Chapter 14
In Patients with Critical Limb Ischemia Does Bypass Improve Limb Salvage and Quality of Life When Compared to Endovascular Revascularization?

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Abstract Lower extremity critical limb ischemia (CLI) is a morbid condition that is marked by intractable foot or ankle pain at rest and/or the presence of ischemic ulcerations or necrotic tissue. It is associated with limb amputation, diminution of quality of life, and mortality. Although CLI is treated with limb revascularization it is unclear whether patients benefit more from open surgical repair or endovascular intervention. Although a number of studies have compared outcomes between open and endovascular approaches to treat CLI most have been hampered by retrospective design, lack of controls, lack of standardization of treatment modalities, sponsor and operator bias, inclusion of claudicants, and short or incomplete follow-up. One randomized trial (BASIL) demonstrated no difference in the quality of life associated with these two interventions, although, amputation free survival was higher with bypass in patients who survived 2 years after randomization. Further randomized trials are needed to compare the role of endovascular therapy and surgical bypass in CLI.

Keywords Rest pain tissue loss • Bypass • Endovascular • Limb salvage • Quality of life

Introduction

Lower extremity critical limb ischemia (CLI) is a debilitating condition that is associated with extended hospitalizations, readmissions, infectious complications, limb loss, and an overall poor quality of life [1–4]. Treatment primarily involves revascularization to improve limb perfusion distal to the zone of arterial stenosis or

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occlusion, often with concurrent management of underlying tissue loss and associated infectious complications. Revascularization modalities include open surgery, which consists of endarterectomy and bypass, and endovascular therapy, which includes balloon angioplasty, stenting, and atherectomy. Although both revascularization strategies are commonly practiced, patterns of use vary widely and there exists much controversy and debate about which revascularization option is optimal for any given patient [5–7].

Two endpoints of particular interest, when comparing revascularization strategies, include quality of life (QOL) and limb salvage. Quality of life is a broad concept and in different studies has different methods of evaluation and definitions [4, 8–10]. In general, this assessment involves the evaluation of both patient physical ability and psychosocial state. This can be objectively assessed by examining both functional ability and social support as well as subjectively assessing the patient's perception through standardized surveys. Factors that contribute to QOL include peri-procedural and long-term functional status, limb preservation, infectious complications, prolonged hospitalizations, and frequent hospital admissions. Limb preservation not only contributes to QOL, but is also an important independent primary outcome. Several studies have compared different revascularization options and the effect of these on limb salvage, freedom from reintervention, QOL, and survival. However, many of these are retrospective analyses where the lesion characteristics and severity of disease are not always analyzed [4, 10–18].

Assessment of which intervention is best for a specific patient is important as the number of patients with CLI rises and, given healthcare reform, physicians must most effectively use their resources to achieve best results and outcomes [1]. This chapter addresses outcomes of open surgical and endovascular interventions as they relate to limb salvage and QOL.

Search Strategy

A literature search of English language publications from 2009 to 2014 was used to identity published data on amputation rates and QOL after bypass and endovascular interventions for CLI using the PICO outline (Table 14.1). Databases searched included PubMed, Google scholar, and Cochrane Evidence Based Medicine. Terms used in the search were ("bypass" OR "endovascular" OR "angioplasty") AND ("critical limb ischemia," OR "limb ischemia") OR "amputation"; and ("critical limb ischemia" OR "angioplasty" OR "limb" OR amputation) AND "quality of

Table 14.1 PICO table for quality of life and limb salvage after surgical bypass and endovascular interventions

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with critical limb ischemia	Endovascular interventions	Surgical bypass	Quality of life and limb salvage

life". Articles were excluded if they did not address either QOL aspects or amputation rates, had the majority of their patients as claudicants, or contained only one treatment arm. One randomized control trial and six single center retrospective cohort studies were included in our analysis. The data was classified using the GRADE system.

