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Comparative Investigation on Polymer Drug-coating Balloons Used in Infrapopliteal Angioplasty Based on Angiosomes Concept

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Abstract: *Atherosclerosis can affect the blood vessels in any region of the body and the stenosis (narrowing) can be located on an artery that vascularize important organs, such as the brain, abdominal organs or limbs. The endovascular surgery is a modern approach to vascular pathology through minimally invasive techniques (puncture, minimally vascular approach) and it represents an enrichment of the arsenal of surgical techniques and brings considerable improvements in post-operative and long-term outcomes The use of polymer drug-coating balloons is an attractive alternative because they can offer the promise of an improved patency compared to the simple balloons and a reduction in the need for stents. The aims of this study were to describe the polymer materials and to compare the medical endpoints obtained in angiosome-targeted infrapopliteal angioplasty using a simple balloon with two layers, based on polyethylene, and respectively a drug-coated balloon that contains a multiblock copolymer from polyethylene, poly(cylohexylethylene), polyisoprene and poly(1,3-butadiene) covered by Paclitaxel. The balloons were characterized by differential scanning calorimetry, stress-strain and puncture tests in order to describe their physical and mechanical characteristics. On the other hand, 51 patients with critical limb ischemia were treated with different balloon angioplasty and they were monitored for 12 months after the intervention; the following parameters have been evaluated: diabetes, hypertension, renal insufficiency, hemodialysis, stroke, dyslipidemia, heart disease, heart failure, body mass index, number of angiosomes, creatinine, and wound healing, leg salvage and amputation-free survival at 1, 2, 3, 6, 9, 12 months. Significant associations were found in the case of anterior-tibial-artery and posterior-tibial-artery angioplasy and the age, hypertension and renal insufficiency. On the other hand, the results indicate that the drug deposition on the surface of the balloons lead to improved values for the observed medical endpoints. In conclusion, this study reveals that angiosome-based infrapopliteal angioplasty with drug-coated balloons can be associated with better wound healing and leg salvage.*

Keywords*: angiosomes concept, DSC, percutaneous transluminal angioplasty, puncture test, stress-strain curve*

1. Introduction

Critical ischemia is a severe obstruction of the arteries of the lower limbs that significantly reduces blood flow, causing severe pain and even skin wounds. It represents the advanced stage of peripheral arterial disease and is produced by progressive thickening of the walls of the arteries, caused by the accumulation of cholesterol. This buildup of cholesterol, also known as atherosclerosis, impairs or blocks blood flow, reducing blood flow to the legs [1]. The main risk factors are: high blood pressure, high cholesterol level, obesity (over 30 body mass index), smoking, diabetes, aging (especially after 50 years), family history of peripheral arterial disease, heart disease, or stroke. Patients with critical

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critical ischemia are at risk of losing their limb, sometimes even life-threatening, in a period of weeks or months without surgical bypass or endovascular revascularization.

The treatment is also difficult because this type of patient has an advanced disease, they are usually older [2].

Endovascular surgery involves simple balloon angioplasty or stent angioplasty. Medium and long-term results vary depending on the location of the lesions, but the trauma to which the patient is subjected is much smaller [3].

The materials used in the manufacture of the angioplasty balloons have a great impact on the final properties of the balloon. The first angioplasty balloons were made of polyvinyl chloride (PVC); they were thick-walled and designed for low pressure. In the mid-1980s, PVC was replaced by cross-linked polyethylene (PE) and polyethylene terephthalate (PET), both of these were able to withstand higher pressures. The latest materials used for angioplasty balloons were polyurethane (PU) and nylon [4].

The plain old balloon angioplasty (POBA) is used for Percutaneous Transluminal Angioplasty (PTA). The material resistance is between 1.9 atm for a diameter equal with 2 mm and 6.3 atm for a diameter equal with 6 mm. It is often used in various interventions above and below the knee. It is a one-time use only device, which cannot be resterilized [5].

On the other hand, a drug-coated balloon (DCB), indicated in PTA, has offered durable and safe outcomes across many clinical trials, as well as across complex patient and lesion types [6]. The manufacturer presents that more than 3,500 patients were enrolled in 21 clinical studies and more than 200,000 patients have been treated using this DCB for treatment of femoropopliteal disease with 75% of patients' reintervention-free at 5 years.

