Atherectomy using a solid-state laser at 355 nm wavelength

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Peripheral arterial disease (PAD), caused by atherosclerotic processes, is allied with an increased risk of ischemic events, limb loss, and death. Recently, the use of a solid-state laser at 355 nm within a hybrid catheter was suggested for that purpose. In this work, short nanosecond pulses of a solid-state laser at 355 nm delivered through a hybrid catheter, composed of optical fibers and a blunt mechanical blade, are used to conduct a pre-clinical study and two clinical cases. The pre-clinical study consisted of an atherosclerotic calcified cadaveric leg and a porcine in vivo trial within the iliac artery, respectively. The clinical cases include chronic total occlusions with a calcified lesion. The occluded cadaveric leg is recanalized successfully and no evidence of thermal necrosis is indicated in the histopathology analysis of the porcine study. No arterial wall damage is demonstrated on the animals’ treated arteries and no significant impact on blood count and biochemistry analysis is noted in the animal trial. Successful recanalization of the occluded arteries followed by balloon angioplasty is obtained in both clinical cases. Our work constitutes a proof of concept for using a solid-state pulsed laser at 355 nm in atherectomy.

1. Introduction

Laser atherectomy for the treatment of peripheral arterial disease (PAD) has been utilized in the last two decades and extensive clinical experience has been gained including in-stent restenosis, the effects of balloon angioplasty and the treatment of diabetic patients [1–3]. Laser atherectomy holds particular promise for the successful management of long calcified chronic occlusions of arteries of the lower extre-
mities, where conventional balloon angioplasty and stenting has a high rate of reocclusion and restenosis. Given the low long-term durability of current endovascular solutions at the infringuinal arteries, adjunct tools such as atherectomy devices, together with drug-coated balloons, are promising tools for improving current clinical results [4]. The unique utilities of laser atherectomy, along with low dependability on the physician’s skills in the procedure’s success, position it in the front line of applicable solutions for revascularization of occluded arteries.

The current laser source for laser atherectomy is the excimer XeCl (xenon monochloride) laser, emitting radiation at a wavelength of 308 nm, and has a typical pulse duration of a few hundred nanoseconds, delivered through optical fibers interwoven in a catheter (Spectranetics Corp., US). The excimer’s radiation is strongly absorbed in tissue chromophores such as hemoglobin, protein and cholesterol, leading to a volumetric concentration of the energy at a shallow penetration depth (e.g., ~30 microns in hemoglobin at 308 nm wavelength [5]). As a consequence, tissue ablation takes place and imposes photo-thermal, photo-chemical and photo-mechanical mechanisms [6]. Several strides have been made in qualifying alternative laser sources for atherectomy, among them are the fundamental wavelength of Nd:YAG laser [7] and an argon ion laser [8]. However, none of these appealed for clinical use, mainly due to adverse trauma following the laser-tissue interaction.

Recently, a solid-state laser at a wavelength of 355 nm (third harmonic of Nd:YAG) was suggested to be applied in the treatment of thrombotic lesions, atherectomy and cardiac lead extraction [9-11]. Within the latter two, unique characteristics, such as selective ablation of the fibrotic lesion and eliminating the necessity of flushing the fluoroscopy contrast media prior to the laser operation, were demonstrated. These recent findings could not have been achieved without the enabled ability to deliver sufficient fluence of laser pulses at 355 nm through optical fibers to ablate a biological tissue. Such ability matured only in the last few years and paved the road to a vast range of utilities using this laser source that were previously inaccessible [12]. Laser sources at 355 nm wavelength typically possess high peak power due to their short pulse durations of less than 10 ns, which is about one order of magnitude shorter than the typical pulse duration employed by the excimer laser. Thus, the third harmonic of Nd:YAG may constitute a potential candidate to open arterial occlusions, and particularly for calcified lesions. Some of the motives for validating the innovative use of a compact, robust and affordable solid-state laser operating in the UV in atherectomy include enhanced accessibility of this treatment for clinics along with potential superiority over current solutions.

