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СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭНДОВАСКУЛЯРНЫХ МЕТОДОВ ЛЕЧЕНИЯ ОСТРОЙ ИШЕМИИ НИЖНЕЙ КОНЕЧНОСТИ

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Под острой ишемией нижней конечности (ОИНК) понимается внезапное уменьшение артериального кровотока в нижней конечности, продолжающееся <14 дней и представляющее непосредственную угрозу ее жизнеспособности. Данное состояние является одной из наиболее частых экстренных ситуаций в сосудистой хирургии, требующих незамедлительной диагностики и лечения, поскольку не своевременно выполненная реваскуляризация нижней конечности приводит к высокой частоте ампутации и летальности в послеоперационном периоде.

В настоящее время существует множество методов реваскуляризации нижней конечности, однако, в сущности, их можно разделить на две большие группы: открытое хирургическое и эндоваскулярное лечение, выбор между которыми зависит от многих факторов. Со времени изобретения катетера Фогарти, баллонная тромбоэмболэктомия стала «золотым стандартом» в лечении ОИНК. Тем не менее, в это же время появились и стали развиваться эндоваскулярные методы лечения, первым из которых был регионарный катетерный тромболизис (РКТ). Со времени появления РКТ постепенно развивался – приходило понимание показаний для его использования, совершенствовалась техника вмешательства, появлялись различные тромболитические агенты и инструментарий. На сегодняшний момент ряд международных рекомендаций определяют РКТ как метод выбора для лечения большинства пациентов с ОИНК.

В 1990-х гг. стали появляться методики эндоваскулярной тромбэктомии, возникновение которых связано с попыткой объединения преимуществ открытой хирургии (быстрое и, при идеальных условиях, полное восстановление кровотока) и эндоваскулярных вмешательств (малоинвазивность). К ним относятся: мануальная аспирационная, реолитическая (гидродинамическая), ротационная, аспирационная тромбэктомия и фармакомеханический тромболизис. Согласно многочисленным исследованиям, данные методики показывают достаточно впечатляющие результаты и, возможно, в скором будущем одна из них может стать новым «золотым стандартом» в лечении ОИНК.

Ключевые слова: *острая ишемия нижней конечности; эндоваскулярное лечение; регионарный катетерный тромболизис; механическая тромбэктомия; ультразвук-ускоренный тромболизис; фармакомеханический тромболизис.*

COMPARATIVE ANALYSIS OF ENDOVASCULAR METHODS FOR TREATMENT OF ACUTE LOWER LIMB ISCHEMIA

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Acute lower limb ischemia (ALLI) is defined as a sudden decrease in lower limb arterial perfusion, which lasts less than 14 days and threatens a limb viability. This condition is one of the most common emergencies in vascular surgery, requiring immediate diagnosis and treatment, because untimely revascularization of lower limb leads to high amputation rate and mortality in postoperative period.

Currently there exist many methods of lower limb revascularization, however, in fact, they all can be divided into two large groups: open, surgical, and endovascular treatment. The choice between them depends on many factors. Since introduction of Fogarty catheter, balloon thromboembolectomy became a «gold standard» in treatment for ALLI. Nevertheless, at the same time endovascular methods appeared, the first one being catheter-based thrombolysis (CBT). Since its appearance, CBT gradually improved with deeper understanding of indications for its use, improvement of the technique of intervention, appearance of different thrombolytic agents and instruments. Nowadays a number of international guidelines determine CBT as a first line treatment of most patients with ALLI.

Endovascular thrombectomy techniques appeared in the 90s of XX century as an attempt to combine advantages of open surgery (rapid and, in ideal conditions, complete restoration of limb perfusion) and of endovascular intervention (minimal invasiveness). They include manual aspiration, rheolytic (hydrodynamic), rotational, aspiration thrombectomy and pharmacomechanical thrombolysis. According to numerous studies, these techniques demonstrate quite impressive results and, probably, in the near future one of them can become a new «gold standard» in treatment for ALLI.