In a recent article, SH Kim *et al*. [7] have reported the use of DCB for treating superficial femoral artery. They have found cases of twisting of the Ranger paclitaxel-coated PTA balloon catheter in the case of two 73-year-old men with history of hypertension and dyslipidemia. As a conclusion, the authors have presented that after the identification of the possible causes and a quick cooperation between the manufacturer and the physician, this problem does not appear again.

The DCB angioplasty can also be used to treat hemodialysis dysfunction. C Lyu *et al*. [8] have reported that the group of patients had the following odds ratio of target lesion revascularization during follow-up: 0.43 [95% CI, 0.23-0.82] at 6 months and 0.74 [95% CI, 0.32-1.73] at 1 year. Based on these results and compared to others obtained in the case of the Plain Balloon Angioplasty (PBA) used for the same disease, DCB was found to be more effective than PBA in preventing hemodialysis access failure after endovascular recanalization.

Angiosome-targeted infrapopliteal endovascular revascularization represents a modern concept and it was already described in the literature [9, 10]: the body is delimited into 3D blocks of tissue fed by specific source arteries and the revascularization is guided by an angiosome design of perfusion during the curative process. The principal aims of this research were to describe the physical and mechanical properties of the balloons and to analyze the impact of the material used for drug-coated balloons in the angioplasty based on angiosomes concept in the treatment of diabetic patients with critical limb ischemia.

2. Materials and methods

2.1. Physical and mechanical characterization

The simple balloon used for POBA contains an inner layer based on high-density polyethylene, while the outer material is based on low-density polyethylene. The second balloon that was investigated is a DCB based on a multiblock copolymer as a mixture of polyethylene, poly(cylohexylethylene), polyisoprene and poly(1,3-butadiene) covered by Paclitaxel.

The thermal behavior of two balloons was comparatively assessed by a Mettler-Toledo DSC1 instrument (Nanikon, Switzerland) with purge inert gas (nitrogen) flow rate of 50 mL/min. between 30-200°C with a 10 degree/min heating speed using 40 μL aluminium crucibles with pierced caps.

Comparative stress-strain curves were obtained by gradually applying load to samples and measuring

the deformation, from which the stress and strain can be determined. A Netzsch Dynamic-Mechanical Analyzer, type DMA 242 C (Selb, Germany), was used in the tension mode, under air atmosphere, at 25^{o}C to obtain the curves.

The puncture test is used to determine the penetration or the puncture strength of materials. ASTM F1306 describes the procedure [11]; an Instron 1011 Universal Testing Machine (Canton, MA, USA) was used with the following parameters: crosshead speed (2 mm/s) and probe size (1.6 mm diameter).

2.2. Patients

A retrospective analysis of 51 consecutive patients presenting with critical limb ischemia (CLI) was performed (39 men, 12 women), which were treated with different balloon angioplasty (28 direct, 12 indirect, and 11 both). 43 patients were treated with POBA, while the other 8 patients were treated with DCB. The study cohort consisted of patients with Rutherford category 5 to 6 only. The data were retrospectively collected between Nov. 1st, 2018 and Nov. 1st, 2019. Study termination at which point follow-up investigations ended was Nov. 1st, 2020. The median follow-up was 12 months (range 11-13 months). 4 patients were lost to follow-up as they did not participate at the follow-up investigation. Included were consecutive patients receiving endovascular revascularization below-the-knee (btk) for short segment occlusion with multiple vessel outflow in the lower leg.

Table 1 presents a simplified illustration of the main characteristics of patients who were divided into two groups in function of the polymer DCB that was used in PTA.

Table 1. Comparative characteristics of patients

Characteristics	Balloon Type		*P*
	Simple	DCB	
Age, years	68.4±8.5	67.4±6.2	.781
Age ≥80 years	4 (9.3)	0 (0.0)	.023
Female	9 (20.9)	3 (37.5)	.892
Diabetes Oral Ad	30 (69.8)	6 (75.0)	.738
Insulin	17 (39.5)	4 (50.0)	.821
Hypertension	39 (90.7)	8 (100.0)	.695
Renal insuff.	9 (20.9)	2 (25.0)	.881
PTA ATA	25 (58.1)	6 (75.0)	.516
ATP	15 (34.9)	1 (12.5)	.787
Truncus	15 (34.9)	8 (100.0)	.161
Per	12 (27.9)	4 (50.0)	.483

ATA= anterior tibial artery; ATP= posterior tibial artery; Per= peroneal artery

2.3. Study design

Measurements of ankle-brachial index were made pre- and post-operatively. Patients with false values increased by medial sclerosis and calcifications (above 1.3 were excluded from the sample. A dorsal and a plantar measurement on the foot were performed pre- and post-operatively in order to assess the angiosomes of the dorsal and plantar foot. Each perfusion measurement sequence lasted 272 s; sequential dorsal and plantar measurements were performed after an interval of 5 min.

