

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Purpose. *The thrombus destroying power of selective low-dose fibrinolytic treatment was intended to be amplified with the mechanical force of the pulse-spray injector. The treatment time was expected to be shortened and the incidence of complications to be reduced.*

Methods. *Seventeen patients with arterial occlusion on the lower extremities underwent selective pulse-spray thrombolysis. All were treated according to a standard thrombolytic protocol. Streptokinase (Kabikinase®) 5.000-20.000 IU/h, or urokinase (Ukidan®) 20.000-40.000 IU/h and heparin 500-1.000 IU/h in physiological saline were administered with pulse-spray injector (Angiodynamics®) till the total dissolving of the thrombus.*

Results. *Between 1995-1997, 17 patients were successfully treated with an average treatment time of 12 hours,. No major complication occurred during this period. Surgical operation in the first 6 months after the treatment was needed in two cases because of reappearance of the clinical symptoms.*

Conclusion. *The pharmacomechanical selective thrombolysis with the pulse-spray technique is a reliable, relatively rapid and safe method for recanalization of occluded native arteries.*

Key words: arterial occlusive diseases-drug therapy; thrombolytic therapy-methods

Introduction

The percutaneous intraarterial selective thrombolysis is a radiologically controlled minimal invasive therapy used mainly in the cases of arterial occlusions of the extremities. Since 1959, when a research group under the leadership of Fletcher introduced for the first time the fibrinolytic treatment with streptokinase, a great progress has been achieved in this field.[1,2]

The method of drug activation of the fibrinolytic system through an intraarterial catheter first applied by Dotter in 1974 has been routinely used in the radiologic departments since the middle of the 1980's. In 1989, Bookstein and his co-workers introduced the pulse-spray pharmacomechanical treatment method.[3] The thrombus removing power of the selective low-dose fibrinolytic treatment was boosted by the mechanical force of a pulse-spray injector incredibly increasing the effective surface of drug and clot interaction.

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After an appropriate selection, patients with lower extremity arterial occlusion have been undergoing selective intraarterial thrombolysis with pulse-spray infusion in our angiographic department since the end of 1995.

Material and methods

Patient selection: For the performance of selective thrombolysis there are various indications and contraindications (Table 1). Appropriate selection and monitoring of the patients are of significant importance for a successful treatment. According to etiology, occlusions may be classified in the following three groups;

- arterial embolization- usually from the left side of dilated heart, after cardiac arrhythmic attack due to an aortic aneurism. Patients were usually admitted in the hospital in an acute stage of clinical manifestation, 1-2 hours after the embolization;
- arterial thrombembolization without a preexisting arterial disease - mainly of iatrogenic origin, usually with good response to thrombolytic treatment, solved within a few hours;
- arterial thrombembolization following a preexisting vessel disease - the most frequently presented form of disease in the lower extremities.

An intimal damage caused by the diabetic or atherosclerotic disease leads to an increase of the surface contact activity and, by destabilizing the homeostasis, activates the chain reaction of coagulation. All the patients who underwent selective thrombolysis in our department were classified into this group (Table 2). They had acute or subacute clinical signs of severe limb ischemia with a preceding history of claudication. All the patients with proper indication for pulse-spray selective thrombolysis were treated in our angiographic department. No one of the patients was excluded from this study. Seventeen patients underwent pulse-spray thrombolysis of acute arterial occlusion which was caused by atherosclerosis obliterans and by diabetic angiopathy in 12 and in 5 cases, respectively.

Table 2. Patients and results in selective pulse-spray thrombolysis

Patients		17
male/female		10/7
Average age		59 (39-83)
Main risk factors	AS*	12
	DM*	5
Fontaine stage III		7
stage IV		10
Therapeutic succes		17
Roecclusion within 6 monts		2

AS* - Atherosclerosis obliterans; DM* - Diabetes mellitus

Table 3. Treatment protocol in selective pulse-spray thrombolysis

1. Baseline angiogram
2. Introduction of guide wire
3. Infusion catheter selection
4. Thrombolytic agents infusion
5. Control angiography
6. Catheter removal
7. Postprocedure management, aftercare

Catheterization technique

In our angiographic department, a well-tested treatment protocol was used (Table 3). The main steps of the treatment protocol are schematically presented in Figure 1;

- pulse- spray technique - the jet spray of the lytic infusion causes a significant change in the intrathrombotic microstructure and improves the effectiveness of the method enlarging the surface for the action of the urokinase or streptokinase (Figure 2). The pulse- spray infusion was performed with an infusion pump through the catheter without blocking the end hole.

