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Лазерные технологии в лечении артериальной патологии

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АННОТАЦИЯ

Введение. Сердечно-сосудистые заболевания занимают ведущую позицию в структуре летальности во всём мире. Лазерные технологии позволяют улучшить результаты эндоваскулярного и хирургического лечения различных форм ишемической болезни сердца и заболеваний периферических артерий. Несмотря на развитие технологий, лазерная ангиопластика и эндартерэктомия сопровождаются рядом осложнений и зачастую требуют дополнительного вмешательства.

Цель. Проанализировать имеющиеся в настоящее время данные об использовании лазеров в лечении артериальной патологии.

Согласно результатам анализа современной литературы, использование лазера уверенно занимает свою нишу в эндоваскулярном лечении острого коронарного синдрома, хронических окклюзий коронарных и периферических артерий, позволяет оптимизировать результаты стентирования и баллонной ангиопластики. Одним из основных недостатков лазерной ангиопластики является то, что процедура в большинстве случаев сочетается со стентированием и/или баллонной ангиопластикой и требует большего введения контрастного вещества и времени операции. Масштабных исследований по открытой лазерной эндартерэктомии не проводилось.

Заключение. Дальнейшее изучение воздействия лазера на атеросклеротическую бляшку и стенку сосуда при открытой эндартерэктомии является перспективным направлением и, возможно, позволит снизить частоту периоперационных осложнений и улучшить отдаленные результаты хирургического лечения заболеваний периферических артерий.

Ключевые слова: *лазерная хирургия; лазерная ангиопластика; лазерная эндартерэктомия; эксимерный лазер*

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Laser Technologies in Treatment of Arterial Pathology

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ABSTRACT

INTRODUCTION: Cardiovascular diseases hold a leading position in the structure of mortality in the world. Laser technologies permit to improve the outcomes of endovascular and surgical treatment of various forms of the coronary heart disease and diseases of peripheral arteries. Despite the development of technologies, laser angioplasty and endarterectomy are associated with a number of complications and often require additional intervention.

AIM: To analyze currently available data on the use of lasers in treatment of arterial pathology.

According to the results of analysis of the modern literature, the use of lasers confidently occupies its niche in endovascular treatment of acute coronary syndrome, chronic occlusions of the coronary and peripheral arteries, permits to optimize the results of stenting and balloon angioplasty. One main disadvantage of laser angioplasty is that in most cases the procedure combines with stenting and/or balloon angioplasty and requires more contrast agent and longer operation time. Large-scale studies on the open laser endarterectomy have not been conducted.

CONCLUSION: Further study of the effect of laser on an atherosclerotic plaque and vessel wall in the open endarterectomy is a promising trend that may probably reduce the incidence of perioperative complications and improve long-term results of surgical treatment of diseases of peripheral arteries.

Keywords: *laser surgery; laser angioplasty; laser endarterectomy; excimer laser*

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LIST OF ABBREVIATIONS

ACS — acute coronary syndrome
AP — atherosclerotic plaque
BAP — balloon angioplasty
CA — coronary artery
CHD — coronary heart disease
CLLI — critical lower limb ischemia
ELA — excimer laser angioplasty
ELCA — excimer laser coronary atherectomy
LAP — laser angioplasty
LE — laser endarterectomy
OE — open endarterectomy
PA — peripheral artery
PCI — percutaneous coronary intervention
SE — successful endarterectomy
TIMI — Thrombolysis in Myocardial Infarction

INTRODUCTION

Use of lasers in cardiovascular surgery for the removal of atherosclerotic plaques (AP) in the arteries was first proposed by E. P. McGaff, et al. in 1963 [1], a year after the invention of laser by T. Maiman. In 1992–1993, the United States Food and Drug Administration approved the production of LAIS Dymer 200+ (Advanced Interventional Systems, Irvine) and Spectranetics CVX-300 (Spectranetics, Colorado Springs) lasers. By the mid-1994, more than 15 thousand excimer laser angioplasty procedures were performed worldwide, with the vast majority of the operations on the coronary arteries (CA). Since that time, a multiplicity of studies and clinical trials have been conducted with use of lasers with different wavelengths and delivery systems for recanalization of stenoses of peripheral arteries (PA) and CA.