In the follow-up clinical investigation, characteristics of the wound was recorded, as well as local pain, the ABI was obtained, as well as duplex ultrasound as an evaluation of the revascularization permeability; The size of the wound was assessed and documented by photography, the wounds were classified at the time of the first investigation using the Wound Score, Ischeemia and Foot Infection Score (WIFI Score) from the Society of Vascular Surgery [12].

Following this score, the risk of amputation after one year was predicted. In addition, the wound "time-to-healing" was assessed for all follow-up patients. At this point, wound healing has been defined as complete epithelialization. Patients who were still injured in the follow-up investigation were defined as unhealed. A comparison of the time to wound healing and the rate of wound healing according to the revascularization method (direct and indirect) was performed.

To address the individual flow of endovascular angioplasty and pedal arch permeability, as well as

individual collateralization, intraoperative digital subtraction angiograms were noted according to the classification of the pedal arch, as suggested by Kawarada [13].

2.4. Ethical approval

The research was done according to the principles of the Declaration of Helsinki. The fulfillment of the informed consent was waived, because the personal data of the patients were evaluated retrospectively and anonymously. Authors declare that all procedures followed the specific regulations and standards; the study was evaluated and approved by the Ethical Committee of "Pius Branzeu" Public Hospital Timisoara, Romania and by the Ethical Committee of "Victor Babes" University of Medicine and Pharmacy Timisoara, Romania.

2.5. Statistics

The statistical analysis was performed using SPSS v. 27.0.0.0 64-bit edition statistical software (IBM SPSS Inc., Chicago, IL, USA) and Excel v. 1808 from Microsoft Office Professional Plus 2019 (Microsoft, WA, USA). Data are presented as categorical variables and frequency distributions. The Kolmogorov-Smirnov test was used for testing the distribution of variables. Variables with normal distribution were presented as mean value and standard deviation. The statistical differences were determined using two-way ANOVA analysis followed by Bonferroni post-test. 67 variables were included; only those with a p value <0.5 were included in the multivariate analysis. No attempt was made to replace missing values. The impact of baseline variables on late outcome was based on the Cox proportional hazards method.

3. Results and discussions

The physical and mechanical properties of materials depend on their chemical structure and they are very important for the products application. The most important properties of the polymers that are used for various balloons are the surface smoothness, puncture resistance and the rupture resistance, but just as important is the provision of a specific length and diameter or an exact size of walls thickness.

The thermal behavior of the two materials is presented in Figure 1 as DSC curves, while Figure 2 presents comparative stress-strain curves in axial and radial directions obtained for the two materials.

