European Journal of Vascular and Endovascular Surgery 44 (2012) 116–119

Contents lists available at SciVerse ScienceDirect

European Journal of Vascular and Endovascular Surgery

journal homepage: www.ejves.com

Part Two: Against the Motion. Endovascular Therapy is the Preferred Treatment for Patients <65 Years Old with Symptomatic Infrainguinal Arterial Disease

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Introduction

During the last thirty years the understanding and medical management of Peripheral Arterial Disease (PAD) has evolved considerably. Though traditional surgical reconstruction had been the mainstay treatment for failure of medical or local wound therapy, the introduction and development of endovascular procedures has significantly expanded the therapeutic options for treating this patient population. Between 1995 and 2000, catheter-based interventions for infrainguinal disease had increased by nearly 1000%.[1] In addition, for the first time, there has been a concurrent decrease in the major amputation rates in "at risk patients", although one has to be cautious about linking this outcome improvement to a specific treatment modality or care improvement.[2]

It is sometimes difficult to assess and compare new modalities of care such as endovascular procedures to traditional bypass surgery. This is especially true when considering lower extremity peripheral occlusive disease, where the type of symptomatic presentation, the corresponding anatomic obstructions, the plaque composition and systemic patient metabolic abnormalities provide a wide spectrum of disease and a very heterogeneous population that makes correlating clinical endpoints between treatment modalities very challenging. This difficulty is further amplified with recent, rapid improvements of medical therapy for atherosclerotic occlusive disease which have had a varied geographic penetration into this population of patients.

Despite these limitations, some comparisons can be made. When analyzing periprocedural outcomes of infrainguinal revascularization during the last decade, endovascular treatment has a significantly lower procedural morbidity/mortality, and hospital length of stay compared to open bypass surgery.[3] With ease of patient tolerance of these procedures, and increased familiarity of vascular specialist of its capabilities, endovascular therapy is increasingly considered as the initial treatment of choice for symptomatic patients with PAD, whether the lesions are simple or complex, focal or diffuse, single or multiple, calcified or non-calcified.[4,5] Multiple clinical trials have confirmed that an endovascular-first approach reduces morbidity, mortality, and costs while preserving surgical options for subsequent revascularizations.[6–8]

Opponents of the use of percutaneous trans-luminal angioplasty (PTA) as the initial treatment emphasize its inferior long-term primary patency when compared to vein-graft bypass surgery. To maintain a comparable mid-term and long-term assisted patency and limb salvation with PTA, patients frequently require secondary procedures more often than after bypass surgery. For this reason, these proponents believe that in young patients with a reasonable long-term life expectancy, bypass surgery should be the first-line treatment. To argue an endovascular first-line strategy even in patients under 65 years-old, the following arguments will be proposed:

- Patients with PAD have a significantly reduced life expectancy, making use of an endovascular approach a timely consideration.
- Periprocedural morbidity and mortality are considerably lower with PTA.
- Secondary interventions after primary endovascular failure are safe, effective and provide assisted-patency and limb salvation comparable to undertaking first-line bypass surgery.
- Bypass failure as compared to PTA failure can be an ominous event for patients with PAD resulting in poor outcome for limb preservation.
- Costs between PTA and bypass are comparable.

Patients with PAD have a significantly reduced life expectancy, making use of an endovascular approach a timely consideration

Excluding the patients with Critical Limb Ischemia (CLI) that have even worse longevity, the 5, 10 and 15 year all-cause mortality rates for patients with symptomatic PAD are 30%, 50% and 70% respectively.[9] In fact, the mortality rate of the patients with claudication is 2.5 times higher than age-matched controls.[9] Patients with chronic CLI have a 20% mortality in the first year after presentation, and the recent long-term results of the BASIL trial showed a 56% mortality rate at 4 years,[10] while another recent

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1078-5884/$ – see front matter
http://dx.doi.org/10.1016/j.ejvs.2012.06.012

cohort study in this patient population identified a 12% annual death rate.[5]