2. Materials and methods

2.1 General

The experimental work described here is of three parts: a cadaveric study in an amputated lower limb, an in vivo study in a pig, and two human cases. The cadaveric study and the pig study are framed as the pre-clinical work and examine preliminary aspects of efficacy and safety, while the clinical cases examine the feasibility in the treatment of typical heterogeneous lesions that include calcified stenosis. Additional experimental work that is related to this work and was used as a background to this study can be found in Refs. [10, 11]. Specifically, Ref. [11] investigates the functionality of the hybrid catheter without a laser (“mechanical only”), solely with a laser (“laser only”) and in a combined mode (“hybrid”). This work was done using the same laser system and using a catheter that is similar to the PAD catheter in reference to aspects of laser-tissue interaction.

2.2 Laser system and catheter

The experimental system included a third harmonic Nd:YAG laser (B-LaserTM Hybrid Atherectomy Laser System EXM-2001-0000, Eximo Medical Ltd, Israel) coupled to a single-use hybrid catheter (B-LaserTM Catheter, 4001-0000, Eximo Medical Ltd, Israel) and operated by a laptop, as described in Figure 1. The hybrid operation is realized in such a way that the laser component applies just enough highly precise energy to allow penetration of the mechanical tip. The mechanical tip then gently completes the separation process until the catheter can continue its progress and detach the blocking deposit or tissue.

The laser emits 355 nm pulses and the duration of each pulse is 6.7 ns full-width-half-maximum...
(FWHM) at a repetition rate of 30 Hz, with beam diameter of \(~5.5\) mm, and coupled to the catheter using dedicated optics. The hybrid catheter outer diameter is 1.5 mm, 1.5 m length, and able to deliver through a guidewire of up to 0.014" diameter. It contains 65 multimode optical fibers, each of which has a core diameter of 100 μm, and a blunt mechanical blade (Figure 2). Each optical fiber delivers an average fluence of 60 mJ/mm² to 70 mJ/mm² per pulse, which is slightly above than the typical ablation threshold for calcified tissues (\(~40\) mJ/mm² using 7.5 ns pulses at 355 nm [13]). Therefore, the catheter is capable of delivering overall energy of \(~35.7\) mJ.

In the event that an intravascular lesion obstructs catheter forward movement through the blood vessel, the laser component can ablate a few tens of microns from the tissue and make a thin, shallow slit to enable the continued penetration of the blunt mechanical blade. The blade is therefore designed to be too blunt to initiate dissection but with enough of an edge to enable deeper catheter penetration into the tissue. This is achieved as the borders of the tissue being ablated possess a transient zone and are mechanically weakened due to the trauma, which facilitates dissection by the blunt blade. In each of the pre-clinical and clinical cases, a single catheter per procedure was used.

### 2.3 Cadaveric study

A freshly frozen lower limb that was known to have PAD was used for the cadaveric study. The cadaver was imported for the study and discarded afterwards per local country regulations (Ministry of Health, Israel) and according to the supplier’s instructions. The study took place at the BioTech Farm at Na’an, Israel. Vascular access was obtained by direct exposure of the superficial femoral artery (SFA) and insertion of a 6 Fr introducer (Pinnacle RSS602, Terumo, US). Assessment of the level of stenosis and calcification was demonstrated using X-ray fluoroscopy and by intravascular ultrasound (IVUS, Atlantis SR Pro2™ Catheter, Boston Scientific, US) within the SFA. Angiography demonstrated a 20 cm long, highly calcified occlusion of the SFA (Figures 3 and 4). The lesion was crossed in a combined antegrade and retrograde approach through the popliteal artery. The occlusion was crossed with an angled guidewire (GW) at 0.035" diameter (GLIDEWIRE GR3506, Terumo, US). The wire was exchanged for a stiff 0.014" GW (ChoICE straight tip super support 12120-01, Boston Scientific, US), the hybrid catheter was inserted to the artery and advanced until it could not further progress in the blockage, and a fluence of 65 mJ/mm² was set. After laser atherectomy was applied, angiography and IVUS were performed to assess the effect of the laser catheter on the lesion and arterial wall.
2.4 Pig in vivo study