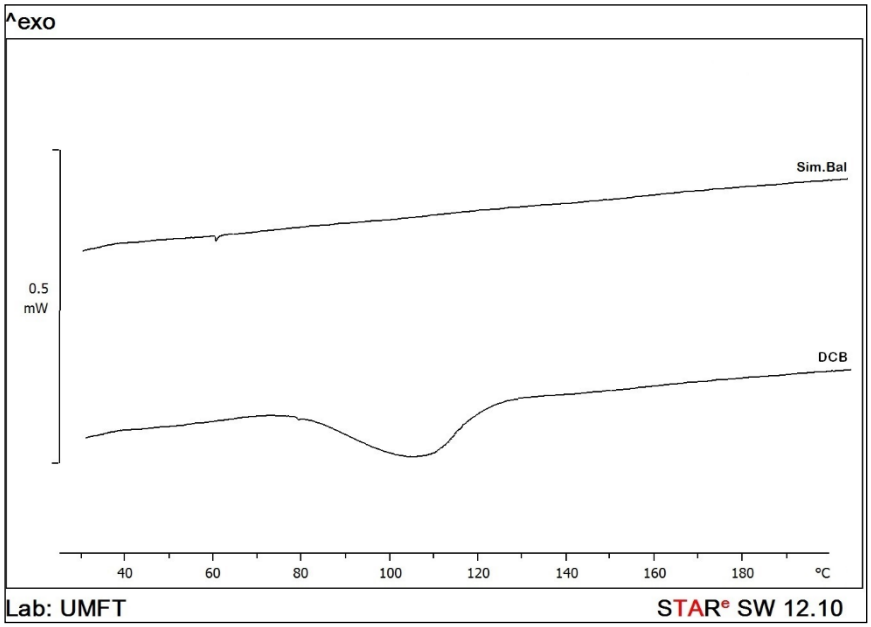

Figure 1. Comparative DSC curves

The DSC thermograms reveal a very good stability of the polymer materials inside the studied temperature range. The glass transition temperature of these polymers is well below 20°C, as in the case of polyethylene with low or high density, polycaprolactone, polypropylene and glass fibers. The large endothermic peak from the DCB curve around 105°C can be assigned to the loss of H_2O and other volatile compounds, such as aldehyde, ketone and ether residues.

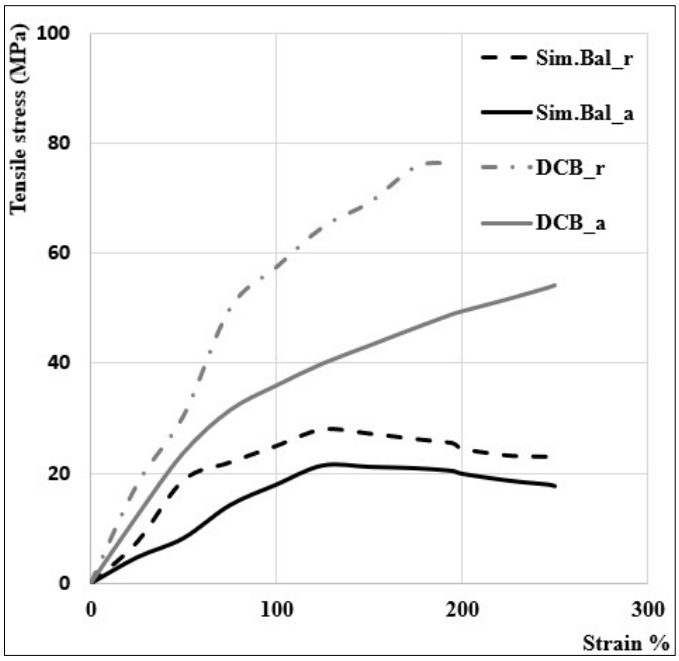

Figure 2. Comparative stress-strain curves

The stress-strain curves contain different parts: the first one content the rise-run ratio (the slope that give the Young's modulus), the second one of strain hardening, the 3rd - necking and the last one is called the fracture [14]. Based on these curves, the Young's modulus, that is the measure of the stiffness of an elastic material, it can be appreciated that higher values were obtained in the case of radial direction than the axial one and in the case of material from DCB than from the simple balloon.

The results of puncture resistance for the two materials are presented in Figure 3. It can be observed that the puncture load is greater for the simple balloon, while DCB has revealed a good yield against puncture but under the level of simple balloon both in deflection distance and penetration force.