Coronary artery disease is by far the most common cause of death among patients with PAD (40%–60%), with cerebral artery disease accounting for 10%–20% of deaths.[9] There are multiple predictive factors of mortality in PAD patients which can further stratify the individual patient's risk, including: age, presence of tissue loss, serum creatinine, extent of coronary artery disease and cerebro-vascular disease, severity of the PAD itself, body mass index, smoking status, pulmonary disease and congestive heart failure.[7,11,12]

Therefore, patients with symptomatic PAD have a significantly shortened longevity compared to the general population. As such, when considering a treatment for symptomatic infrainguinal disease, minimizing periprocedural morbidity and rehabilitation time take on a higher importance while extended durability of the reconstructions, though always a high priority, need to be considered relative to the patient's life expectancy.

Peri-procedural morbidity and mortality are considerably lower with PTA

There has been good evidence that the more extensive the vascular procedure, the higher the peri-procedural morbidity and mortality.[13,14] In a large, prospective, contemporary series of 2404 patients (mean age 67years) undergoing infrainguinal bypass surgery, the 30 day mortality was 2.7% with the composite mortality/major morbidity rate of 19.5%.[13] Major complications occurred in 18.7%, which encompassed 9.4% of wound infections and 7.4% graft thromboses. A subanalysis of this data for only claudication patients (52%), revealed a lower mortality (2%) and composite major morbidity and mortality (14.5%). Results were comparable in the prospective, randomized PREVENT III trial (mean age 68 years), of vein graft bypass in patients with CLI that identified a 30-day mortality of 2.7% with major complications of 17.8%.[15]

With judicious hydration and limiting iodinated contrast administration, peri-procedure morbidity after PTA is unusual and mostly due to groin hematoma, bleeding and development of a pseudoaneurysm.[5] Complication rates have been reported as 1–5% in patients with claudication[16,17] and 2–5% in the CLI patients.[7] In a recent large study of PTA in CLI patients (mean age 70 years) there was a rate of 4% of groin or retroperitoneal hematoma requiring transfusion.[5]

Mean hospital stay after an infra-inguinal PTA is 1day (±0.02 days) with an immediate return to active life especially in intermittent claudication patients, while length of stay after surgery is 4.52 ± 0.31 days.[18] Examining short term outcomes of infrainguinal vein bypass, hospital readmissions within 6 months have been reported in 49% of patients, 65% of which were related to problems resulting from the index operation.[6] As there is lower complication rate for PTA, the 30 day hospital re-admission rate has been reported to be 6%.[19]

Peripheral Arterial Disease and especially CLI causes natural reduction of physical function. The ultimate goal in these patients is a functional status and quality of life. At 6 months, a study evaluating diabetics undergoing infrainguinal bypass for limb salvage reported that less than half of the patients felt being "back to normal" and 74% of patients required devices to assist with walking.[20] Interestingly, the functional status at follow-up was independent of patient age in this primarily diabetic cohort of patients. Another study focusing on functional outcomes after bypass for CLI identified a 19% loss of ambulation and a 5% loss of independent living.[21] A recent meta-analysis examined pre- and post-operative ambulatory status and independent living in patients undergoing revascularization for CLI. Of the 10 studies that reviewed bypass outcomes 6–12 months postoperative, there was a 12% decline in ambulatory status and a 15% loss of semi-independent living.[22] In the meta-analysis there was only one study that evaluated ambulatory status 12 months after PTA in a cohort of 122 patients. In that cohort of patients there was a 6% loss of ambulatory status.[22] The BASIL trial also addressed this issue in their short and long term follow up data with no significant improvement in quality of life between the PTA and bypass groups.[23]

In summary, infrainguinal treatment for symptomatic PAD with PTA offers a lower rate of peri-operative morbidity and mortality than Bypass for both patients with claudication and CLI, resulting in a faster return to normal daily activity.