The study took place at the BioTech Farm at Na’an, Israel, and was approved by the national animal care and use committee, in compliance with the state animal welfare regulations. A female domestic pig weighing 66 kg was used for the in vivo safety study. The animal was tranquilized and sedated with IM ketamine HCl 10 mg/kg, xylazine 1–2 mg/kg, and atropine. Thereafter, 5–10 mg of diazepam were given via ear vein along with a 5% isoflurane mask. Following this, the animal was intubated and anesthetized with 1–3% isoflurane via positive ventilation (IPPV) utilizing 100% oxygen at 2 L/min.

A 6 Fr guiding catheter (Destination RSC05, Terumo, US) was introduced to the carotid artery and a baseline blood sample was given to maintain ACT greater than 250 seconds. The guiding catheter was navigated under fluoroscopy, over the wire to the external iliac artery. A 0.014” GW (ChoICE straight tip super support 12120-01, Boston Scientific, US) was inserted through the guiding catheter and further advanced under fluoroscopy to the distal SFA. The laser catheter was inserted over the wire on a segment length of 10 cm, from distal to proximal within the left and right iliac arteries with reference diameter of about twice the diameter of the catheter (Figure 5). The procedure was repeated twice, where in each of which the catheter’s advancement was first mechanically only (laser was off) and later a 65 mJ/mm² fluence was delivered through the catheter for 92 seconds. A specimen of the treated artery was sent for histopathological evaluation by a certified pathologist.

2.5 Clinical cases

Both clinical cases were conducted in Katowice, Poland, and were part of a broader clinical study that includes more than 20 patients, approved by the local authorities: Ministry of Health, Poland, and Ethical Committee, Katowice, permits no. UR.D.WM. DNB.93.2015 and KNW/0022/KB1/81/I/15. In addition, a certification for conducting an identical clinical trial was approved by the local authorities in Israel, Ministry of Health, Jerusalem, permit/number 20151492, which has not been applied in this specific work.

In both clinical cases, anticoagulants were given prior to and during the procedure, heparinized saline (5000 IU/L) was used to flush the distal tip of the catheter before and during lasing, and no embolic protection device was used. The laser fluence was set to 60 mJ/mm² and both procedures were done antegrade.
The first clinical case was a 69 year-old female with intermittent claudication who underwent percutaneous transluminal angioplasty (PTA) and stent implantation in her left iliac artery a year earlier. The ankle-brachial index (ABI) of the right leg at baseline was 0.4 with a stage 3 Rutherford classification. On diagnostic angiography, a 6 cm long, severely calcified chronic total occlusion (CTO) of the distal SFA was found. A 6 Fr introducer sheath (Avanti 504-606X, Cordis, US) was used. A 190 cm length 0.014” GW (High Torque Winn 200, Abbot, US) was used, and was later replaced with a 300 cm length 0.014” GW (Hi Torque Command, Abbot, US) using a low profile non-inflated 2.5 Fr balloon (Sleek 426-1201X, Cordis, US), which was inserted as a working channel. The hybrid catheter was later inserted over the 300 cm GW and advanced until it could not further progress in the blockage.

The second clinical case was a 66 year-old male with intermittent claudication and a history of ischemic heart disease, prior myocardial infarction and coronary bypass a decade earlier. The ABI at baseline was 0.4 with a stage 3 Rutherford classification. The lesion was located in the popliteal and tibial arteries of the right leg, with 5 cm long CTO with moderate-to-severe calcification. A 6 Fr introducer sheath (Avanti 504-606X, Cordis, US) was used, along with a 0.014”, 300 cm length GW (High Torque Winn 200, Abbot, US). The hybrid catheter was later inserted over the 300 cm guidewire and advanced until it could not further progress in the blockage.