Keywords: *acute lower limb ischemia; endovascular treatment; catheter-based thrombolysis; mechanical thrombectomy; ultrasound-accelerated thrombolysis; pharmacomechanical thrombolysis.*

Acute lower limb ischemia (ALLI) is a sudden reduction of the arterial blood flow in the lower limb lasting for less than 14 days and directly threatening its viability. Incidence of ALLI may range from 10 to 26 cases per 100 000 of population per year [1]. There are two main reasons for ALLI: arterial thrombosis based on already existing atherosclerotic lesion of the artery (target lesion), and peripheral embolism that in most cases results from disorders in cardiac rhythm, mostly from atrial fibrillation [2]. With this, nowadays, due to a wide use of oral anticoagulants, peripheral thromboembolism is a rare cause of the disease with increase in the incidence of acute arterial thrombosis which in some cases may account for 95% of all cases of ALLI [3].

At present there exist many methods of lower limb revascularization which can be classified into two main groups: open surgical and endovascular treatment. The choice of a method of treatment depends on several factors: the degree of acute ischemia of a lower limb, etiology and localization of the lesion, and of the general condition of the patient. Besides, a difficulty in choice of revascularization method is associated with urgency of the situation, in particular, with limited time for a thorough examination and preoperative preparation of the patient which determines a high intrahospital and 30-day lethality in treatment of ALLI [1].

Surgical methods of treatment for ALLI appeared much earlier than endovascular. G. Labey (1911) was the first to successively perform open embolectomy having removed an embolus from the femoral artery in 6 hours after development of the disease. Nevertheless, 30-day lethality after such intervention made 52% [4], which greatly reduced the effectiveness of the operation. This high mortality rate could be associated both with the absence of the exact time criteria and clinical criteria for embolectomy, and with the absence of knowledge of the processes occurring in the limb in the phases of ischemia and reperfusion that began to come to understanding only in the mid-XX century [5]. Only in the 1960s T.J. Fogarty, in his experiment with the urinary catheter managed to modify it and obtained the world famous Fogarty catheter. In 1965 the first results of its use were presented with the survival rate of patients 80% and with salvage of the limb in 96% cases [6].

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Since invention of Fogarty catheter, no principially new methods of surgical treatment for ALLI were developed. But after their appearance in the early 60s of XX century, the endovascular treatment methods enjoyed a rapid growth in the subsequent years and nowadays there exist a great variety of different methods and devices that can effectively and with sufficient safety restore the blood flow in the lower limbs in acute ischemia with minimal operational trauma. Endovascular methods of treatment for ALLI offer a less invasive method of revascularization decreasing the mortality rate, especially in aged patients.

Endovascular interventions include regional catheter-based thrombolysis (RCBT) with its special type, ultrasound-accelerated thrombolysis, and different techniques of endovascular thrombectomy: manual aspiration, rheolytic (hydrodynamic), rotation, aspiration (suction) and pharmacokinetic thrombolysis. All the mentioned methods remove thrombus occluding the vessel lumen, with restoration of blood flow in the limb. A positive side of endovascular methods is a possibility to identify the target lesion of the vessel after elimination of thrombus with subsequent treatment of the vessel in the nearest time which in many aspects improves the long-term results of restoration of the patency of the vessel and of salvage of the limb.

According to the last Clinical Recommendations (CR) of American Heart Association (ACA) and American College of Cardiology (ACC) 2016, RCBT is an effective method of treatment of patients with ALLI and with a viable limb (I, A: here and hereafter – class, level of evidence), here, RCBT may be effectively supplemented with methods of endovascular thrombectomy (IIa, B-NR), while surgical thomboembolectomy may be more effective in patients with embolism and a viable limb (IIa, C-LD) [7]. However, both American and European CR emphasize that the choice of method of revascularization should depend on potentialities of a medical institution and on the experience in treatment of such patients [7,8]. With this, American CR set rather strict time limits for revascularization depending on the degree of ischemia: for I degree acute ischemia according to Rutherford – 6-24 hours, for IIa and IIb – 6 hours [7]. At the same time CR in European Society of Cardiology (ESC) no any exact indications as to use of a specific method of revascularization are given, but it is only mentioned that in case of neurological deficit it is recommended to use methods lead to a rapid restoration of the circulation in the limb by both endovascular techniques (endovascular thrombectomy) and surgical techniques (thrombectomy, shunting), and in case of the absence of neurological deficit or the presence of a severe accompanying pathology the most reasonable method of treatment is regional catheter-based thrombolysis.