Table 1. Indications and contraindications for selective pulse-spray thrombolysis

Indications
acute and chronic native artery occlusion
acute and chronic graft occlusion
reoclusion after percutan angioplasty
Contraindications
Absolute
Active internal bleeding
Cerebrovascular accident, disease or surgical intervention within the last 2 months
Relative
Surgical operation or parenchymal organ biopsy within the last 2 weeks
Recent major trauma
Uncontrollable hypertension
Gastrointestinal ulcer
Pregnancy/postpartum
Embolization from a distant source

– infused lytic drugs - in arterial selective thrombolysis, the drug dose administered with the pulse-spray technique was lower than the ones indicated in systemic infusion protocols. The reports of early clinical successes in literature show significant preference of urokinase to streptokinase.[4-9] However, this observation has not been proved yet although it was explained in randomized trials with pharmacokinetic mechanisms of the drugs.[10] In our intraarterial treatments, 20000-40000 IU/hour urokinase (Ukidan®), or 5000-20000 IU/hour streptokinase (Kabikinase®) and 500- 1000 IU/hour heparin were administrated through the catheter.

Postprocedure management: In order to prolong the patency rate of the reopened vessels, a post- procedural care and change in lifestyle was proposed to all the patients. To prevent puncture site bleeding, false pulsating aneurysms and extensive haematoma 20-30 minutes after manual compression, a sand sack was placed on the bandage of the puncture site for 6 hours. Care was taken that the patients made exercises to increase blood flow in the affected extremity in order to prevent local or venous thrombosis due to the transient stasis under the compression and slow flow because of bed rest. The patients were kept in bed for the next 24 hours. Diuretics, if any, were excluded from the treatment in the ward, and, in cases of diabetes mellitus, the concentration of serum glucose was kept steadily within the normal limits. The 3rd-5th day after the treatment a daily dose of 2 x 50 to 2 x 100 mg of sodium pentosan polysulphate (SP 54®) was administered i.v. (occasionally s.c.). Smoking was prohibited to the patients while life-long physical exercises, low-fat and low-cholesterol diet were recommended to them. Control examinations (physical and Doppler-flowmonitoring) and laboratory tests (hematocrite, serum cholesterol, serum triglycerid, plasma fibrinogen) were made at the discharge from the hospital, 30 days and 3 months after the therapy and, later on, in 6 month intervals for life time.

Results

Selective thrombolysis was considered clinically successful in the cases in which the ischemic signs disappeared or significantly improved for a period of more than 30 days

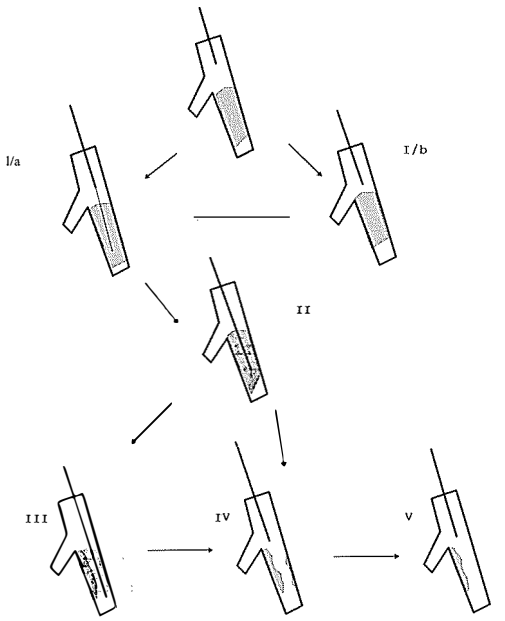

Figure 1. Main steps of treatment procedure. After the baseline angiogram a guide wire is introduced into the thrombus (I/a). If this is not possible the treatment starts with continuous selective thrombolytic infusion (I/b). If possible the infusion catheter is positoned in the thrombus leaving a thrombus plug at the distal end. After excluding the chance of accidental subintimal position pulse-spray lysis is initiated (II). After 4-6 hours of treatment if the control angiography shows reopening of the vessel (III), the pulse-spray technique may be converted to continuous infusion (IV) till the total dissolving of the thrombus. In cases of small persistent wall irregularities (V) percutaneous transluminal angioplasty is also performed.