Cardiovascular diseases occupy a leading position in the structure of mortality worldwide. Laser technologies permit to improve the outcomes of endovascular and surgical treatment of various forms of coronary heart disease and diseases of PA. Despite this, one of the main limitations with the use of lasers in cardiovascular surgery in treatment for atherosclerosis is the continuing high level of perioperative complications [2]. The most common of these are perforation of arteries, restenosis, thrombosis, dissection and distal embolism [3]. However, with the introduction of new laser technologies and accumulation of experience, the frequency of these complications declined [4]. Another limitation of laser is a weak ablation effect on calcified plaques, which requires the use of additional devices or a hybrid intervention.

Concerns about thermal injury observed in laser angioplasty, have led to the development of intermittent laser angioplasty. Continuous-wave argon, Nd:YAG and CO2 lasers vaporize tissue with a thermal damage. On the contrary, delivery of laser energy in pulsed, or intermittent, mode, eliminates gross and microscopic signs of thermal injury [5]. All this permits to reduce the frequency of rethrombosis and other complications after laser angioplasty.

The **aim** of this study to analyze the currently available data on the use of lasers in the treatment for arterial pathology.

Use of Lasers in Treatment for CHD

Excimer laser coronary atherectomy (ELCA) is a long-established procedure that can be used in percutaneous coronary intervention (PCI). The use of lasers in the treatment of CHD has been studied in its different forms: acute coronary syndrome (ACS) [6], in-stent restenosis [7], chronic occlusions of CA. In LAVA registry, the most common indications for use of ELCA were CA lesions with impossibility of recanalization (43.8%), impossibility of adequate stent expansion (40.8%) and thrombotic lesions, with a high technical success rate (90.0%) and a low rate of serious adverse cardiac events (3.45%) [4].

With increasing number of complex coronary interventions, ELCA has become a key tool for AP exposure. A. J. Kirtane, et al. (2016) reported 50 thousand laser angioplasty procedures on coronary arteries performed in the period from 2010 to 2016 [8]. The only laser system approved by the United States Food and Drug Administration for coronary angioplasty is CVX-300 excimer laser system (Spectranetics). It uses xenon chloride as an active medium. The emitted light has a wavelength of 308 nm and tissue penetration depth of up to 30 μm. It has been shown that the interaction of ultraviolet radiation at 308 nm wavelength with platelets leads to a decrease in their aggregation and in the production of platelet factors [9]. In addition, the excimer laser has the ability to dissolve thrombotic masses and remove APs from CA. The advantage of using laser in ACS is rapid removal of thrombus due to vaporization of procoagulant factors and a reduced risk of distal embolization [10]. N. Shibata, et al. (2020) also showed the safety and effectiveness of using endovascular laser angioplasty in patients with intracoronary thrombosis and ST segment elevation [11].

Use of Lasers in ACS

Clinical data confirming the use of ELCA in ACS, remain limited. The largest to date is the CARMEL multicenter study. The study involved 151 patients with ACS, 65.0% of whom had an extended thrombus in the infarction-affected artery. After ELCA, the blood flow grade on TIMI (Thrombolysis in Myocardial Infarction) scale increased from 1.2 to 2.8, with the respective decrease in angiographic stenosis (from 83.0% to 52.0%). A low frequency (8.6%) of serious adverse coronary events was noted [12].

The randomized Laser AMI trial (M. Dorr et al., 2007) enrolled 66 patients with acute myocardial infarction. The optimal technique of laser angioplasty was used with saline flushing and slow advancement (0.2 mm/s–0.5 mm/s) of the guidewire. Most lesions were treated with the laser angioplasty–stenting method (only in two patients, balloon angioplasty was required before stenting). The primary angiographic endpoint was TIMI flow. The TIMI score increased from 0.2 ± 0.4 at baseline to 2.65 ± 0.5 after laser therapy and 2.9 ± 0.3 after stent placement (both parameters relative to baseline, $p < 0.01$). The *no-reflow* phenomenon occurred in 11.0% of cases after laser exposure, and in one case dissection occurred. There were no intraprocedural deaths, and the complication-free survival rate was 95.0% at 6 months, with left ventricular remodeling in 8.0% of patients [13].

