Ultrasound-guided Intralesional Diode Laser Treatment of Congenital Extratruncular Venous Malformations: Mid-term Results

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WHAT THIS PAPER ADDS
At our center, laser ablation as a minimally invasive method has shown, over the short term, promise in the treatment of congenital extratruncular venous malformations. In this study, the results show that endovenous laser ablation is a minimally invasive treatment with the advantages of safety, effectiveness, and simplicity in ameliorating symptoms associated with venous malformations in appropriately selected patients.

Objective/Background: Over the short term, endovenous laser ablation (EVLA) has been found to be safe and effective for endovenous ablation in extratruncular venous malformations (EVMs). We report our experiences in percutaneous ultrasound (US)-guided treatment of congenital EVMs with respect to effectiveness and safety over the mid-term.

Methods: This was a retrospective analysis of a collected database of consecutive US-guided intralesional diode laser treatments of congenital EVMs (2007–2013). A consecutive series of 164 patients (86 women/girls [53%] and 78 men/boys [46%], aged 1.5–68.0 years [mean age 20.78 years]) were treated using EVLA for congenital EVMs at our institution. All of the patients were symptomatic. The primary outcomes for assessing safety were mortality and morbidity, including laser-related adverse events, thrombotic events, and important nerve or vessel injuries, and so on. Effectiveness was assessed according to reduction of the mass, the absence of pain, and technical success.

Results: One hundred and ninety procedures were undertaken in 164 patients, achieving a 100% immediate technical success rate. Most complications were minor and improved quickly, except in one patient, who suffered a peroneal nerve injury. Spot skin burn injuries occurred in one procedure (0.53%). Paresthesia in the treated area was noted after 15 procedures (7.89%). For complaints related to swelling, cosmetic outcomes, and pain, the clinical success rates were 65.71%, 68.97% and 97.74%, respectively. After a mean follow-up of 23.91 months, no patient suffering from pain, hemorrhage, or limited range of motion had returned with recurrent symptoms after initial successful treatment (resolved). Recurrence rates in patients with heavy sensation, swelling, and deformity were 6.89% (two of 29), 7.41% (two of 27), and 11.11% (one of nine), respectively. One hundred and twelve (59.00%) treated lesion areas were classified as “excellent”, 59 lesions (31.00%) were “good”, and 19 lesions (10.00%) were “fair” using duplex US imaging at the final follow-up visit.

Conclusions: EVLA is a minimally invasive treatment with the advantages of safety, effectiveness, and simplicity in ameliorating symptoms associated with EVMs in appropriately selected patients.

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Keywords: Congenital venous malformation, Laser, Ultrasound

INTRODUCTION
Venous malformations (VMs) are congenital, comprise two-thirds of vascular malformations, and are formed from venules and large veins. Based on the Hamburg Classification System, 1 congenital VMs are appropriately classified into extratruncular VM (EVM) or truncular VM using criteria that take into account the underlying anatomical, histological, pathophysiological and hemodynamic status of the defects, which are arise at different embryonic stages. The EVM...
subtype is a histologically benign lesion that typically grows in size with the patient; it may undergo accelerated growth during adolescence, pregnancy, surgery, or trauma. The truncular subtype preserves the embryonic characteristics of the mesenchymal cells, along with the potential to grow and proliferate, resulting in a high risk of recurrence. Their specific biological characteristics make it the most difficult lesions to treat, posing a major clinical challenge.

The clinical manifestations of EVMs include venous stasis, ischemia, skeletal anomalies, coagulopathy, disseminated intravascular coagulation, and so on. Surgical resection remains the only solution for “cure” of EVMs; however, generally, it requires surgical excess with high morbidity (e.g., excessive blood loss, adjacent nerve damage, movement limitations, scars). Incomplete resection of the lesion will result in higher risks of recurrence. Repeated foam sclerotherapy for the treatment of EVMs is not ideal. Because most vascular malformations have complicated venous networks with irregular lumens, it is difficult to control the dosage of sclerosing reagents owing to their progressive dilution and irregular distribution in the vessels. Thrombotic occlusion with mild endothelial injury caused by irritants has been associated with recanalization rates ranging from 1% to 15. Even worse, the irritants may enter into the systemic circulation during sclerotherapy and induce cardiovascular events.

As a minimally invasive method, laser ablation has shown great success in the treatment of saphenous vein insufficiency and tributary varices. The fibrotic obliteration of the lumen caused by laser ablation has achieved an overall long-term closure rate of 94–97%. Histological analysis has shown that the main damage occurs along the path of the laser’s contact with the wall, implying that the primary mechanism of action of endovenous laser ablation (EVLA) is thermal injury caused by direct contact and by the heated bubbles of steam created. It has also shown promise, over the short-term, in the treatment of congenital EVMs.