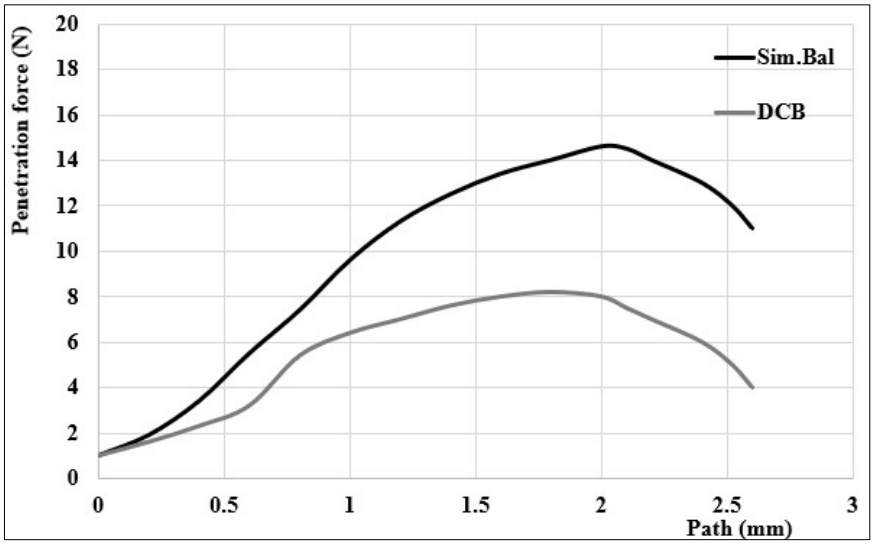

Figure 3. Comparative puncture test

Pre- and post-operative data and baseline patient characteristics were assembled from the collected database. The comparison between the two types of balloons used as endpoints the following parameters that have been evaluated for 12 months after the clinical intervention: wound healing, leg salvage, and amputation free survival.

The Cox proportional hazards analysis showed that PTA ATA can be associated with age (HR= 0.978, 95% CI 0.935-1.024), with hypertension (HR= 0.565, 95% CI 0.166-1.927), and with renal insufficiency (HR= 0.835, 95% CI 0.281-2.475), while PTA ATP with age (HR= 0.974, 95% CI 0.918-1.034), with hyper-tension (HR= 1.037, 95% CI 0.133-8.075), and with renal insufficiency (HR= 1.035, 95% CI 0.287-3.731). Also, the number of major amputations can be associated with age (HR= 1.050, 95% CI 0.806-1.367), while the number of minor amputations can be associated with age (HR= 0.987, 95% CI 0.893-1.091) and with hyper-tension (HR= 0.266, 95% CI 0.027-2.591).

The safety and the efficacy of direct vs. indirect PTA have been comparatively investigated by many other research groups; the majority of these studies have revealed that direct PTA may be performed safely as an alternative to thrombolytic therapy in patients with acute occlusion of the arteries [15]. In our study, the direct PTA was associated with a wound healing (HR 0.924, 95% CI 0.125-6.813) and with limb salvage (HR 0.380, 95% CI 0.019-7.781); no significant association was found between indirect PTA and the medical endpoints.

Our treatment focus on identification and specific treatment of ischemic foot ulceration, aims to support the body's own healing processes, to prevent infection of the wound, to reduce microbial load and to eliminate infection and tissue necrosis zones. Figure 4 presents a comparative evolution of wound healing in our studied groups.

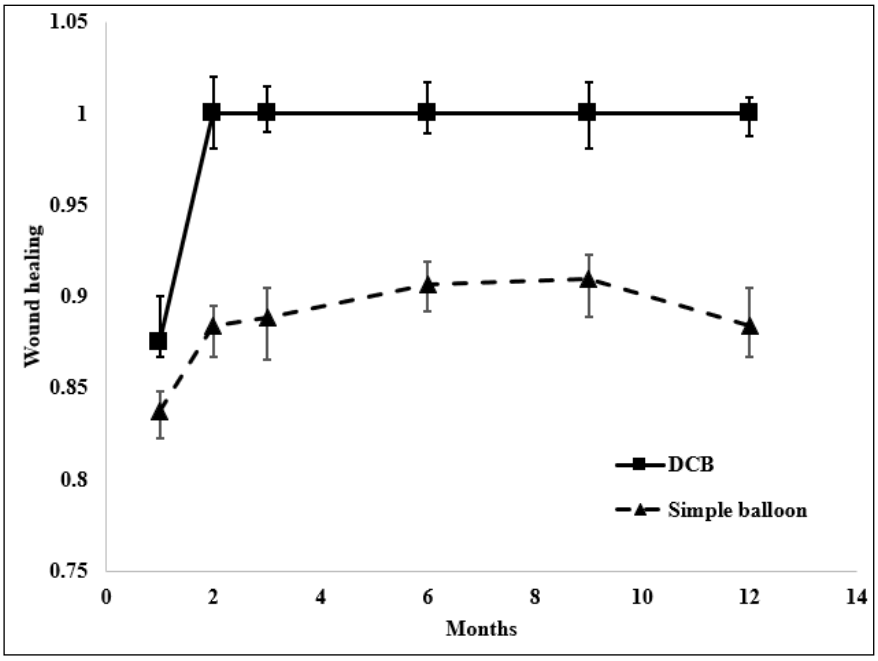

Figure 4. Comparative evolution of wound healing; P<0.05

The overall 1-year wound healing rate was 90.2%; it was found that the highest wound healing rate was achieved in the case of DCB (100%) and the worst in the case of simple balloons (88.4%). It appears that drug-coating balloons avail a more efficient influence in wound healing. H. Ang et al. [16] described that the progress and the development of drug-coating balloons represents an emerging alternative treatment in peripheral and coronary artery; the authors have highlighted four key-elements of these balloons: the drug, the excipients, the platform and the coating process. The acute drug transfer occurs almost immediately after positioning and inflating of the balloon and it deliver the antiproliferative drug

from its surface to the walls of vessel, the majority being bind to hydrophobic binding sites of wall, and a little part being transported by diffusion.