The role of ELCA was also studied in patients with late revascularization (from 12 to 72 hours) after the occurrence of ACS with ST segment elevation. The *re-flow* phenomenon was shown to be much rarer when using laser angioplasty compared to the standard method (17.8% vs. 52.2%; $p = 0.019$). Besides, ELCA can be useful in reducing the frequency of distal embolism [14]. Apart from angiographic characteristics, the use of ELCA in ASC improves myocardial functional parameters and reduces myocardial necrosis markers [15].

Use of Lasers in In-Stent Restenosis

Despite the achievement in PCI and the availability of high-pressure balloon catheters, in-stent restenosis remains one of the most common complications in the long-term period. Ten to 50% of patients with installed base metal stents have restenosis [16]. Recently, there appear publications demonstrating the effectiveness of laser angioplasty in preventing and treating in-stent restenosis.

S. Hirose et al. (2016) showed that endovascular laser angioplasty is relatively safe and feasible in patients with coronary artery in-stent restenosis compared to balloon dilation alone [17]. Compared with bare metal stents, the installation of drug-eluting stents significantly improved long-term outcomes [18]. S. Hajibandeh, et al. (2019) proposed a combination of drug-eluting stents, laser and balloon angioplasty with a significant improvement in the clinical effect [19]. Paclitaxel drug-coated balloons and laser angioplasty have been shown to be safe and effective alternatives in the modern treatment of in-stent restenosis [20].

A number of authors note that the results of balloon angioplasty used alone are inferior to the results of balloon angioplasty in combination with laser angioplasty [21].

Use of Lasers in Complex Lesions of CA

Another problem of endovascular surgery of CA is percutaneous interventions in calcified APs and chronic occlusions. Using laser angioplasty, it is possible to perform recanalization of chronic occlusion with subsequent balloon angioplasty and stent implantation [22]. However, with marked calcification, the effectiveness of excimer laser angioplasty is considerably reduced. In this regard, one of the main methods of treatment for calcified lesions remains to be rotational atherectomy [23]. A combination of rotational atherectomy and laser angioplasty of the coronary arteries in patients with calcified coronary lesion is called *RASER* in the literature. The use of the combined method has been shown to have advantages over isolated rotational atherectomy [24].

In the study by J. Karacsonyi, et al. (2021) [25] in chronic occlusions that cannot be treated with standard techniques, the use of laser was associated with higher technical (91.5% vs. 83.1%, $p = 0.010$) and procedural (88.9% vs. 81.6%, $p = 0.033$) success rates and with a similar rate of major adverse cardiac events (3.92% vs. 3.51%, $p = 0.805$). Use of laser was associated with longer procedure time (169 [109, 231] vs. 130 [87, 199], $p < 0.0001$) and fluoroscopy time (64 [40, 94] vs. 50 [31, 81], $p = 0.003$).

Thus, it is a combination of laser angioplasty with other methods of treating CHD that provides the best results both in the short- and long-term period.

Use of Laser in Case of Stent Under expansion

Another indication for the use of laser in the surgical treatment of CHD is the inability to expand a stent using standard methods [26]. ELCA remains the only method that can reduce the underlying resistant AP by delivery of energy to the surface of the stent above it, without disrupting the stent architecture. This leads to a decrease in the total resistance providing subsequent complete stent expansion and reduces the risk of thrombosis through improving endothelialization of the stent [26].

This effect can be optimized by use of contrast injection during laser angioplasty [27]. T. Lee, et al. (2019) demonstrated the use of ELCA being associated with a larger final minimum arterial lumen area and increased area of the previously implanted stent (6.15 mm^2 vs. 4.65 mm^2, $p < 0.01$) according to the data of optical coherence tomography [28].

Complications after ELCA

The overall complication rate after ELCA decreased over time to 3.5%, reaching 33.0% in the 1990s [25]. This improvement is likely to be connected with the improved catheter delivery technologies, increases availability of catheter sizes, and also the operator experience (choice of pulse speed and repetition rate, methods of infusion of saline, blood, or contrast agent).

The mean complication rate estimated from the available literature, over time was as follows: perforation 0.76%, *no-reflow* phenomenon 1.49%, arterial dissection 6.9% to 8.8%, restenosis 4.6%, thrombosis 0.5%, side branch occlusion 0.28%, and distal embolism 1.48%. The most common complications with ELCA occur in recanalization of chronic occlusion [3].

