OHTAC Recommendation

Endovascular Radiofrequency Ablation of Varicose Veins

Presented to the Ontario Health Technology Advisory Committee in August 2010, January 2011

January 2011

OHTAC Ontario Health Technology Advisory Committee

Background

The Ontario Health Technology Advisory Committee (OHTAC) met on August 27th, 2010 to review the effectiveness and safety of endovascular radiofrequency ablation (RFA) for the treatment of primary varicose veins based on an evidence-based review by the Medical Advisory Secretariat (MAS). A second presentation was made to OHTAC on January 28th 2011 after receiving advice from an OHTAC convened expert advisory panel.

Clinical Indication

Varicose veins (VV) are tortuous, twisted, or elongated veins caused by poorly functioning valves and decreased elasticity in the vein wall resulting in reflux (reversed venous blood flow). The symptoms of venous reflux can include: aching leg pain, leg swelling, throbbing, night cramps, restless legs, leg fatigue and heaviness or itching and burning. Untreated venous reflux has been associated with various complications such as varices rupture with hemorrhage and superficial thrombophlebitis.

Pronounced venous reflux left untreated can lead to chronic venous insufficiency (CVI) a pathological condition of the skin and subcutaneous skin resulting from prolonged stasis of venous blood flow. The clinical signs of CVI include a spectrum of conditions: edema, hyperpigmentation, eczema, lipodermatosclerosis and ulcers. Chronic venous disease is associated with a reduced quality of life (QOL) particularly in relation to pain, physical function and mobility. In severe cases such as VV with ulcers, QOL has been rated to be as poor or worse as other chronic diseases such as back pain and arthritis.

VV of lower limbs has a familial predisposition and is a very common disease affecting adults – estimated to be the 7th most common reason for referral to a physician in the US. The prevalence of VV worldwide ranges from 5% to 15% among men and 3% to 29% among women and the annual incidence estimated from the Framingham Study was reported to be 2.6% among women and 1.9% among men and did not vary within the age range (40-89 years) studied.

Approximately 1% of the adult population has a leg ulcer of venous origin at any one time and 4% are at of risk of leg ulcer. The majority of leg ulcer patients are elderly with simple superficial vein reflux. Episodes of leg ulcers are lengthy lasting in some cases for several years and despite the effectiveness of compression and multilayer bandaging, recurrence is high. Recent trials involving superficial vein surgery for treatment of leg ulcers resulted in healing and significantly reduced recurrence.

The Technology

RFA is an image-guided minimally invasive treatment alternative to surgical vein stripping of superficial venous reflux. The treatment does not require an operating room or general anaesthesia and can be performed in outpatient settings by a variety of medical specialties including surgeons and interventional radiologists. Rather than surgically removing the vein, RFA works by destroying or ablating the refluxing vein segment using heat energy delivered through a radiofrequency generator. Two different intravascular RFA catheter designs have been used in the procedure.

The treatment initially involves Doppler ultrasonography to confirm and map all areas of venous reflux to devise a safe and effective treatment plan. The RFA procedure involves the introduction of a guide wire into the target vein under ultrasound guidance followed by the insertion of an introducer sheath through which a radiofrequency catheter is advanced. Once satisfactory positioning has been confirmed with ultrasound, a tumescent anaesthetic solution is injected into the soft tissue surrounding the target vein

along its entire length serving to anaesthetize the vein as well as to insulate the heat from damaging adjacent structures, including nerves and skin. The RFA generator is activated and the catheter is slowly pulled back along the length of the target vessel. At the end of the procedure, hemostasis is achieved by applying pressure to the entry point.

Adequate and proper compression stockings and bandages are applied after the procedure to reduce the risk of venous thromboembolism, and to reduce postoperative bruising and tenderness. Patients are encouraged to walk immediately after the procedure. Follow-up protocols vary, with most patients returning 1-3 weeks later for an initial follow-up visit and often a second follow-up visit 1- 3 months following RFA to evaluate clinical and technical results. If required, sclerotherapy may be performed during the RFA procedure or at any follow-up visits.