Regional Catheter-Based Thrombolysis (RCBT). RCBT is an endovascular method of revascularization of a lower limb that consists in a selective introduction of a thrombolytic agent (TA) at the site of thrombosis of the vascular bed in the set regime with the aim of lysis of thrombotic masses. The method consists in positioning of a special infusion catheter inside a thrombus (or as close to it as possible) and in initiation of thrombolysis in the required regime.

Historically, the first thrombolytic agent used for thrombolysis, was streptokinase produced by β-hemolytic streptococci. However, since use of streptokinase was often associated with side effects, it appeared necessary to find an alternative TA that did not possess antigenic properties. Thus, for RCDT urokinase started to be used which for a long time remained the main TA in the USA, however due to problems in production of the drug and appearance of more specific TA (alteplase, reteplase, tenecteplase), its active use stopped [9].

All TA available at the moment, do not induce direct degradation of fibrinogen, but are actually activators of plasminogen (PA) causing its conversion to plasmin, which degrades fibrin and fibrinogen present in a thrombus, into fibrin degradation products. At present the best studied and commonly used TA is the first generation of recombinant forms of natural tissue plasminogen activator (tPA) – alteplase whose action was confirmed in a randomized controlled study (RCS) of D.C. Berridge, et al. (1991) [10]. Streptokinase and urokinase are non-fibrin-specific activators of plasminogen, while tPA, on the contrary, is a fibrin-specific agent that primarily activates fibrin-bound plasminogen [9].

Reteplase is the second generation of tPA and is a synthetic fragment of natural tPA consisting of 355 amino acids. Reteplase does not bind with fibrin as strongly as alteplase which permits the drug to more freely penetrate through thrombotic masses and not only bind to the surface of thrombus as alteplase. Tenecteplase is the third generation, with replacement of three amino acid residues in three regions of the initial molecule by methods of genetic engineering. All this led to increase in the half-life period, to a more evident fibrin-specificity and to 200-fold increase in resistance to inhibitors of plasminogen activators [11].

I. Robertson, et al. (2013) carried out analysis of all randomized controlled studies that compared effectiveness and safety of TA in treatment for ALLI. In result tPA and urokinase were found to be preferable TA for RCBT in patients with ALLI [12].

Regimes of infusion of thrombolytic agent. After positioning of a catheter inside a thrombus, the required dosing regime is set depending on the used TA, on the existing degree of ALLI, and accordingly, on the time allowed for restoration of the blood flow in the lower limb.

1. *Long-term permanent infusion (LPI)* is the most common infusion regime where TA is introduced at a constant dose within the required time.

2. *Stepwise infusion* is infusion regime with a gradual advance of a catheter in the direction from proximal to distal part the thrombus as far as it is dissolved by TA. Here, several milliliters of the active substance are introduced into the thrombus, then in 5-15 minutes, the catheter is moved further under fluoroscopic control. Despite the fact that this regime permits to reduce the total dose of the introduced substance and the time of thrombosis, it is rather labor-intensive, since a patient and a nurse should stay all the time in X-ray operating room.

3. *Gradually reduced infusion* is the regime of infusion with a periodical reduction at the dose of introduced TA with the maximal dose in the first several hours [11].

4. *Forced periodical infusions (‘pulse-spray’ technique)* – the regime is based on periodical bolus injections of TA at low doses with 15-30 sec intervals with the aim to break thrombus into fragments and to increase its surface accessible to the acting substance. S.F. Yusuf, et al. (1995) showed this method to considerably accelerate thrombolysis (average time is 195 min) in comparison with LPI (1390 min, $p<0,002$). Nevertheless, the effectiveness of the intervention showed no statistically significant differences due to a small number of included patients [13].

5. *Bolus infusion.* In this case bolus means initial introduction of a large dose of TA with the aim of fragmentation of thrombus along its entire length with saturation of thrombus with the acting TA after which infusion continues in LPI regime. This method permits to reduce the time of thrombolysis with similar clinical results [14].