Despite the low complication rates, ELCA has several disadvantages. First, due to longer procedure time and need for visualization, patients are injected with more contrast agent, which may lead to renal complications. Second, there is a weak ablation effect on calcified plaques, which requires the additional use of various atherectomy devices.

Thus, ELCA is an effective atherectomy technique with unique advantages. In the modern era of growing number of complex PCIs, this method will improve the arsenal of the modern interventional surgeon and improve short-term and long-term outcomes.

Use of Lasers in Diseases of PA

Standard methods of surgical treatment of diseases of the lower limb arteries include open and endovascular methods or their combination (hybrid operations). One endovascular method of treating PA diseases is balloon angioplasty (BAP). The main disadvantage of this method is a high rate of restenosis/vascular occlusion, which usually develops at 3–12 months. Frequency of restenosis varies from 6.0% to 60.0% and depends on the location, type and length of lesion [29].

The main cause of restenosis is believed to be an injury to the arterial wall during BAP. In particular, during balloon inflation, the AP undergoes excessive stretching, compression, and rupture. This local injury leads to production of growth factors that stimulate proliferation of endothelial and smooth muscle cells, intimal hyperplasia and arterial restenosis [30]. It was shown that best long-term results of angioplasty are achieved if APs are removed, rather than compressed or destructed. Currently, these methods are called ‘ablation methods’ and include endarterectomy, mechanical thrombectomy and laser angioplasty (LAP).

Currently, the main treatment for restenosis is repeat PCI or open surgery. Currently, of particular interest is the use of excimer laser angioplasty (ELAP) in the treatment of this problem. The use of an excimer laser can eliminate the vascular occlusion and facilitate the delivery of the device or BAP. In addition, LAP in combination with BAP reduces the incidence of balloon barotrauma, dissection, vessel wall hyperplasia, and the need for stent implantation [31].

EXCITE ISR (Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis) was the first large prospective randomized multicenter study comparing ELAP in combination with BAP and BAP alone. It analyzed 250 patients with in-stent restenosis in the femoropopliteal segment. Patients were randomized into two groups: ELAP + BAP and BAP alone in a 2:1 ratio. The mean lesion length was 19.6 ± 12.0 cm and 19.3 ± 11.9 cm, respectively. ELAP + BAP group demonstrated a higher and significant success rate of the procedure — 93.5% compared to BAP — 82.7% ($p = 0.01$), with significantly fewer procedural complications. The 6-month freedom from repeat revascularization was significantly higher in the ELAP + BAP group and was 73.5% compared with 51.8% in the BAP group ($p < 0.005$), and the incidence of serious adverse events within 30 days was 5.8% versus 20.5% ($p < 0.001$), respectively. ELAP + BAP was associated with a 52.0% reduction in repeat revascularization [32].

The multicenter prospective SALVAGE study [33] investigated the safety and effectiveness of excimer laser treatment of femoropopliteal segment restenosis followed by implantation of the VIABAHN endoprosthesis. The study included 27 patients. The average lesion length was 20.7 ± 10.3 cm. Technical success was achieved in 100.0% of cases. Primary patency after 12 months was 48.0%. The ankle-brachial index increased from initial 0.58 ± 0.24 to 0.90 ± 0.17 after 12 months. There was an improvement in all quality-of-life parameters. The repeat revascularization rate at 12 months was low — 17.4%.

To note, ELAP is used not only in treatment for restenosis after endovascular interventions, but also as a primary intervention. In the study by D. Scheinert, et al. (2001) [34] 411 chronic occlusions of the superficial femoral artery of the average length of 19.4 ± 6.0 cm, were eliminated using ELAP with additional BAP and stenting. The technical success was 90.5%. Complications included acute re-occlusion (1.0%), perforation (2.2%) and distal embolization (3.9%). The primary and secondary patency rates at 1 year were 65.1% and 75.9%, respectively.

H. J. Steinkamp, et al. (2003) [35] published a study involving 215 patients with popliteal artery occlusion with average length of 10.4 cm. This prospective, non-randomized study compared ELAP with subsequent BAP (127 patients) and BAP used alone (88 patients). The average follow-up period was 36 months, and the primary and secondary patency rates were 21.7% and 50.8% in patients who underwent ELAP + BAP, and 16.3% and 35.2% in the BAP group, respectively. However, no statistically significant differences were found between the groups.