after the therapy. In all 17 patients, the occluded arteries of the lower extremity were successfully reopened. In two of the treated cases, a surgical treatment was performed within the first 6 month after the therapy because of the recurrence of clinical symptoms. The first patient had diabetes mellitus for more than 15 years. After successful lytic treatment of the occlusion in the distal part of the popliteal artery, an amputation of the third left foot finger (previous amputation of the 4th and 5th finger on the same side in his clinical history) was carried out. The other patient did not adhere to the proposed post-procedure drug therapy and lifestyle changes. He underwent a successful transluminal endarterectomy of the popliteal artery 4 months after our treatment. Occult bleeding, allergic reactions, myocardial spasm, or distal embolization with an occurrence rate of 0.5-5%, which were often reported in literature,[4,11-15] were not observed during our procedures in spite of the careful control with laboratory tests, angiography and instrumental flow measurements.

Discussion

After the thrombolytic treatment we performed, in three of our cases, a percutaneous transluminal angioplasty on the chronic stenotic plaques detected by the control angiography and made visible only after solving the thrombotic deposits from the surface of the vascular wall.

To our opinion, a continuous selective infusion cannot provide an optimal concentration of the lytic enzymes in the thrombus where the activation of the plasminogen is required. The pharmacomechanical thrombolysis, which has appeared after a vast number of experimental research trials includes,

- shooting tiny jets of thrombolytic agent into the mass of thrombotic deposits;
- maceration of the thrombus;
- supplying in this way a larger surface for the action of the lytic enzyme,
- providing a simultaneous destruction of the majority of fibrin in the treated segment of the occlusion.

The maceration of thrombembolism is due to the jet effect of the infusion, i.e. its mechanical power. The duration of this process and the total thrombolysis as reported in literature has really a broad scale.[4,5,13,14,16,17] The explanation of this fact seems to be found in a multifactorial reason