In 2004 a review was published where an attempt was made to combine randomized studies performed by the moment with the aim to compare infusion regimes and to select the most optimal one. However, due to a small number of patients and an evident heterogeneity of studies, it was impossible to car-

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ry out any significant comparison of the regimes and to obtain the answer to the set question. It was found that high-dose infusion in LPI regime and 'pulse-spray' method although permitting a faster restoration of the blood flow in the lower limb than low-dose infusions, do not provide increase in the initial patency and do not improve the results of salvage of the limb. Besides, these regimes increase the rate of incidence of hemorrhagic complications [15].

Complications. Despite low invasiveness, RCBT, as any intervention, possesses certain complications. Their frequency may significantly vary depending on the risk factors of the patient himself, on the kind of RCBT with its infusion regime and on the additional conservative therapy (doses of anticoagulants). All complications may be divided into 2 groups: related to thrombolysis and related to reperfusion.

The first group includes hemorrhagic complications and distal embolism. The most common complications of RCBT are hemorrhages (Table 1). They are in turn divided to large ones requiring blood transfusion or a surgical intervention, and small ones. The most threatening complication is intracranial hemorrhage which in most cases (75%) leads to lethal outcome [16].

Table 1

Incidence of Complications of Regional Catheter-Based Thrombolysis (Adapted from C. Gilliland, et al. [1])

Complication	Incidence, %
Intracranial hemorrhage	0-2,5
Large hemorrhage	1-5
Small hemorrhage	10-20
Distal embolism	5-10
Compartment syndrome	5-10
Acute renal failure	0-2

Other dangerous but rather rare hemorrhages include retroperitoneal, intraabdominal, gastrointestinal hemorrhages and hemorrhages from the urinary tract. The most common hemorrhagic complication is hemorrhage from the site of access, but these are usually small hemorrhages.

The second important complication of this group is distal embolism (Table 1). In case of this complication it is required to increase the dose of TA in infusion, and in the absence of the effect in 1-2 hours to carry out angiographic control to verify the complication and to probably change treatment tactics [11].

The second group of complications incudes a compartment syndrome of a lower limb and acute renal failure (ARF). Compartment syndrome occurs when accumulation of fluid in a lower limb leads to derangement of the venous outflow from separate musculofascial envelopes which, in turn, causes increase in blood pressure in these spaces with further impairment of venous outflow and capillary blood flow, which eventually leads to stoppage of the blood flow in the limb. This situation may be managed by fasciotomy within the region of the shin and even of the hip. ARF develops in result of pronounced myoglobinuria resulting from rhabdomyolysis of muscles of the lower limb. Here, the probability for its development increases with the extent of acute ischemia [17].

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In conclusion it would be reasonable to summarize advantages and disadvantages of RCBT in treatment for ALLI (Table 2).

Table 2

***Advantages and Disadvantages of Regional Catheter-Based Thrombolysis in Treatment for Acute Lower Limb Ischemia* [1,3,11]**

Advantage	Disadvantage
- low-invasive intervention with low operational risk; - no damage of the vessel wall, first of all, of the endothelium; - restoration of the blood flow in small and collateral vessels; - improvement of the blood flow in distal vascular bed which opens a possibility for shunting; - simultaneous treatment of lesions of the lower limb arteries; - reduction of the scope of open surgical intervention, if it is necessary; - lowers the level of amputation in it is necessary.	- delayed effect; - necessity to be under observation in intensive therapy unit; - existence of contraindications (absolute, relative); - increased risk of hemorrhages in comparison with open surgery; - impossibility to be used in acute thrombosis of the shunt directly after vascular reconstruction.

A special kind of RCBT is ultrasound-accelerated catheter-based thrombolysis (UST). For this different devices are used, the most popular being endovascular system EkoSonic (BTG International Ltd (Great Britain). Besides TA infusion, it uses high-frequency low power ultrasound (US) generated by transducer elements located on a conductor. The mechanism of action of US consists in rupture of bonds between fibrin fibers which increases permeability of thrombus and exposes more receptors for binding plasminogen. Besides, US causes acoustic cavitation understood as formation and collapse of microscopic cavities in the medium exposed to ultrasound. Thus, all these influences facilitate penetration of TA through thrombotic masses which accelerates thrombolysis. Here, unlike in pharmaco-mechanical thrombolysis, no mechanical fragmentation of thrombus occurs [18].