Two main possibilities to restore the arterial flow to leg are well-known in the literature: the endovascular procedures (the arterial flow is restored using balloons or stents that enlarge and repermeabilize the occluded or narrowed arteries (with minimally invasive) and the bypass re-vascularization, which involves bypass surgery to nourish the ischemic muscles and tissues [17]. Our study used the first procedure for the leg salvage and the comparative results are presented in Figure 5.

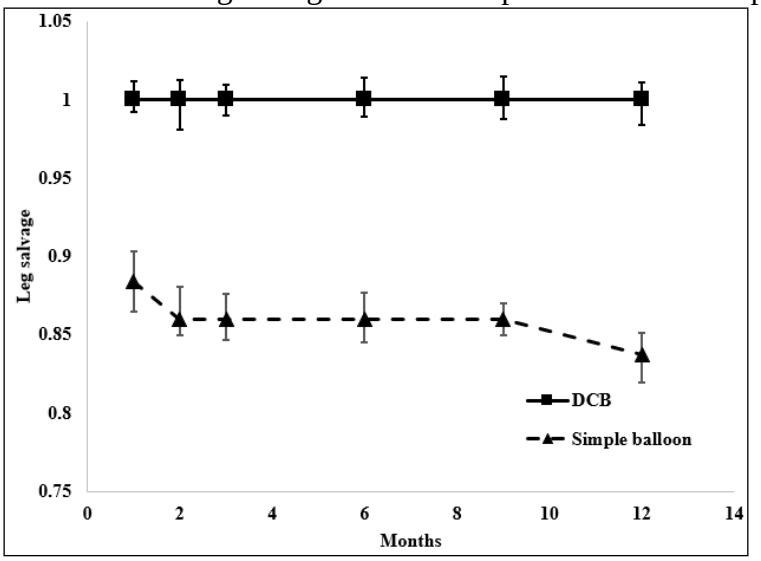

Figure 5. Comparative evolution of leg salvage; P< 0.01

The overall 1-year leg salvage rate was 86.3%; it was found that the highest wound healing rate was achieved in the case of DCB (100%) and the worst in the case of simple balloons (83.7%). wound healing, lower limb rescue and preservation are different therapeutic goals from improving gait, existing often also time constraints. E. Tukiainen *et al*. [18] has determined persistent outcome and anticipating factors for extreme surgery by vascular and plastic surgical teamwork for leg salvage in patients with critical limb ischemia (CLI) extensive tissue defects in 2157 cases of vascular or endovascular revascularizations; they have found good and very good rates in 1- and 5-year leg salvage (73 and 66%), survival (91 and 63%), and amputation-free survival (70 and 41%); they have concluded that endovascular interventions rep-resent a solution for advanced limb salvage in patients with CLI and/ or a major tissue defect.