The multicenter prospective CELLO study included 65 patients, 52 patients with femoropopliteal segment stenosis (> 70.0%) and 13 patients with femoropopliteal segment occlusion. The primary endpoint was the reduction in stenosis diameter measured by ultrasound after laser ablation. Initially (before ELAP), stenosis was 77.0 ± 15.0% and was reduced to 34.7 ± 17.8% after ELAP. Additional BAP was performed in 64.6%, BAP and stenting in 23.1%. Twelve-point three percent did not receive any subsequent treatment after ELAP. Survival rates (restenosis < 50.0%) were 59.0% and 54.0% at 6 and 12 months, respectively [36].

Patients with critical lower limb ischemia (CLLI) often have a severe comorbid pathology, high surgical risk and diffuse lesion of arteries with the impossibility of bypass surgeries [37].

The aim of LACI (Laser Angioplasty for Critical Limb Ischemia) multicenter study was to investigate the effectiveness and safety of LAP in patients with CLLI. Treatment of a total of 155 limbs with a high amputation risk was conducted. All patients had a very high risk of the open surgical treatment because of concomitant cardiorespiratory diseases.

A total of 426 femoropopliteal and infrapopliteal lesions were treated. PCI was performed after ELAP in all cases. A stent was implanted in 45.0%. Procedural success, defined as < 50.0% residual stenosis, was achieved in 86.0% of cases. At 6-month follow-up, limb salvage was achieved in 92.0% of cases [37].

Another multicenter prospective study by M. Boisers, et al. (2005) included 48 patients with critical ischemia and high-risk, or unsuitable anatomy for bypass surgery. The treatment consisted in passing the occlusion or stenosis with a guidewire followed by LAP with additional BAP or stenting. Limb salvage at 6 months was achieved in 90.5% with freedom from critical ischemia in 86.0% [38].

In a retrospective study by Y. P. Yang, et al. (2023) which included 70 patients with critical ischemia and occlusive lesions of arteries below the inguinal ligament, LAP was performed using an excimer laser and a low-pressure balloon. Technical success was achieved in 87.1% of patients, and the limb salvage rate at 6 months was 78.8%. A higher Rutherford class was associated with poor long-term results [39].

Advantages and Disadvantages of LAP in PA Diseases

LAP is a safe method, since the complication rate does not exceed that of standard BAP. Arterial perforation In ELAP is relatively rare (on average, 2.0% of cases) [37]. In larger studies, distal embolization varies from 2.5% to 9.0% [40].

A LAP advantage is an easier passing across chronic and calcified occlusions. According to the literature, crossing such occlusions with standard guidewires may be unsuccessful in 8.0%–34.0% of cases. In these cases, ELAP is performed in a step-by-step manner with the laser radiation used simultaneously with the guidewire to recanalize the occlusion. Upon that, the laser catheter more commonly advances inside the lumen, and not subintimally [41].

Some larger studies reported positive results in patients with CLLI using ELAP + BAP method that permitted to avoid amputation. However, these studies were not randomized, and the follow-up period was relatively short (6 months) [37].

The disadvantages of ELAP include the fact that the modern multi-fiber laser catheters (even their modifications) cannot create a wide enough channel in the occluded artery. This requires subsequent balloon dilation which can affect the long-term LAP results. Besides, a disadvantage of LAP is a higher cost compared to conventional BAP/stenting [41].

Open Laser Endarterectomy

Based on the above studies, the use of laser technologies in endovascular treatment of patients with cardiovascular diseases is a promising technique. However, the use of laser in open surgery has not been sufficiently studied. Open endarterectomy (OE) is one of the fundamental methods of reconstructive vascular surgery. Successful endarterectomy (SE) depends on the formation of a smooth surface on the artery and fixation of the transition zone to reduce the risk of dissection. Laser endarterectomy (LE) is a new modification of the generally accepted technique that allows achieving these parameters [41], but its study in humans is currently limited.

J. Eugene, et al. (1985) [42] performed OE in rabbits using an argon laser with a wavelength of 488 nm to 514 nm. As a result of the study, the authors concluded that it is possible to perform precision SE with a laser. Since the OE procedure is performed under visual control, the complication rate is minimized. Electron microscopic examination data revealed a smooth surface after endarterectomy.