C. Wissgott, et. al (2007) carried out a retrospective non-randomized study for evaluation of effectiveness and safety of UST (n=25). Technical success of the intervention was 100% with a complete lysis of thrombus in 22 patients (88%), partial lysis in 1 patient (4%) and with absence of the effect in 2 patients (8%). It is also worth noting that during the intervention only one hemorrhagic complication occurred associated with dislocation of the catheter. Besides, not a single case of death and amputation of the limb was identified within one month of observation [19]. A.M. Schrijver, et. al (2015) published the results of RCS and showed that UST considerably reduces duration of the procedure in comparison with RCBT (17.7±2.0 hours against 29.5±3.2 hours; p=0.009). However, in comparison by other important parameters, UST loses to RCBT although no statistically significant differences were revealed between the groups; technical success was 75% against 84% (p=0.52), 30-day mortality rate and incidence of severe complications were 29% against 19% (p=0.54), the primary patency was 71% against 82% (p=0.35) [20].

Thus, there exists some disagreement in the data of effectiveness of UST in treatment for ALLI, so this technology requires further development and study in large randomized research with presentation of clinically significant outcomes in the form of end points.

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Endovascular methods of thrombectomy (TE). TE is the next stage in development of endovascular methods of treatment for ALLI which appeared as an attempt to combine advantages of the open surgery and of endovascular interventions which would permit to reduce the dose and time of TA infusion or to refuse from it altogether, and also to reduce the period of observation in the intensive care unit, to accelerate restoration of the blood flow in a limb, to reduce the number of complications and cost of treatment with saving the limb and even with improvement of the effectiveness of the intervention. Besides, these methods permit to expand the range of indications for endovascular methods of treatment for ALLI, in particular, to include patients who need emergency revascularization (IIb class by Rutherford) and patients with a high risk of hemorrhagic complications or with contraindications to RCBT. Nowadays there exist the following methods of TE:

1. Manual aspiration (suction) TE;
2. Mechanical TE that depending on the mechanism of action of used devices, is subdivided to further types:

2.1. Rheolytic (hydrodynamic) TE;
2.2. Rotation TE;
2.3. Aspiration (suction) TE;
2.4. Pharmacomechanical thrombolysis (PMT).

Manual suction thrombectomy. The point of this method is use of a catheter with a large inner lumen that is connected to a syringe where negative pressure is created for suction of thrombus from the vessel. At the modern level this method, as a rule, is not used independently, but usually in a combination with other methods due to a high level of technical failures it possesses [21]. In the international market there is a sufficiently high amount of devices for use in the peripheral vascular bed: Eliminate (Terumo, Japan), Nautilus (iVascular, Spain), Sofia Plus Aspiration Catheter (MicroVention, Terumo, USA), Euca AC (Eucatech AG, Germany), Aspire Max (Control Medical Technology, USA) and others. Besides, there exist other suction catheters intended for coronary and cerebral vascular pools that may be successfully applied in vessels of the lower limbs, in particular in vessels of shin.

Rheolytic (hydrodynamic) TE. The principle consists in use of a flow of fluid and of hydrodynamic forces for removal of thrombus from the vessel lumen. At present there exist a number of devices in the European market for performing rheolytic TE in the peripheral vascular bed, the most popular of which is AngioJet (Boston Scientific Corporation, USA). The device consists of a special catheter, pump and control panel. The catheter is a double-lumen tube: one lumen, of smaller diameter, is made of stainless steel and serves to deliver controlled high-speed flow of saline (350-450 km/hour) generated by a pump; the second lumen, of larger diameter, is for driving through a conductor and for evacuation of thrombotic masses (efferent lumen). To note, the first lumen is inside the second, in its lower part, and ends on the tip of the catheter with a closed loop with holes from which high-speed streams of saline rush in the backward direction via the efferent lumen. Due to this, on the tip of the catheter with suction holes along the whole periphery, a zone of extremely low pressure is created (Ventiri effect/Bernoulli principle) which results in fragmentation of thrombus and to suction of its fragments into the efferent lumen. Somewhat proximally to suction holes, infusion holes are located (Cross-Stream technology) for entry of additional streams of saline for additional fragmentation of the thrombus and facilitation of its suction. The above described regime of work is called thrombectomic regime. Besides, this regime also includes thrombolytic regime («power pulse spray» regime) with infusion of TA into the thrombus for implementation of pharmacomechanical thrombolysis (PMT). After some delay (5-20 min) the device is shifted to the regime of thrombectomy for elimination of thrombus. This regime permits to reduce the number of complications of the intervention and increases the probability for success [22]. The most dangerous complication of the method is hemolysis of red blood cells leading to hemoglobinuria with subsequent development of ARF. Another important complication is damage to the vessel wall which may cause early or late rethrombosis in this region of the vessel. It should be noted that the probability for development of complications is directly linked with the number of passages of the catheter through a thrombosed portion of artery.