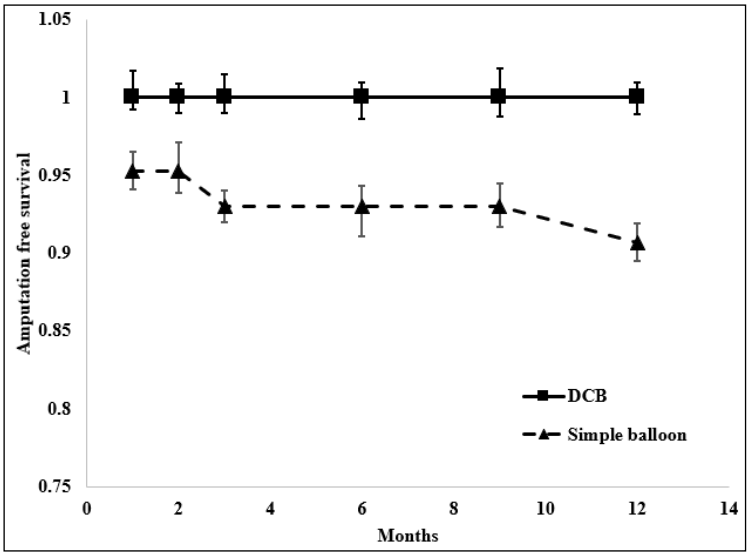

Figure 6. Comparative evolution of amputation free survival, P<0.05

The overall 1-year amputation free survival rate was 92.2%; it was found that the highest wound healing rate was achieved in the case of DCB (100%) and the worse in the case of simple balloon PTA (90.7%) (Figure 6). Based on the definition of E. Benoit *et al*. [19], the amputation-free survival represents a composite endpoint of mortality and amputation and it is the preferred outcome measure in CLI. On the other hand, J.H. Lin *et al*. [20] considered that the endovascular approach is the best therapy in CLI. The DCB used by our team have al-ready been described as a device with a significant advantage in amputation-free survival after the treatment of femoropopliteal artery in a 4-year follow-up compared to uncoated balloons [21].

Based on E. Beropoulis *et al*. [22], the wound-ischemia-foot infection (WIfI) represents a possibility to classify the prediction of the amputation risk in patients with CLI. The Society for Vascular Surgery often use this parameter (Table 2) to have a predictive ability after lower extremity revascularizations and after infrapopliteal endovascular interventions in CLI [23, 24]. A comparative analysis of WIfI in our observed groups is depicted in Figure 7.

Table 2. Detailed description of the wound-ischemia-foot infection (WIfI) grades [23]

Wound grade	Ischemia grade	Infection grade
0 (no wound)	**0** (TP >60 mm Hg, ABI >0.80 ASP >100 mm Hg)	**0** (no symptoms or infection signs)
1 (small, no exposed bone and no gangrene)	**1** (TP 40-59 mm Hg ABI 0.60-0.79 ASP 70–100 mm Hg)	**1** (small local infection)
2 (deeper ulcer and gangrene limited to digits)	**2** (TP 30-39 mm Hg ABI 0.40-0.59 ASP 50–70 mm Hg)	**2** (local infection with erythema on more than 2 cm)
3 (extensive and deep ulcer)	**3** (TP <30 mm Hg ABI <0.39 ASP <30 mm Hg)	**3** (local infection with SIRS signs)

TP= toe pressure; ABI= ankle-brachial index; ASP= ankle systolic pressure; SIRS= systemic inflammatory response syndrome