Regulatory Status

The Closure System® radiofrequency generator for endovascular thermal ablation of varicose veins was approved by Health Canada as a class 3 device in March 2005, registered under medical device license 67865. The RFA intravascular catheter was approved by Health Canada in November 2007 for the ClosureFast catheter, registered under medical device license 16574. The Closure System® also has regulatory approvals in Australia, Europe (CE Mark) and the United States (FDA clearance). In Ontario, RFA is not an insured service and it is currently being introduced in private clinics.

Evidence

The MAS evidence–based review on the safety and effectiveness of endovascular RFA ablation of VV was performed to support public financing decisions. The literature search was performed on March 9th, 2010 using standard bibliographic databases for studies published up until March 2010. The MAS search identified the following evidence: three HTAs, nine systematic reviews, eight randomized controlled trials (five comparing RFA to surgery and three comparing RFA to ELT), five controlled clinical trials and fourteen cohort case series (four were multicenter registry studies).

The majority (12/14) of the cohort studies (3,664) evaluating RFA for VV involved treatment with first generation RFA catheters and the great saphenous vein (GSV) was the target vein in all studies. Major adverse events were uncommonly reported and the overall pooled major adverse event rate extracted from these cohort studies was 2.9% (105/3,664). Imaging defined treatment effectiveness of vein closure rates were variable ranging from 68% to 96% at post-operative follow-up. Vein ablation rates at 6-month follow-up were reported in four studies with rates close to 90%. Only one study reported vein closure rates at 2 years but only for a minority of the eligible cases. A large prospective registry trial that recruited over 1,000 patients at thirty-four largely European centers reported on treatment success on selected patient subgroups at various follow-up points up to 5 years. However, the follow-up for eligible recruited patients at all time points was low resulting in inadequate estimates of longer-term treatment efficacy. The two studies reporting on RFA ablation with second generation catheters involved better follow-up and reported higher ablation rates close to 100% at 6-month follow-up with no major adverse events.

The overall level of evidence of randomized trials comparing RFA with surgical ligation and vein stripping (n = 5) was graded as low to moderate. In all trials, RFA ablation was performed with first generation catheters in the setting of the operating theatre under general anaesthesia, usually without tumescent anaesthesia. Procedure times were significantly longer after RFA than surgery. Recovery after treatment was significantly quicker after RFA both return to usual activity and return to work with on average a one week less of work loss. Major adverse events occurring after surgery were higher [(1.8%

(n=4) vs. 0.4% (n = 1) than after RFA but not significantly. Treatment effectiveness measured by imaging defined vein absence or vein closure was comparable in the two treatment groups. Significant improvements in vein symptoms and quality of life over baseline were reported for both treatment groups. Improvements in these outcomes were significantly greater in the RFA group than the surgery group in the post-operative period but not in later follow-up. Follow-up in these trials was inadequate to evaluate longer-term recurrence after either treatment. Patient satisfaction was reported to be higher for RFA.

The studies comparing endovascular treatment approaches (RFA and ELT) for VV were more limited. Three RCT studies compared RFA (two with the second generation catheters) with ELT but mainly focused on post-operative outcomes such as pain, complications and recovery. Vein ablation rates except for one small trial involving bilateral VV, were not evaluated in the trials. Pain responses in patients undergoing ablation were extremely variable and mean pain levels were significantly less with RFA than ELT ablation up to 2 weeks but not at 1 month. Recovery, evaluated as return to usual activity or return to work, however, was similar in the treatment groups. Vein symptom and QOL improvements were improved in both groups over baseline but were significantly better in the RFA group than the ELT group again, at 2 weeks but not at 1 month. Vein ablation rates were evaluated in several controlled clinical studies by comparing the treatments between centers or within centers between individuals or over time. Comparisons in these studies were inconsistent with vein ablation rates for RFA reported to be similar to, higher than and lower than those with ELT.