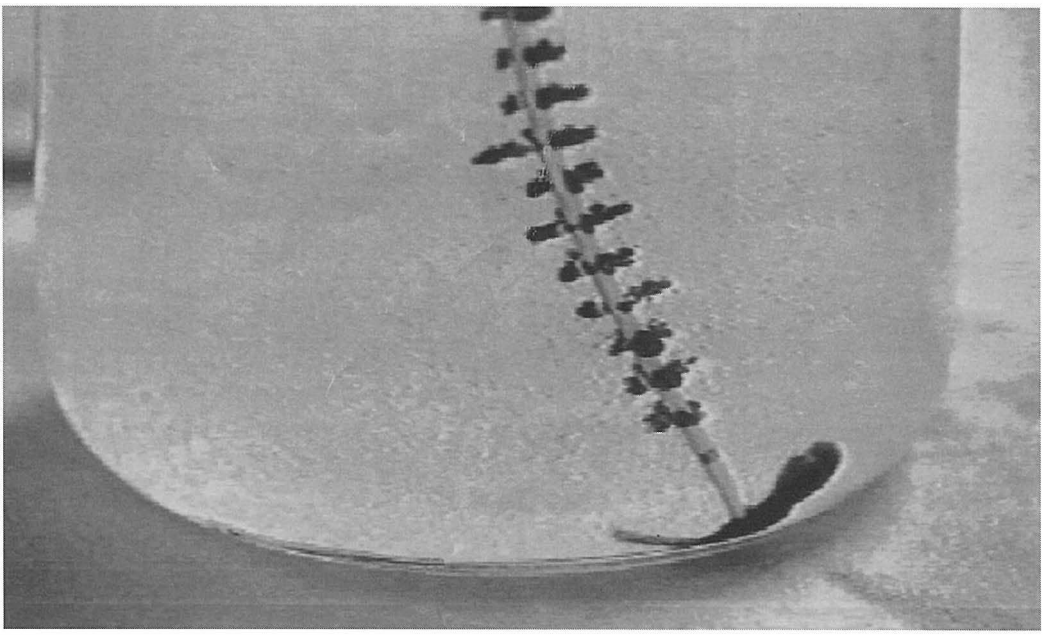

Figure 2. The pulse-spray system. Using the mechanical force of an automatic pump on the 1 cc syringe a bolus (0,1 - 0,5 ml) of saline solution containing 10% thrombolytic agents is infused in the thrombus with high pressure through the pressure responsive slit orifices of the catheter. The frequency of the jet spray varies from 6 to 120 seconds.

theory. The average treatment time in our study was 12 hours and was calculated from the treatment times ranging from 6 to 27 hours. These differences were mainly due to the site and size of the thrombus, its underlying disease and duration of ischemic conditions. It has been observed that chronic limb ischemia seems to be more resistant to thrombolysis,[18] but it should not considered as a relative contraindication.[13,14]

After an appropriate selection of patient, premedication and catheter technique, the next important step to achieve a really good and long-term clinical success is the establishment of a proper thrombolytic treatment plan and the monitoring of the patients. The role of partial thrombin time (PTT), thrombin time (TT) and fibrinogen serum concentration in „holding the treatment in hands" is discussed in the literature, and fibrinogen level under 1 g/l is often associated with occult bleeding.[1,10,11,14,17] This is especially significant in patients with clinical history of ulcer, cerebrovascular accident, recent major trauma, or surgery, especially around the pancreas and the prostate gland.

With the use of the pulse-spray technique, new requirements emerged. In order to reopen the occluded vessel as quickly as possible often thrombolysis of the whole length of the thrombus was attempted from the very start of the procedure.[19,20] An occasional distal embolization should be further treated with thrombolytic infusion or percutaneous thrombus aspiration. Other teams start the lytic therapy from the distal end of the thrombus and go further in proximal direction.[21] In the majority of our cases, most of these techniques proved to be non beneficial because of the hardness of the occlusion. Even in those cases, when the guide wire was easily introduced into the thrombus we suggest that, because of thehigh pressure, a short thrombotic plug left behind at the dis-