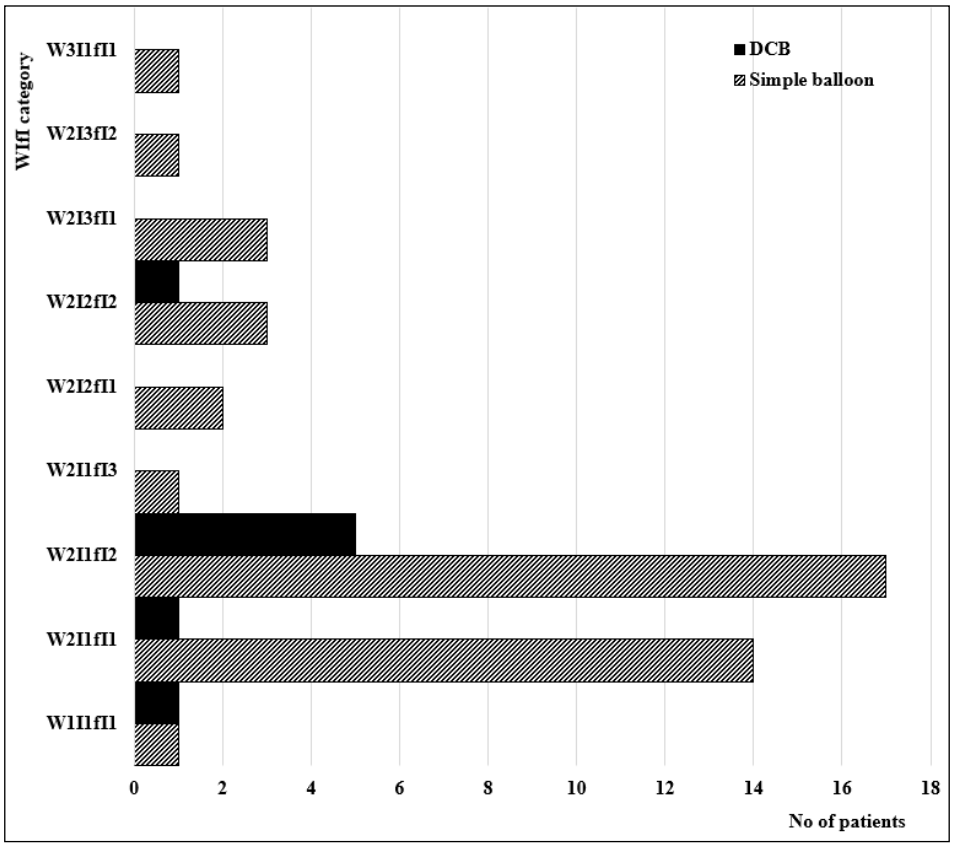

Figure 7. Comparative classification of patients based on WIfI grades

Our results have shown a strong correlation between the patients treated with DCB and the WIfI grades - in their cases the highest value (3), that has not been found for any of the three parameters. The WIfI classification system of Society for Vascular Surgery appeared useful to predict 1-year amputation, reintervention, amputation, stenosis events, and wound curing in patients with CLI undergoing various procedures of endovascular infrapopliteal revascularization.

A series of correlations have been calculated in order to observe any association between the evaluated parameters and it was found an inverse proportionality between the diabetic patients treated with oral antidiabetics and the presence of wounds on both limbs (Pearson's correlation coefficient, r = -0.313, P=0.025).

The use of PTA drug-coated vs. uncoated balloons represents a new step in the investigations of vascular surgeons; J.A. Mustapha *et al*. [25] have reported a 442-patient randomized study with six-month results. They found that efficacy, defined as lack of ankle amputation, occlusion, and clinically driven target-lesion revascularization, was significantly better for the DCB group than the PTA group (difference= 13.1%; P= 0.0079) at 6 months. A meta-analysis and systematic review of a research group from Netherlands [26] about the DCB vs standard PTA has comparatively verified the efficacy and the clinical outcomes obtained by these two techniques. Ten studies representing 1593 patients who met the inclusion criteria were analyzed, but the results revealed no statistically significant differences.

One of the most similar studies to ours is that of T. Zeller *et al*. [27]; they have enrolled 358 patients with CLI who were randomized 2:1 to DCB angioplasty or PTA. The conclusion of their study was that the safety and efficacy did not differ significantly between subjects treated with DCB angioplasty and subjects treated with PTA; although the rate of major amputations was still slightly higher (almost 1.5x) with DCB angioplasty compared to PTA over 5 years, the difference was not significant. In their conclusion, the results showed that treatment with paclitaxel did not correlate with higher mortality or major amputation rates in patients with CLI.

4. Conclusions

The world of polymers abounds with materials with various applicability: from automotive to industrial insulation and from medical devices to drug delivery nanoparticles; all of these have been discovered and developed in recent decades. This research has compared two materials in terms of material structure (the physical and mechanical tests) and in terms of their application as balloons used in angioplasty.

Endovascular revascularization using POBA vs. DCB, revealed significant differences by using multivariate analysis. The overall 1-year wound healing, limb salvage, and amputation-free survival rate were superior for DCB in comparison to POBA in this study. According to our feasibility rates, the results indicate no significant differences between direct and indirect angioplasty. The attachment of Paclitaxel to polymer surfaces can be modified by several parameters such as substratum topography, roughness and macromolecular chain’s structure. Various investigation on its binding affinity to different surfaces lead to the development of drug-coating balloons with enhanced efficacy in angioplasty.

Future perspective

It is now justifiable to ask questions about the future of this research. The scientific progress in the field of vascular surgery and in novel modeling technique of DCB will lead to superior polymer materials capable of providing better values for the medical endpoints. An appropriate continuation of this study is to assay the connection between the angiosomes concept and the number of minor and major amputations. It is also very important to study DCB that have different drugs attached on their surface and to comparatively present the results from the point of view of the vascular surgeon. Finally, a collaboration between surgeons and chemists would lead to the creation of virtual models based on in silico studies to imagine new polymer materials capable of being used in the manufacture of tomorrow's DCB.

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