3. Results

3.1 Cadaveric study

In the cadaveric study, after successful crossing of the occlusion with a GW, the laser was activated and the catheter’s advancement was enabled at an advancement rate of approximately 1 mm/s. After three minutes and thirty seconds of work the catheter was removed and fluoroscopy imaging was applied along with the injection of contrast media, which demonstrated that the occluded SFA was recanalized successfully, as described in Figure 6. Prior to the laser operation, signs of perforation of the SFA were noted and were attributed to manipulations of the guidewire. The high confidence in not relating this perforation to the device is due to the chronological sequence of the procedure and its protocol.

3.2 Pig in vivo study

In the pig in vivo study, the catheter was advanced twice through the defined path within the iliac artery, without laser and later with the laser operation for 90 seconds, and no dissections or perforations were indicated by fluoroscopy in both advancements. Vital signs and cardiac parameters of the animal during the procedure were shown to be normal at all times, as well as 20 minutes afterward, and gross pathology of the iliac showed no arterial injury (Figure 7). The histopathological analyses indicate partial sloughing of the endothelium in all samples with minimal subendothelial pyknosis (Figure 8). There was no evidence of thermal necrosis and no significant changes in blood counts before and after the procedure (Table 1).
3.3 Clinical cases

In the first clinical case presented here, the GW crossed the CTO and the catheter was advanced over it within the true lumen until it encountered the occlusion and could not advance further. The laser was operated for 20 s and the catheter succeeded to advance at an initial advancement rate of about 0.6 mm/s. Following a reduction in the advancement rate, the catheter was inserted inside a 6 Fr guiding catheter (Vista Brite tip, Cordis, US) for additional support and the fluence was increased to 70 mJ/mm². After an additional 80 seconds of lasing, the catheter succeeded to cross the lesion in a single pass. The acute results post-catheter residual stenosis in the target lesion were estimated as \( \approx 67\% \) (33% reduction). The adjunctive therapy included a 4 × 60 mm balloon (SAVVY 435-406, Cordis, US) and a 6 × 100 mm stent (SMART C06100MV, Cordis, US). No signs of dissection, perforation or embolization were observed, neither following the laser application nor after the balloon angioplasty (Figure 9), and the post-adjunctive therapy residual stenosis in the target lesion was estimated as 0%.

In the second clinical case presented here, the GW also crossed the CTO and the catheter was advanced over it within the true lumen until it encountered the occlusion and could not advance further. The laser was operated and the catheter succeeded to advance at a rate of 0.81 mm/s. The total lasing duration was 62 s and the lesion was crossed by a single pass (Figure 10). The acute results post-catheter residual stenosis in the target lesion were estimated as \( \approx 68\% \) (32% reduction). The adjunctive therapy included 1.5 × 100 mm and 3 × 40 mm inflated bal-

### Table 1

<table>
<thead>
<tr>
<th>Station</th>
<th>Before procedure</th>
<th>20 min After procedure</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>14.32</td>
<td>13.79</td>
<td>10³μL</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>5.71</td>
<td>5.49</td>
<td>10³μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.3</td>
<td>9.9</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.0</td>
<td>32.9</td>
<td>%</td>
</tr>
<tr>
<td>MCV</td>
<td>59.6</td>
<td>59.9</td>
<td>fL</td>
</tr>
<tr>
<td>MCH</td>
<td>18.1</td>
<td>18.1</td>
<td>pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>30.4</td>
<td>30.1</td>
<td>g/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>397</td>
<td>424</td>
<td>10³μL</td>
</tr>
</tbody>
</table>

The laser was operated and the catheter succeeded to advance at a rate of 0.81 mm/s. The total lasing duration was 62 s and the lesion was crossed by a single pass (Figure 10). The acute results post-catheter residual stenosis in the target lesion were estimated as \( \approx 68\% \) (32% reduction). The adjunctive therapy included 1.5 × 100 mm and 3 × 40 mm inflated bal-

Figure 8 Histopathology of the porcine iliac artery following the procedure, all at magnification of ×20, presenting (a) Absence of endothelium on the intimal surface and minimal pyknosis of sub-endothelial cells (marked by blue arrows). Most of the smooth muscle of the media is normal and the internal elastic lamina is continuous. (b) Absence of endothelium with minimal protein deposition and minimal pyknosis of sub-endothelial cells (marked by blue arrows), and the internal elastic lamina is intact.