Secondary interventions after primary endovascular failure are safe, effective and provide assisted-patency and limb salvation comparable to undertaking first-line bypass surgery

Results of the BASIL randomized study confirmed that endovascular and vein-graft bypass treatment of CLI have a similar amputation-free survival and assisted clinical success rates at 2 years.[6] Comparison between 2 meta-analyses of infrageniculate reconstruction for CLI: popliteal-to-distal vein bypass grafts[24] and infrapopliteal angioplasty[25] provided similar outcomes. Both studies used similar methods and targeted the same patient population. At one month, six months, 1 year, 2 years, and 3 years, primary patency were higher with bypass reconstruction. However, overall limb salvage was comparable in both meta-analyses (82%).[24,25]

Using PTA to treat the femoral-popliteal segment also provides very respectable outcomes with primary and assisted patency at 3 years of 65% and 93% respectively.[17] Infra-popliteal PTA with 40 months average follow up identified a primary patency of 62%, an assisted patency of 90% and an overall limb preservation rate of 86%.[7] More recently, an evaluation of 409 CLI patients treated with PTA as a first-line therapy demonstrated at 5 years, a low primary patency (31%), an assisted patency that improved to 75%, and an excellent limb salvage rate (74%).[5]

The BASIL study is the only randomized study to try to answer the question of superiority of bypass surgery-first vs PTA-first in treatment of CLI patients.[6] The 5 year results do indicate that in the analysis of only the subgroup of patients who have survived 2 years after randomization (subset of survivors, not all patients), there was a significantly higher overall survival in the bypass-first group but not a significant higher amputation–free survival, even suggesting they may be different patient cohorts.[26] There was also a higher early failure rate of PTA-first patients compared to surgery-first patients, and that many of the PTA-first patients ultimately required bypass surgery. Another conclusion was that surgical patients who had undergone prior PTA had worse outcomes than those who only had surgery.[10] However, this did not address the specific question of whether a prior PTA later excluded, by loss of anatomic runoff, a subsequent surgical option, but rather that patient who had surgery after failed PTA did not fare as well as those that had only a primary surgery. Indeed, as this is a group of a failed intervention, they may have been more appropriately compared to the group of surgery after a failed surgical procedure.

Although the BASIL trial is level 1 evidence data, there are several problems with it that would indicate some caution in the data interpretation. The investigational site audits, including the suitability of randomization, consent, and crossover to the opposite arm of the study resulted in approximately 1 in 10 presenting patients actually enrolling in the study arm that they were originally randomized to, thus somewhat pre-selecting the cohort of

patients entered into the study. In addition, the PTA arm of the study was undertaken primarily by radiologists and the surgery arm by the surgeons, which may introduce differences in the approach and the treatment of these complex patients with multilevel disease.[10]

A large prospective registry-based study on infrapopliteal procedures in CLI highlighted that bypass and surgery achieved similar 5-year leg salvage (75.3% vs 76.0%), survival (47.5% vs 43.3%), and amputation free survival (37.7% vs 37.3%) rates.[27] To reduce confounding factors, a propensity score was used to analyze the data which yielded equivalent results of both PTA-first and bypass-first treatment arms.

PTA of the superficial femoral artery has better primary, assisted primary and secondary patency than prosthetic bypass in the above knee position.[28] Femoro-distal bypass with a prosthetic graft have a very low secondary patency (25% at 5 years) and are known to have loss of outflow during graft failure.[29] Therefore, in patients with no available venous conduit, or are at a high risk for bypass, PTA can be considered the preferred initial therapy for TASC B and C lesions.[30]

In summary, infra-inguinal vein bypass have the highest primary patency rates long-term. However, through close follow-up and secondary interventions similar limb salvation rates can be achieved with PTA treatment. Mid-term and long-term patency is better with PTA when compared to prosthetic bypass.