In this study, a consecutive series of 164 patients (86 women/girls [53%] and 78 men/boys [46%]) being treated with EVLA for congenital EVMs at our institution from May 2007 to February 2013 were analyzed retrospectively. This article recounts our experiences with EVLA in the treatment of EVMs, and evaluates its efficacy and safety over the mid-term.

**MATERIALS AND METHODS**

**Patient profiles and treatment procedures**

We reviewed the records of all of patients who received laser ablation treatment. All of the patients signed informed consent forms, and the protocols of this study were approved by the ethics committee of the 9th People’s Hospital. The clinical data of the patients are listed in Table 1, and a database was set up using a spreadsheet. Data included the extent of the lesion, different anatomical sites, the age of the patient, and the extent of clearance of the lesion as the treatment’s end point. The main criterion for study inclusion was a diagnosis of EVM according to The Hamburg Classification System.

Inclusion criteria were as follows:

- lesions were visible on ultrasound
- lesions (size, anatomical location, or both) ranged widely, were dispersing or localized, or the patient was unwilling to undergo surgical treatment
- low-flow lesions, resulting in no change after conservative management
- declining quality of life for patients with swelling, pain and other symptoms.

Exclusion criteria included contraindications, such as fibrinogen levels <1.0 (normal range 2–4 g/L), or intolerance of anesthesia, and deep lesions not visible on ultrasound (US).

**Pre-procedure patient care and anesthesia**

For treatment planning, all of the patients had magnetic resonance imaging (MRI) of the affected areas, and only patients with US-visible lesions were selected for laser ablation. All of the patients were treated under general, epidural, lumbar, or local anesthesia.

**Laser technique**

Only the portions of the lesions visible on US were treated. For small, localized lesions, we attempted to treat the entire lesion in one session. For large and diffused lesions, only parts of the lesions, chosen by patient direction and visible protrusion of the swelling, were treated per session.
The procedure has been previously described, in detail, by Lu et al. In brief, percutaneous access was established by US guidance with a 16- or 18-gauge intravenous catheter, or a 3-F sheath. It was confirmed that placement of the catheter was accurate by the clear back-flow of blood after puncture. A coaxial 600-μm laser fiber (810 nm wavelength; DIOMED, Cambridge, UK) was inserted into the lesions, avoiding superficial vessels. An 810-nm diode laser was used to generate sufficient heat to cause thermal damage to the venous endothelium. The sheath, or catheter, was withdrawn to expose 2–3 cm of the distal laser fiber. The laser energy ranged from 10 to 13 W (1-second pulses separated by 1-second intervals), depending on the size of the lesions. Meanwhile, the pulse duration of each second was triggered by a foot pedal. In this series, US guidance was used not only to confirm the position of the laser fiber, but also to monitor the formation and distribution of microbubbles in real time. The aim of selecting the appropriate level of energy was to treat the variously sized venous channels effectively and to lower the risk of nontarget thrombosis.

The fiber was slowly withdrawn toward the border of lesion, with the microbubbles filling the channels. If the microbubbles were not sufficiently in contact with the vein walls, the number of pulses was increased to generate more energy. If bubbles were seen to move towards known outflow veins, treatment was stopped in that channel to avoid the risk of systemic embolization. If the laser fiber was too superficial to the skin, it was an indicator of early skin burns. During the procedure, manual compression was applied to the treated area, which improved the vessel wall apposition around the laser fiber tip; thus, better laser fiber–endothelial contact, and even energy emission by the laser, were achieved to completely shrink and occlude the venous trunk.

Multiple punctures were then applied in the same way. With US guidance, puncture points were placed around the circumference of the lesions (Fig. 1; Supplementary Video).

In addition, when the laser fiber was so superficial that the red aiming beam was visible through the skin, the skin was directly injected with a normal cooling solution to reduce early skin burn. With US guidance, the catheter position within the lesion with no back-flow of blood signaled the end point of treatment. The delivered energy was calculated as a product of the power (in watts), pulse duration (in seconds), and the total number of pulses. This value was recorded in the surgical notes. On the completion of treatment, external pressure was applied to the treated areas with elastic bandages for 5 days. For EVMs on limb extremities, a class III (30–40 mmHg), full-thigh, graduated support stocking or panty hose were worn for at least 1 month at all times (except during sleep or showering) over the course of follow-up.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2014.02.014.