Figure 9 (a) Fluoroscopy imaging of the SFA of the 6 cm CTO ATK prior to the procedure, (b) recanalization following only laser atherectomy by the hybrid catheter delivering nanosecond pulses at 355 nm, and (c) after balloon angioplasty.
loons (Sleek 426-1510X, and 426-3004X, Cordis, US, respectively). No signs of dissection, perforation or embolization were observed, neither following the laser application nor after the balloon angioplasty, and the post-adjunctive therapy residual stenosis in the target lesion was estimated as 0%. In both clinical cases, no evidence of adverse events or complications were found in the 30 days follow-up visit or in the six months follow-up visit.

4. Discussion

These clinical cases of laser atherectomy using a pulsed solid-state laser at 355 nm are, to our knowledge, the first to be carried out. We described here two calcified CTO lesions both BTK and ATK, which constitute representative scenarios in which the device is expected to work. The laser source that we used (the 3rd harmonic of Nd:YAG) has been known for decades; however, its usability in laser-assisted procedures was considered to be limited due to the inability to deliver sufficient fluence through optical fibers to ablate a tissue. A recent breakthrough in fiber delivery limits [12] provided access to laser-atherectomy in the UV regime, based on a laser source other than the XeCl laser.

The combination of the excimer’s pulse duration, which enables temperature confinement and stress confinement, and the operation in the UV regime, assists in minimizing the collateral damage to the ablation surrounding. However, the relatively long pulse duration of the excimer laser (a few hundred nanoseconds) restricts the ability of debulking calcified lesions due to a moderate peak power [14]. The elongation of the excimer’s pulse duration is necessary to avoid dielectric damage of the optical fibers [15]. Thus, using a laser source with a much shorter pulse duration within the UV spectrum that is capable of delivering sufficient fluence through the optical fibers for ablation may constitute a viable solution for treating highly calcified lesions. As evident, the clinical cases included severe calcifications, which were crossed successfully using the over-the-wire hybrid catheter and within reasonable advancement rates.

As in any pre-clinical studies, the examined scenario is different in some aspects from the clinical implications. Therefore, we chose to divide the pre-clinical studies to test the treatment in calcified lesions, and to test the laser operation in the presence of blood in the ablation surrounding, which may lead to the creation of an embolus or thrombus and damage the endothelial wall. These concerns were relieved in the cadaveric and the pig in vivo studies. Furthermore, ablating directly in blood as was applied in the pig study is an extreme and aggressive working point in comparison to ablating a lesion in blood surrounding. Therefore, the absence of dissections and perforations, and no significant change in blood count in the pigs’ study, implies the safeness of the suggested device.

In the histopathology study, regeneration of the endothelium is expected to occur rapidly and the minimal pyknosis of the few subendothelial smooth muscle cells should heal with minimal degree of fibrosis, and possibly minimal non-stenotic neo-intima formation, which does not raise any concerns with vessel patency. These findings have minor significance and are expected with the passage of a catheter in an artery.

5. Conclusion

In conclusion, the pre-clinical and clinical results presented in this work confirm the feasibility of using a short nanosecond-pulsed laser at 355 nm in atherectomy. Despite the availability of various solutions for the treatment of PAD, using a versatile hybrid tool that is capable of dealing with complex heterogeneous lesions invigorates the use of laser atherectomy in using a nanosecond-pulsed laser at 355 nm. The fact that a solid-state laser is cost-effective, compact and does not contain toxic gases, in comparison to gas-based lasers, may mark this technology as a significant milestone in the development of an innovative solution in atherectomy.

References