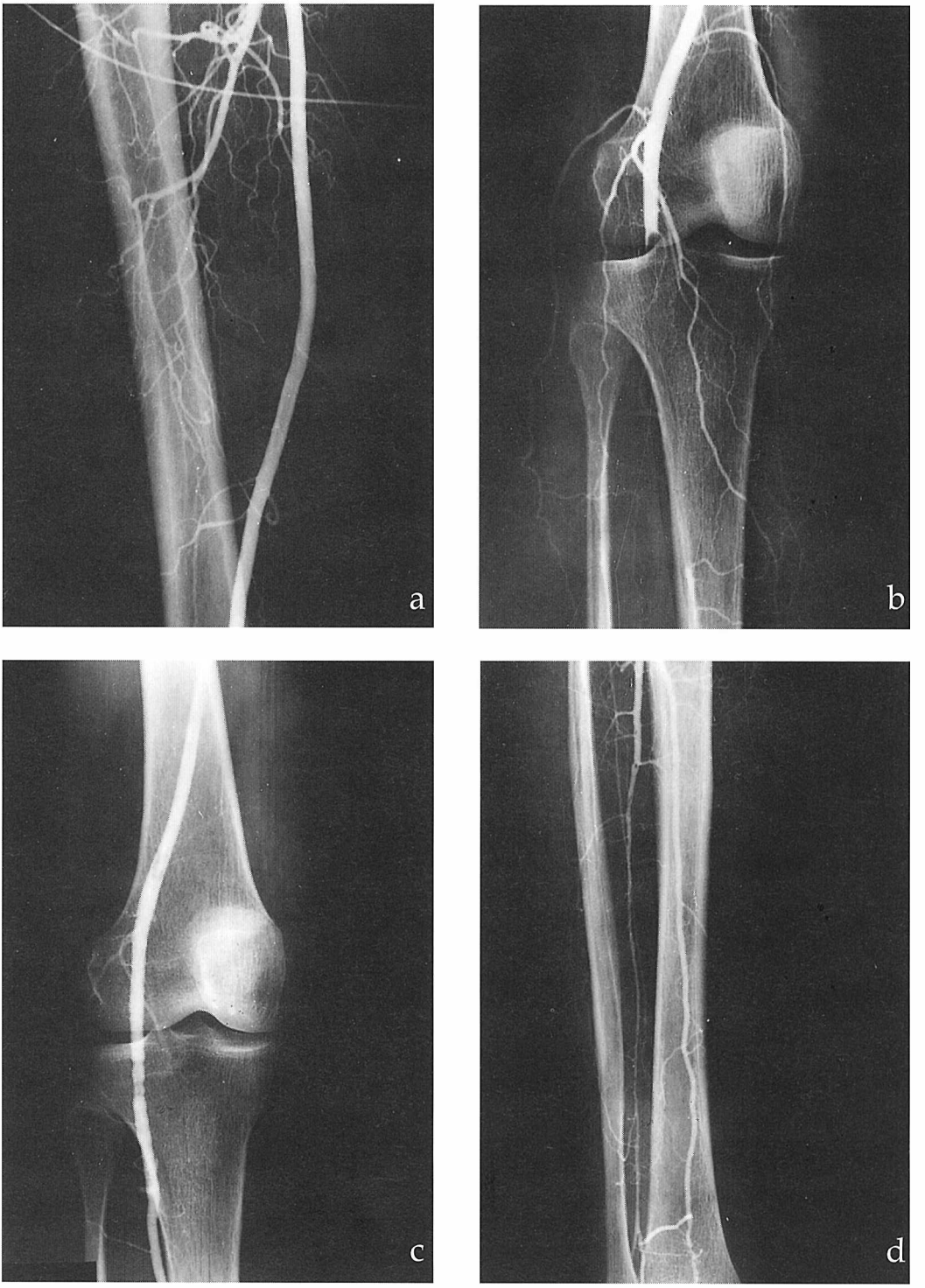
a
b
c
d

Figure 3 a-d. Case report. E. K. 63 year old female patient with a clinical history of diabetes mellitus for 10 years, complicated by hypertension in the last 3.5 years. Trigliceride and cholesterol level were slightly elevated. Complains started a week before her arrival in the department and increased in the last 2 days. The clinical picture was Fontaine IV. The right leg under the knee joint was livid, cyanotic and there was no pulse in the popliteal artery and distaly to that.
Selective angiography was performed with a cross-over technique, which demonstrated a total occlusion of the right popliteal artery (a, b). Pulse-spray infusion was initiated after positioning the catheter in the thrombus. The result of 1 hour control angiography was encouraging, so, pulse-spray technique was continued for further four hours. After nine hours of treatment, the control angiography showed total recanalization (c, d). The clinical picture at discharge from the hospital was Fontaine I- II. Three years after the procedure, strictly adhering to the postprocedure protocol, the patient had no significant increase of ischaemic symptoms.

tal end might be useful for the profilaxis of embolization (Figure 3).

The patency rate of the reopened arteries is in strong dependence of a proper postprocedural management. It seems to be obvious that, without a proper aftercare, thrombolysis is not going to result in a satisfactory long-term patency, especially in cases of pre-existing progressive disease, although this assumption has not been proved in randomized studies on selective thrombolysis.

Conclusions

Till date, there has been a relative reluctance from the wide use of selective thrombolysis, mainly because of the long duration of the procedure, quite high radiation, lack of experience and a number of other reasons. The introduction of the pharmacomechanical method proved to be a great step forward in managing the occlusion with combined chemical and physical forces. The mechanical power of the jet spray multiplies the action of the lytic drug helping, on the one hand, its deeper penetration into the thrombus and, on the other, mechanically destroying the thrombus.

The selective thrombolysis with pulse-spray technique is a radiological treatment of occlusions which may be part of the complex treatment, including surgical procedures, or applied as a curative therapy alone.

With an appropriate selection of patients, a well-tested treatment protocol and proper post-treatment care of the patients both, the acute and subacute artery occlusions may be successfully treated and amputation rate significantly lowered.

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