The first clinical results of application of AngioJet in ALLI came to light in 1998-1999 with success of the intervention in more than 90% of cases with saving the limb in more than 85% of cases [23]. The results of a sufficiently large PEARL register confirm a high and long-term effectiveness of the intervention with salvage of the limb after a year in 81% of patients [24]. At present, AngioJet device is more often used just for PMT which showed the results comparable with those of RCBT, but with much faster reperfusion of the lower limb [25].

Rotation thrombectomy (RT). System of mechanical thrombectomy Rotarex® S (Straub Medical AG, Switzerland) is the most popular device in Europe for RT in the peripheral vascular bed. It consists of a catheter, motor, control console and draining sack. The catheter is a multilayered tube with a steel spiral inside of 'Archimedian screw' type rotating at average speed of 40 000 rpm. High speed of rotation of the spiral creates vacuum inside the catheter which sucks thrombotic masses which move along the spiral into the drainage sack. The tip of the catheter consists of two cylinders positioned one on another, each having lateral slits through which thrombus is sucked. The inner immovable cylinder (stator) is connected to the catheter body; the outer movable cylinder (rotor) is connected to the rotating spiral which creates a cutting 'head' which actually 'drills' a thrombus inside the artery, that is, causes its fragmentation that facilitates aspiration [26].

S. Heller, et al. (2017) obtained the total success of the intervention 90.5% (with use of RCBT in 21.8% of cases) [27]. Moreover, there were noted very low amputation and mortality rate (2.0 and 0.7%, respectively). B. Freitas, et al. (2016) presented the results of treatment of 525 patients with acute (40.2%) and subacute (59.8%) ischemia of a lower extremity: success of the intervention was 97.7% (with additional RCBT in 13.9% of cases). After a year of observation, the results of the intervention remained unchanged in 74.1% of patients, here the number of amputations, repeated revascularizations and mortality rate were 2.3%, 10.1%, 8.0%, respectively [28]. In retrospective analysis of RT and RCBT the total survival rate and the rate of salvage of the limb practically did not statistically differ despite a better primary and secondary patency in the RT group ($p<0.05$ [29].

Thus, RT is a good alternative to RCBT and is gradually beginning to be used as a method of choice for treatment of ALLI in some European centers. The only imitation for its use is thromboembolic damages to the arteries of shin associated with a high risk of their perforation, however, the recent experience shows that the device can also be used in proximal parts of the shin arteries [30]. And, nevertheless, for a further spread of the method, randomized controlled studies are required.

Aspiration (suction) thrombectomy (AT). At present the most popular devices for AT are Aspirex S (Straub Medical AG, Switzerland) and Penumbra System (Penumbra Inc., USA). However, both devices were initially intended for use in other vascular pools. Aspiration system Aspirex S, unlike a similar device Rotarex of the same manufacture, is intended to use in venous system. Both devices operate by the same principle, but have one important difference in the

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structure of the tip: it has no moving (rotating part) – rotor. Accordingly, catheters are intended for aspiration of thrombotic masses only through lateral holes of the tip. The point is that the rotating head of the catheter could cause damage to venous valves and could imply a very high risk of perforation of the thin venous wall. Nevertheless, if the device is available and it is urgent to quickly restore the blood flow in a lower limb, it can be used with a good clinical result in treatment for ALLI as well which was shown by B. Teyman et al (2017). The technical success of the intervention was 75% (with additional use of RCBT only in 12.5% of cases), the primary patency the target vessel after a year was 75%, here, not a single case of death and not a single amputation above the shin was recorded [31].