The following is the supplementary video related to this article:Video S1

**Post-procedure patient care and monitoring**

Ambulatory activities were encouraged after each operation. A local tape and gauze pressure dressing was applied to the treated area for at least 2 days. The patients were discharged after 4–6 days of observation, with instructions to take acetaminophen or ibuprofen if needed, and to call or return to the hospital if they had severe local pain, numbness, chest pain, dyspnea, or skin changes. All of the patients were followed up on an outpatient basis for physical examinations and postoperative complaints, and duplex ultrasonography or MRI was performed at 2 weeks, 3, 6, and 12 months, and then annually.

**Study endpoints and definitions**

Technical success was defined as a catheter or needle entering the lesion, under US guidance, with visible back-flow of blood from the lesion, and, subsequently, the
laser fiber being inserted through the catheter or needle to confirm that the laser fiber was located within the venous lumen. In this situation, the power can directly injure endothelial cells. After treatment, the treated area was filled with microbubbles, and no blood was drained out after multiple punctures around the lesion by US guidance. Clinical success was defined as resolution or marked improvement of the presenting symptoms according to the patient. The subjective improvement of symptoms was further assessed simultaneously using objective evidence of improved clinical signs, including a reduction in the size of the lesion, decreased general swelling, or improved range of motion of the joint. Minor complications were defined as complications requiring no therapy, or minimal therapy with no consequences. Major complications were defined as complications requiring therapy, an increased level of care, or permanent adverse sequelae. Imaging studies were analyzed by one radiologist and one surgeon. Duplex US was used to assess blood flow within a lesion: complete cessation of flow at the treated area was defined as “excellent”; almost-complete cessation, but with some suspicion along draining veins was defined as “good”. A drastic reduction, but with substantial evidence, of residual venous flow of the treated area was defined as “fair”. Periodic follow-up evaluations of the treatment results were made every 6 months by the multidisciplinary team.

RESULTS

Patient characteristics

One hundred and sixty-four patients (86 women/girls [53%] and 78 men/boys [46%]) aged 1.5—68.0 years (mean age 20.78 years) who underwent EVLA over a 71-month period were retrospectively evaluated in this study.

Therapeutic effects

Percutaneous access and intralesional placement of laser fibers were achieved in all of the patients. All patients tolerated the procedure well and recovered uneventfully (Supplementary Fig. 1). They were encouraged to return to ambulatory activities, normal daily activities, and work at 1, 3, and 10—14 days, respectively, after the procedure. Depending on the severity of the lesions, the entire procedure lasted 30—100 minutes (mean 45 minutes). EVLA

Table 2. Therapeutic effects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Limited</th>
<th>Infiltrating</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean diameter (cm)</td>
<td>4.9</td>
<td>13.4</td>
<td>11.81</td>
</tr>
<tr>
<td>Number of procedures</td>
<td>1 (36)</td>
<td>1 (106)</td>
<td>190</td>
</tr>
<tr>
<td>Number of passes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16.6</td>
<td>24.3</td>
<td>22.83</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>23.36</td>
<td>24.04</td>
<td>23.91</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>21</td>
<td>112</td>
<td>133</td>
</tr>
<tr>
<td>Unresolved</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Resolved</td>
<td>17</td>
<td>67</td>
<td>84</td>
</tr>
<tr>
<td>Markedly improved</td>
<td>3</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Heavy sensation</td>
<td>9</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>Resolved</td>
<td>2</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Markedly improved</td>
<td>3</td>
<td>13</td>
<td>16</td>
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<tr>
<td>Limited range of motion</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Resolved</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Markedly improved</td>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
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<td>6</td>
</tr>
<tr>
<td>Resolved</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Markedly improved</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Swelling</td>
<td>17</td>
<td>88</td>
<td>105</td>
</tr>
<tr>
<td>Resolved</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Markedly improved</td>
<td>1</td>
<td>41</td>
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<tr>
<td>Deformity&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Resolved</td>
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<tr>
<td>Markedly improved</td>
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<td>11</td>
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<td>Ultrasound assessment</td>
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<td>Excellent</td>
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<td>112</td>
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<tr>
<td>Good</td>
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<td>46</td>
<td>59</td>
</tr>
<tr>
<td>Fair</td>
<td>4</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup> Passing of one fiber tip (or the number of punctures) into the lesion.
<sup>b</sup> Morphological changes of local sessions.