Economic Analysis

RFA and surgical vein stripping, the main comparator reimbursed by the public system, are comparable in clinical benefits. Hence a cost-analysis was conducted to identify the differences in resources and costs between both procedures and a budgetary impact analysis (BIA) was conducted to project costs over a 5-year period in the province of Ontario. The target population of this economic analysis was patients with symptomatic varicose veins and the primary analytic perspective was that of the Ministry of Health and Long-Term Care.

The average case cost (based on Ontario hospital costs and medical resources) for surgical vein stripping was estimated to be $1,799. In order to calculate a procedural cost for RFA it was assumed that the hospital cost and physician labour fees, excluding anaesthesia and surgical assistance, were the same as vein stripping surgery. The manufacturer also provided details on the generator with a capital cost of $27,500 and a lifespan of 5 years and the disposables (catheter, sheath, guidewire) with a cost of $673 per case. The average case cost for RFA was therefore estimated to be $1,356. One-way sensitivity analysis was also conducted with hospital cost of RFA varied to 60% that of vein stripping surgery (average cost per case = $627.08) to calculate an impact to the province.

Historical volumes of vein stripping surgeries in Ontario were used to project surgeries in a linear fashion up to five years into the future. Volumes for RFA and ELT were calculated based on share capture from the surgery market based on discussion with clinical expert opinion and existing private data based on discussion with the manufacturer. RFA is expected to compete with ELT and capture some of the market. If ELT is reimbursed by the public sector then numbers will continue to increase from previous private data and share capture from the conventional surgical treatment market. Therefore, RFA cases will also increase since it will be capturing a share of the ELT market. A budget impact to the province was then calculated by multiplying volumes by the cost of the procedure.

RFA is comparable in clinical benefits to vein stripping surgery. It has the extra upfront cost of the generator and cost per case for disposables but does not require an operating theater, anaesthetist or

surgical assistant fees. The impact to the province is expected to be 5 M by Year 5 with the introduction of new ELT and RFA image guided endovascular technologies and existing surgery for varicose veins. The conclusions on the major comparative outcomes between RFA and surgical ligation and saphenous vein stripping and between RFA and laser ablation for VV treatment are summarized below.

Table 1. Outcome Comparisons of Endovascular Radiofrequency Ablation for Varicose Veins

Outcome Comparators	RFA vs Surgery	RFA vs ELT
Post procedural pain, minor complications	RFA < Surgery	RFA < ELT
Recovery	RFA < Surgery	RFA ~ ELT
Major adverse events	RFA < Surgery	RFA ~ ELT
Effectiveness - Imaging vein occlusion	RFA ~ Surgery	RFA ? ELT
Effectiveness -Vein symptom improvement	RFA ~ Surgery	RFA ~ ELT
Effectiveness - Quality Of Life	RFA ~ Surgery	RFA ~ ELT
Recurrence	RFA ? Surgery	RFA ? ELT
Patient satisfaction	RFA > Surgery	RFA ? ELT
Patient preference	RFA > Surgery	RFA ? ELT
Procedure costs	RFA < Surgery	RFA ~ ELT
Budget impact	RFA < Surgery	RFA ~ ELT

ELT refers to endovascular laser ablation; RFA, radiofrequency ablation

The outcomes of the evidence-based review on these treatments for VV based on different perspectives are summarized below:

RFA First Generation versus Second Generation Catheter with Segmental Delivery

- Ablation with second generation catheters and segmental ablation offered technical advantages with improved ease and significant decreases in procedure time. RFA ablation with second generation catheters is also no longer restricted to smaller (< 12 mm diameter) saphenous veins.

- The safety profile with the new device and method of energy delivery is as good as or improved over the first generation device. No major adverse events were reported in two multicenter prospective cohort studies in 6 month follow-up with over 500 patients and post-operative minor complications were significantly less with RFA ablation than ELT in two RCT trials.

- RFA treatment with second generation catheters has ablation rates that were higher than with first generation catheters and were more comparable with the consistently high rates of ELT.

Endovascular RFA versus Surgery

- RFA has a quicker recovery attributable to decreased pain and lower minor complications.