Aspiration system Penumbra was initially intended for use in cerebral vessels in treatment for acute ischemic stroke where it proved to be effective and safe. [32]. On the basis of the same system but intended for use in other peripheral vascular beds, Indigo system was created (Penumbra Inc.). These systems operate on the same principle, with the only difference being the size of catheters, in particular, in arteries of limbs catheters with a larger inner lumen are used. The system consists of a pump providing a constant negative pressure, armored tube, catheter and conductor-separator used for fragmentation of thrombus on the tip of the catheter to prevent its occlusion with a large thrombus. A peculiarity of these catheters is a maximally large inner lumen with the smallest outer diameter. With this, these catheters exist in a range of sizes for use in different arteries of lower limbs, from iliac arteries to the arteries of shin. Thus, both systems can be used in treatment for ALLI [33,34].

F. Baumann, et al. (2016) carried out a retrospective study for evaluation of the effectiveness and safety of Penumbra and Indigo systems in patients with ALLI. The study included 30 patients with 33 lesions, 10 of which were iatrogenic complications of endovascular interventions. The total rate of technical success was 72.7% with a higher parameter in the arteries below the knee (85.0%) against arteries above the knee (53.9%) [33]. This difference is most likely to be associated with the absence of larger 8F catheters at the moment of operation intended for use in arteries of a larger diameter. To note, in a third of cases RCBT was used, both before AT (24.2%), and after it (12.1%). An important positive moment for application of these devices was the absence of cases of distal embolism which evidences safety of their use.

G. L. Adams (2016) presented final results of the first retrospective multi-center study of use of Penumba and Indigo systems in patients with acute ischemia of the limbs and internal organs with ALLI in 90% of cases [34]. In 53% of cases only Penumba/Indigo systems were used, in 24.1% of cases after a failure with RCBT, in the rest of cases – after use of other devices for mechanical TE+/-RCBT. Successful revascularization was achieved in 96.3% of cases, and complete restoration of the blood flow – in 76.5% of cases. Complications were observed in 11 patients (12%), however, not a single of them was associated with the studied device.

Very recently a retrospective study of C.H.R. Kwok, et al. (2018) was published comparing AT and RCBT as methods of initial choice in treatment of patients with iatrogenic ALLI. Despite a small number of patients, technical success in the group of RCBT was much higher (89 against 53%) although complications in this group were more frequent (29.6 against 13.3%) including one lethal case from intracranial hemorrhage [35]. Nevertheless, this study cannot de demonstrative because of small amount of treated patients and insufficient experience of use of the given system by researchers themselves.

Pharmacomechanical thrombolysis is an intervention that combines two kinds of action on a thrombus: intrathrombotic thrombolysis with TA at a low dose and mechanical impact on thrombus with a certain device. These devices include: AngioJet (considered above) and peripheral infusion system Trellis (Covidien LLC, Medtronic, USA). Here, peripheral infusion system Trellis was intended for isolated PMT. Isolation of the site of exposure is achieved by inflation of two balloons in the distal part of the catheter positioned at some distance from each other (10-30 cm) and from the so called 'working zone' of the catheter. Fragmentation of thrombus is achieved by vibrations of nitinol conductor (500-3000 per minute) which has a portion of sinusoidal shape corresponding to the length of the working zone of the catheter, with infusion of TA through a respective port in the proximal part of the catheter. Theoretically, inherent advantages of this device are isolated effect of TA on the thrombus and protection against distal embolism [36].

T.P. Sarac, et al. (2004) used this system in treatment of 26 patients, 15 (58%) of which had ALLI. The general technical success was 92% with total 30-day survival without amputation 96% with the slightly lower parameter in the group of ALLI (93.8% against 100%; p=0.45). Here, it was possible to considerably reduce the amount of introduced TA. However, in this study 3 cases (11.5%) of distal embolism happened during intervention which were attributed by the authors to a lack of time for lysis and inability of the catheter to aspirate large fragments of unsolved thrombus. Very likely, it was connected with the implementation of the intervention itself, because in the study of R. Gupta, et al. (2012) no cases of distal embolism were noted [36].

Comparative Analysis of Regional Catheter-Based Thrombolysis and Surgical Methods of Treatment for Acute Lower Limb Ischemia

Meta-analysis of the main prospective randomized controlled studies (RCS) comparing RCBT with surgical treatment methods (ST) shows no statistically significant differences between these methods both in clinical effectiveness judged by salvage of the limb, and in the mortality rate in all periods of observation [38]. Nevertheless, there exist some aspects worthy of attention, because it is the data of randomized controlled studies [39-41] that served the basis for active promotion of RCBT as a method of treatment for ALLI.