In April 1988 J. Eugene commenced a study of application of LE in patients with brachiocephalic artery disease. Ten patients were operated on. Laser radiation was used to dissect the atheroma and fix the terminal sections. Residual atheromatous formations were vaporized by laser exposure. The average length of endarterectomy was 3.9 ± 1.1 cm. The average clamping time was 22.5 ± 7.9 min.

A complication analysis did not reveal arterial perforations or other damages induced by laser exposure. Postoperative observations, which lasted on average 12 months and varied from 5 months to 19 months, showed satisfactory results. Subsequent angiographic examinations were not performed [43]. Similar results were obtained in the treatment of patients with atherosclerosis of the arteries of the lower extremities [44]. Unfortunately, further large-scale studies of OE in patients with PA diseases were not conducted.

CONCLUSION

According to the results of the analysis of modern literature (Table 1), lasers have confidently occupied their niche in the endovascular treatment of acute coronary syndrome, chronic occlusions of the coronary and peripheral arteries and allow optimizing the results of stenting and balloon angioplasty. One main disadvantage of laser angioplasty is that the procedure in most cases is combined with stenting and/or balloon angioplasty and requires more contrast agent and longer operation time.

Thus, both excimer laser coronary atherectomy and angioplasty of peripheral arteries are effective treatment methods with unique advantages. In the modern era of the increasing number of complex endovascular interventions, these methods will expand the armamentarium of X-ray endovascular surgeons and will improve both immediate and long-term outcomes.

Large-scale studies on open laser endarterectomy have not been conducted. Further investigation of effect of laser radiation on atherosclerotic plaque and vessel wall in open endarterectomy is a promising trend and will probably reduce the perioperative complication rate and improve the long-term outcomes of surgical treatment of peripheral arterial diseases.

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Table 1. Comparative Effectiveness of Use of Excimer Laser according to Different Authors' Data

Authors	Year of publication	Kind of inter-vention	Number of observa-tions	Method effectiveness	Disadvantages	Advantages
Coronary heart disease						
O. Topaz, et al. [12]	2004	ELCA	151	93.3%	–	Low frequency of adverse coronary events (8.6%)
M. Dorr, et al. [13]	2007	ELCA	66	96.6%	No-reflow (11.0%) Artery dissection (1.51%)	–
H. Kujiraoka, et al [14]	2023	ELCA	319	–	–	Reduction of frequency of *no-reflow* phenomenon, distal embolism
J. Karacsonyi, et al. [25]	2021	RASER	23	91.5%	Long duration of procedure and X-ray examination	Low incidence of adverse cardiac events (3.92%)
T. Lee, et al. [28]	2019	ELCA	81	–	–	Increases the final minimum arterial lumen area and the area of the previously implanted stent
C. McQuillan, et al. [3]	2021	ELCA	331	–	Perforation (0.76%) *no-reflow* phenomenon (1.49%) Arterial dissection (6.9–8.8%) Restenosis (4.6%) Thrombosis (0.5%) Side branch occlusion (0.28%) Distal embolism (1.48%)	–
Diseases of lower limb arteries						
E. J. Dippel, et al. [32]	2015	ELA + BAP	250	93.5%	The need for balloon angioplasty	Reduction in the number of procedural complications, 2 times reduction in the frequency of repeat revascularization, improvement of long-term results
J. R. Jr Laird, et al. [33]	2012	ELA + implantation of endoprosthesis	27	100.0%	–	–
D. Scheinert, et al. [34]	2001	ЭЛА + БАП/стен-тирование	411	90.5%	Acute re-occlusion (1.0%) Perforation (2.2%) Distal embolization (3.9%)	–
H. J. Stein-kamp, et al. [35]	2003	ELA + BAP	215	–	Primary and secondary patency is comparable to BAP	–
R. M. Dave, et al. [36]	2009	ELA/ ELA + BAP	65	59.0% (at 6 months) 54.0% (at 12months)	–	–
J. R. Laird, et al. [37]	2006	ELA + BAP/ Stenting	426	86.0%	Arterial perforation (2.0%)	Limb salvage in the long term (6 months) in 92.0%
M. Boisers, et al. [38]	2005	ELA + BAP/ Stenting	48	–	–	Limb salvage at 6 months 90.5% Freedom from critical ischemia at 6 months 86.0%
Y.–P. Yang, et al. [39]	2023	ELA + BAP	70	87.1%	–	Limb salvage at 6 months 78.6%

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