- RFA, in the short term was comparable to surgery in treatment effectiveness as assessed by imaging defined anatomic outcomes such as vein closure, flow or reflux. Other treatment outcomes such as symptomatic relief and HRQOL were significantly improved in both groups.

- Longer-term follow-up was inadequate to evaluate recurrence after either treatment.
- Patient satisfaction was higher for RFA than for surgery at various follow-up and patient preference is more strongly for an endovascular approach.

Endovascular RFA versus ELT

- RFA has significantly less post-operative pain than ELT but differences are not significant when pain was adjusted for analgesic use and differences did not persist at 1 month follow-up.
- Treatment effectiveness between groups was similar in the short term (*within 1 month*) when measured as symptom relief and QOL improvement.
- Treatment effectiveness measured as imaging defined vein ablation was not reported in any RCT trials and results were inconsistently reported in observational trials.
- Follow-up was inadequate to assess longer term recurrence after either treatment.

System Outcomes – RFA replacing Surgery or Competing with ELT

- RFA, like ELT, may offer system advantages in that the treatment can be offered by several medical specialties in outpatient settings and because it does not require an operating theatre or general anaesthesia.
- The treatment may result in decanting of patients from OR, decreased pre-surgical investigations, decreased demand on anaesthetists' time, decreased hospital stay, decreased wait time for VV treatment and provide more reliable outpatient scheduling.
- Procedure costs may be less for endovascular approaches than surgery but the budget impact may be greater with insurance of endovascular treatments because of the transfer of cases from the private market to the public payer system.
- Competition between RFA and ELT endovascular approaches is likely to continue to stimulate innovation and technical changes to advance patient care and result in competitive pricing.

Decision Determinants

Based on the evidence reported in the MAS Endovascular Radiofrequency Ablation for Varicose Veins review and the deliberations of OHTAC on August 28th, 2010 pertaining to this evidence, OHTAC made the following ratings with respect to the decision determinants criteria:

	Endovascular Radiofrequency Ablation of Varicose Veins	
Overall clinical benefit	●	high
Consistency with expected societal and ethical values	◉	moderate
Value for money	◉	moderate/uncertainty

	Endovascular Radiofrequency Ablation of Varicose Veins	
Feasibility of adoption into the health system		moderate/uncertainty

For additional information on the decision determinants criteria, please refer to the OHTAC website at http://www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html .

In considering the above ratings, OHTAC took into account the: 1) high burden of venous disease, need and moderate evidence of effectiveness and safety; 2) consistency with expected societal and ethical values; 3) moderate uncertainty of cost-effectiveness due to similarities of treatment costs and effects and limited economic studies; and 4) moderate uncertainty of feasibility of adoption into the health system.

Based on the following conclusions:

1. RFA endovascular thermal ablation should be considered a safe and effective treatment for varicose vein reflux based on moderate quality evidence.

2. For RFA, ablation with second generation catheters should be the preferred method because of the improvements to design and energy delivery that increase technical ease and success while maintaining the high safety profile.

3. There is insufficient evidence, particularly on treatment effectiveness or durability, to recommend one method of endovascular thermal ablation, RFA or ELT, over the other.

OHTAC Recommendations

OHTAC therefore made the following recommendations

1. Endovascular treatment of varicose veins is a less-invasive, safe and cost-effective alternative to vein stripping that should be made available to people with symptomatic varicose veins and saphenous venous reflux demonstrated on a full duplex ultrasound investigation, and when feasible, following a failed trial of conservative management.

2. While there is an absolute medical necessity for a surgical approach by any method including RFA or ELT for treatment of varicose veins associated with venous ulcer, thrombophlebitis or bleeding the decision to recommend a similar treatment approach based on other moderate to severe symptoms attributed to chronic venous reflux, such as leg pain, oedema, pigmentation, eczema, or lipodermatosclerosis, should be made on an individual basis and guided by established definitions of disease severity such as the Venous Clinical Severity Score.

3. Mechanisms to ensure quality assurance for both the physicians performing endovascular treatments and the facility where the treatments are being performed, should be considered as part of any implementation plan.