Effectiveness of RCBT in treatment of ALLI was shown already in the first RCS – Rochester – with a high survival rate of patients without amputation both in a month (*p*=0.04), and in a year of observation (*p*=0.02) [39]. However, the next published RCS – STILE – did not reveal any statistically significant difference in the end point in a month of observation and showed only a higher amputation rate in the group of ST in a month of observation (17.9% against 5.7%, p=0.061) [40]. Nevertheless, as early as in 6 months survival rate of patients without amputation was considerably higher in the group with RCBT (*p*=0.01). The third RCS – TOPAS – did not show any statistically significant differences between groups of RCBT and ST in the survival rate without amputation both in 6 months (71.8% against 74.8%; *p*=0.43), and in a year of observation (65.0% against 69.9%; *p*=0.23) [41]. It should also be noted that despite similarity of the results of effectiveness of Rochester and STILE studies, the first study noted a higher mortality rate in the group of ST, and the second – a higher number of amputations which was significantly higher in patients with occlusion of shunts than in patients with occlusion of a native artery (*p*=0.002) [40].

Concerning safety of the interventions we would like to notice evident predomination of the amount of hemorrhagic complications in the group of RCBT: Rochester (11% against 2%, *p*=0.06), STILE (5.7% against 0%, *p*=0.157), TOPAS (12.5% against 5.5%, *p*=0.005) [39-41]. Here, their connection with reduced level of fibrinogen and with parallel infusion of heparin was identified [41]. Be-

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sides, one should not forget about perioperational complications associated with ST which also was rather high (49% against 16% (p=0.001) [39]; 20.5% against 10.0%, p=0.098 [40]).

TOPAS researchers carried out a multifactor analysis of 28 variables to identify parameters that could predict a better outcome for a patient treated for ALLI by surgical or endovascular method. Patients with thrombosis <30 cm appeared to have a better outcome with ST, and with thrombosis >30 cm – with use of RCBT. Besides, the analysis revealed a number of parameters that improve survival rate without amputation in both groups: white race; young age; no history of CNS diseases, malignant neoplasms and chronic cardiac failure. On the other hand, the presence of pain at rest, mottled or cyanotic skin worsened the prognosis.

Conclusion

Despite a considerable progress in treatment for acute ischemia of lower limbs, mortality rate and the rate of amputations continue to remain at a significantly high level. This is linked with many factors, first of all with time-lag of revascularization of a lower limb. The data of meta-analyses do not show any statistically significant difference between endovascular and surgical methods of treatment, however, numerous studies indicate a considerable difference between endovascular and surgical methods of treatment in favor of regional catheter-based thrombolysis which is reflected in the international recommendations.

Despite the fact that the given method of treatment has specific indications and, as any other intervention, possesses typical of it complications, a range of endovascular methods of treatment is constantly being enriched and renewed. For example, new devices for mechanical thrombectomy show impressive results especially when used by experienced specialists. They not only level out the main drawback of the regional catheter-based thrombolysis – a rather high frequency of hemorrhagic complications, but also expand indications for their use due to a quicker reperfusion of a lower limb. And, perhaps, in the near future these methods will become a new ‘golden standard’ in treatment for acute ischemia of lower limbs. However, this requires multi-center prospective randomized controlled studies to compare methods of mechanical thrombectomy both with regional catheter-based thrombolysis and with surgical methods.

But it should not be forgotten that both endovascular and surgical methods of revascularization do not ‘cure’ acute ischemia of a lower limb, but only cope with emergency situations. Therefore after application of these methods a rather aggressive prophylaxis of repeated events is required through treatment of diseases that led to clinical presentation of acute lower limb ischemia, with correction of risk factors for cardiovascular diseases.

In conclusion we would like to note that whatever are advantages of endovascular method over surgical one, the final choice will be individual for each patient and will be determined by many factors: patient’s condition, extent of acute ischemia, experience of a duty vascular and/or roentgen-endovascular surgeon and potentials of the medical institution.

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Дополнительная информация [Additional Info]

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