Figure 2. Magnetic resonance imaging demonstrates the treated lesion segments became fibrose, and were difficult to identify. (A) Before the procedure; (B) 1 year after the procedure.
resulted in treated vessel occlusion by 2 weeks of follow-up in all cases, defined as no flow detectable on duplex US investigation. The postoperative clinical classes of the patients are shown in Table 2. The symptoms of all of the patients were significantly improved between 2 weeks and 24 months, except for one patient who had a large number of phleboliths and continued to suffer pain within 2 months of follow-up. One patient with finger lesions selected an open procedure for slight pain alleviation after a second laser ablation. At the 6–9-month follow-up visit, treated vessel occlusion was substantial (>50% reduction in diameter); at 1 year and beyond, the lesions existed as minimal residual fibrous cords with no detectable flow (Fig. 2). After a mean follow-up of 23.91 months, no patient suffering pain, hemorrhage, or limited range of motion had returned with recurrent symptoms after initial successful treatment (resolved). After the same follow-up period, the recurrence rates of patients with sensation, swelling, and deformity problems were 6.89% (two of 29), 7.41% (two of 27) and 11.11% (one of nine), respectively.

For complaints related to swelling, cosmetic outcomes (deformity), and pain, the clinical success rates were 65.71% (65 of 105), 68.97% (20 of 29), and 97.74% (130 of 133), respectively (Table 2). All the patients had a US scan at the final visit. Upon duplex US imaging, 112 (59%; 19 limited EVMs and 93 infiltrating EVMs) treated lesions were classified as “excellent”, 59 (31%; 13 limited EVMs, 46 infiltrating EVMs) were “good”, and 19 (10%; four limited EVMs, 15 infiltrating EVMs) were “fair”.

**Complications**

Pain, ecchymosis, induration, and phlebitis were the common adverse events associated with EVLA, but they were self-limiting. In the early period after EVLA, ecchymosis—or discoloration beneath the skin along the course of the treated veins—was experienced in 22 procedures (11.58%), but it usually abated within 2–4 weeks. The size of the original mass decreased significantly, leaving a hard texture. Two patients who had numerous phleboliths were still experiencing pain within 6 months of follow-up, so we suggested further surgical therapy. One young patient suffered a right common peroneal nerve injury due to heat damage, and showed foot drop and sensory loss in the right lower limb for 6 months.

Only 19 patients required treatment with over-the-counter analgesics (ibuprofen) for 1–2 weeks. Five percent of the procedures resulted in indurations, but no case required further treatment. Spot skin burn injuries occurred in one patient (0.53%) and resolved in 2–4 weeks. No other potential minor or major complications, such as allergic reactions or hematomas developed, and all of the abovementioned minor complications resolved without sequelae. Ecchymosis along the course of the treated segments usually abated in 2 weeks in affected patients. Thrombus-like indurations over the treated lesions with slight or moderate pain resolved in 3–6 weeks. Paresthesia in the treated area was noted in 15 procedures (7.89%), and abated in 1–2 months. There were no other minor or major complications such as thrombosis, pulmonary embolism, or systematic allergic reactions.

**DISCUSSION**

Previous studies have suggested that laser treatment of VM is, in fact, the method of choice in some settings owing to its high success rate and very low incidence of complications when employed properly. However, the sample sizes have been relatively small, and studies have only been conducted over the short term. In this study, more than 160 patients were recruited, and the effectiveness of laser ablation in the treatment of congenital EVMs was assessed. Our success rate in lesions was 97.74% for pain relief and 65.71% for swelling. These results were comparable with the 100% clinical success obtained in Sidhu et al.’s series on laser treatment. The response to laser ablation in patients with EVMs depends on the size of the incompetent veins and muscle involvement. Our outcomes showed excellent results in limited malformations of small and moderate size, whereas the progression and growth of malformations of greater size, especially malformations with muscle involvement, could only be controlled as their eradication was difficult to achieve.