Bypass failure as compared to PTA failure can be an ominous event for patients with PAD resulting in poor outcome for limb preservation

When performed by an experienced interventionist who understands the limits of the technique and the subsequent surgical options for revascularization, an attempted or failed PTA for infra-inguinal arterial disease can very often be safely treated either by a new PTA or surgical bypass. Multiple studies have demonstrated that first-line therapy with PTA/stent does not preclude re-intervention with PTA or secondary surgical revascularization.[17,31,32] All studies showed that secondary bypass feasibilities, patency and limb salvation rates were similar to the primary bypass patency and feasibilities.[33,34] The contradiction of these observations in the BASIL study[10] has been addressed in the previous section. Another study raised the question of a prior PTA resulting in a lower success rate of subsequent bypass.[35] There were several limitations in this study. The data were obtained from a database where the anatomic site and the number of PTA prior to bypass were unknown. In addition the group with a prior PTA was mostly female and required the use of arm vein conduit, two factors associated with inferior long term patency.

Consequences of a failed infra-inguinal bypass can be more deleterious.[36] Early graft failure (within 1 month of surgery) has been reported in approximately 5%–10% of cases[37,38] and has been correlated with increased limb loss.[37] In addition, the long-term secondary patency of a thrombosed vein graft that has undergone thrombectomy or thrombolysis is around 36% at 1 year.[39] Re-operative bypass surgery for a failed graft also has inferior results. Results of those secondary bypass surgeries are also poor (14% early graft failure with vein graft and 30% with prosthetic grafts, 50% primary patency at 5 years with venous bypass), which is mainly due to severe scarring in the operative field or lack of ipsilateral saphenous vein necessitating use of alternative poor vein conduits or prosthetic grafts.[40,41]

The percutaneous procedure should be always undertaken with consideration of backup surgical options should the initial PTA be unsuccessful or fail. Thrombosis of a bypass is a poor prognostic factor as secondary patency is poor and secondary bypasses have diminished long term patency.

Costs between PTA and bypass are comparable

In the BASIL trial, the peri-procedural morbidity of PTA-first was significantly lower than bypass-first line strategy. As a consequence, the resource utilization and hospital length of stay were significantly higher in the surgery group. This was responsible for a mean hospital cost one third higher in the bypass group during the first year.[6,42] Owing to a higher rate of re-intervention over the duration of the study in the PTA-first cohort, the cost between the 2 groups equalized by the end of the study.[23] Cost analysis is also dependant on practice patterns, use of stents, and differences in patient's clinical presentation. In addition, the equipment expenditure between 2001 and 2007 has seen the average cost for PTA increased over 60% for claudication and limb threatening ischemia, reaching $14,084 and $23,196 respectively.[18] From, recent data comparing PTA and surgery treatment in appropriately selected patients, the amortized cost per day of patency is comparable in both claudication or chronic limb ischemia patients.[8]

Conclusion

Although treatment of risk factors for PAD has made significant advances in the last several decades, failure of medical therapy resulting in symptomatic infrainguinal occlusive disease relies on either PTA or bypass to improve perfusion. As patients with PAD have a shorter life expectancy than the general population, the most effective method of revascularization to get the patients back to their functional state would be ideal. This would entail symptomatic relief, with minimal morbidity and lesion healing, if present, as the critical end-points. In addition to minimal peri-procedural morbidity, PTA has a better limb salvage rate and assisted patency than prosthetic bypass and results that approach the gold standard of venous bypass. Nevertheless, as bypass surgery may become a future treatment modality, care should be taken not to undertake PTA options that may obviate those possible future treatments. Even as the present algorithms of medical, interventional and surgical care for claudication and limb threatening ischemia remain highly controversial, they have resulted in a 25%decrease the major lower extremity amputation rate within the last 15 years.[2]

Acknowledgements

This was supported, in part, by grants form the Monte and Rita Goldman Fund and John F. Murphy and the Bay State Federal Savings Foundation.

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