Owing to the characters of embryonic differentiation in VM endothelial cells, inappropriate stimulation may accelerate the development of the disease. Therefore, optimal treatment should destroy endothelial cells, not injure them. To date, two theories have been proposed to be directly involved in the action of laser ablation, one of which is bubble steam theory. Intravenous temperatures during EVLA have confirmed that the peak temperatures at the fiber tip exceed 1,200 °C, and continuous temperatures of at least 300 °C are maintained in the firing zone during the whole process. The phenomenon of turbulent bubbles formed at the laser tip during the application of energy was first described by Proebstle et al., who noted that destructive steam bubbles cause thermal injury to the venous endothelium when the steam contacts the vein wall, resulting in thrombotic occlusion of laser-treated vessels. The second theory involves the idea of direct contact. Post-EVLA pathological specimens have shown severe transmural tissue damage, troughing deformities, and carbonization along the path of laser and wall contact, implying the primary mechanism of action of EVLA is thermal injury mediated by direct contact between the laser and the vessel wall. As it is known that vein walls in EVMs are abnormal owing to the effect of embryonic differentiation, quickly burning through the laser can also damage endothelial cells, although some theoretical data are lacking. Based on the two theories, in this study bubbles were applied as an indicator to adjust the laser power. If the bubbles filled the lesions, we considered that the energy was enough and that the laser fiber should be retracted. During the procedure we applied mild compression, which may have promoted a thorough destruction of endothelial
cells. We did not know how much compression was needed, and did not develop a standard compression because the lesions were irregular and control of the compression was difficult. If the lesion was not deep, we could feel the production of steam bubbles when the laser fiber contacted the lesion directly; as such, we think enough compression was applied in this situation. The choice of wavelength, energy level, and pulse duration of the laser exposure were all related to the type and size of the target vessels and tissue conduction. Previous researchers have used only 3—10 W. We suggest that it may be necessary to use 10—13 W. With the experience gained in this study, we realized that higher laser energy levels could destroy the malformed veins more thoroughly, which might have resulted in a lower recurrence rate.

It should be noted here that the effect of each EVLA is not always ideal, and there are poorer results in a number of symptoms, particularly with regard to deformity (31.34%, 9 of 29) and swelling (34.39%, 36 of 105). In this situation, other options were recommended, such as surgery, absolute alcohol, for example. Among the patients in whom treatment was deemed a technical success, more than half (52.78%, 19 of 36; Table 2) of treated vessels in the limited malformations were shown by US to have disappeared. Very pleasing results were obtained with the localized type; in most of these lesions, palliation was achieved after only one procedure. Patients with diffuse lesions required repeat sessions in untreated areas with relief of symptoms. For those lesions containing a large number of phleboliths, the efficacy of laser treatment was not satisfactory because laser treatment alone could not clear the phleboliths. Thus, a combination of lasers and surgery may be a better option. For those lesions with muscle involvement, as long as the symptoms improved we did not recommend further treatment because excessive EVLA leads to muscle fibrosis, which may cause discomfort when walking. The best results were obtained in patients with pain, hemorrhage, and a limited range of motion. Amongst patients experiencing heavy sensation, swelling, and deformity, we found, during follow-up, five to have recurrent symptoms. A possible explanation for this is that remnants of endothelial cells still have the capacity to regenerate. In this study, the follow-up time was not long; it is likely that more recurrent cases will be found as a result of longer follow-up. The laser treatment was considered as a palliative, minimally invasive treatment and not as an option for cure; therefore, if the patient did not feel better after this treatment, other treatments (surgery or sclerotherapy) were recommended.

With the help of US, the fiber tip can reach the targeted parts of the lesions quickly and accurately, making the procedure safer and more efficient. In this series, US guidance was used not only for confirming the laser position, but also to monitor the formation and distribution of microbubbles in real time in order to choose the appropriate level of power with which to treat individually the selected venous channels (which varied in size), and to decrease the risk of nontarget thrombosis. However, US is not the gold standard for post-EVLA assessment, but it is an easily accessible, inexpensive tool that allows the assessment of blood flow velocity. If US examination of the lesion demonstrated reduced blood flow, the treatment was considered to be effective. It is worth mentioning that even though a nerve trunk can be discerned by US, serious nerve injury may occur owing to the heat conduction effect. In this series, one patient suffered a right common peroneal nerve injury due to thermal damage along the pulsed laser incisions, and showed foot drop and sensory loss. In our experience, when lesions were involved in important nerve tissues, directing the laser tip into the nerve trunk should be avoided; our previous cases (proximity to brachial plexus) showed that directing the laser a short distance away from the nerve trunk can also obtain a good result. Otherwise, sclerosant (lauromacrogol) was recommended as a good option.

CONCLUSIONS

In this series of patients treated with US-guided laser ablation for EVMs, there was improvement or resolution of the presenting symptoms in most patients, and a decrease in the size of all of the lesions, with quite low morbidity. Although this approach only allows moderation of the progression and reduction of the size of lesions with lower flow rates, our experience suggests that EVLA is an effective treatment when patients are selected appropriately. Future prospective studies, including more standardized clinical, photographic, and imaging follow-up data, will be useful in further defining the role of this technique in the treatment of EVMs.

FUNDING

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CONFLICT OF INTEREST

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2014.02.014.

REFERENCES