Results

Limb Salvage

The only randomized clinical trial comparing open bypass to endovascular interventions for CLI is the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial [9, 11, 14]. This was a prospective multicenter study sponsored by United Kingdom National Institute of Health Research Technology Assessment Program and included patients with severe limb ischemia which is a less stringent definition of ischemia that does not include ankle or toe pressure thresholds. To be enrolled in BASIL, patients had to be suitable for either open surgery or endovascular intervention and were randomized to a bypass surgery first or balloon angioplasty first strategy. Primary endpoints were amputation free survival (AFS), overall survival, heath-related QOL, and cost-effective use of hospital resources. In the initial year, surgery was associated with lower rate of early failure and reintervention, while having similar perioperative mortality, and higher perioperative morbidity [11]. Initial analysis of this trial showed that there was no significant difference in AFS at 1 and 3 years (68 % and 57 % for surgery and 71 % and 52 % for angioplasty first) [11]. Surgery was associated with significantly more morbidity and perioperative complications (57 % vs. 41 %, difference 15.5 %, 95 % CI 5.8–24.8). Most of these events were infections, wound complications, and cardiovascular events. Post-hoc survival curve analysis showed a reduced hazard in amputation-free survival (HR 0.37, 95 % CI 0.17–0.77, p = 0.008) and all-cause mortality (0.34, 95 % CI 0.17–0.71, p = 0.004) for surgery compared to angioplasty among patients who survived more than 2 years [11].

Long term follow up revealed that the surgery first strategy was associated with a lower hazard for amputation free survival (HR 0.85; 95 % CI 0.50–1.07; p = 0.108) and improved overall survival (HR 0.61; 95 % CI 0.50–0.75; p = 0.009) [14]. Furthermore, patients who underwent bypass surgery after an initial failed angioplasty had significantly worse outcomes than those who underwent bypass as the initial therapy, highlighting the potential negative implications of an endovascular-first approach. Surgical patients treated with vein bypass had significantly higher amputation free survival compared to those treated with prosthetic grafts [14, 15]. Soga et al. performed a retrospective review of CLI patients over a 6 year period at 14 centers in Japan [12]. These authors compared initial treatment using bypass versus endovascular therapy. Amputation free survival, limb salvage, overall survival and major adverse cardiac events were not different between the two groups,

overall and when adjusted for covariates. Freedom from major adverse limb events (HR, 0.66; 95 % CI: 0.47–0.92, P = 0.01) and major adverse cardiovascular and limb events (HR, 0.75; 95 % CI: 0.58–0.97, P = 0.02) were lower in the endovascular therapy group. Trans-Atlantic Intersociety Consensus (TASC) II classification, lesion length and percent stenosis were all recorded in this study. However multivariate analysis was based on comorbidities alone and did not include anatomical characteristics. Bypass was used to treat significantly more TASC II D lesions as well as longer, more stenotic, and more chronic total occlusions than endovascular therapy, thus potentially skewing results.

Dosluoglu et al. performed a retrospective single center analysis of patients undergoing infrainguinal revascularization for CLI to assess patient characteristics and outcomes. Patients in the endovascular group were older, had more diabetes, tissue loss, and renal insufficiency. The open group had a higher level of infrapopliteal revascularization. The 30 day mortality was higher in the open group (6 % vs. 2.8 %), however this did not reach statistical significance (P = .079). There was no difference in AFS, overall survival, or primary patency. Secondary patency and primary assisted patency were higher with endovascular interventions. However, in this study the endovascular patients had less extensive disease therefore a side by side comparison cannot be accurately assessed. The open group had 99 % TASC II D lesions and the endovascular group has 52 % TASC II D lesions. TASC II classification was not adjusted for in multivariate analysis.

Korhonen and colleagues performed a single center retrospective study comparing AFS between endovascular interventions and bypass [17]. Patients undergoing endovascular therapy had lower AFS (42 % vs. 53.7 %, p = .003) and freedom from surgical re-intervention (86.2 % and 94.3 %, P</001). Propensity score analysis showed that leg salvage and freedom from surgical re-intervention were worse after endovascular therapy than after bypass (among the 241 propensity score-matched pairs, 74.3 % vs. 88.2 %, p = 0.031, and 86.1 % vs. 89.8 %, p = 0.025, respectively). Differences in survival, AFS and freedom from any re-intervention were not observed. The same group then published their data in octogenarians. The propensity match scored two cohorts based on comorbidities, indications, and vessel involvement for patient greater than 80 years old with CLI [16]. The endovascular cohort at 2 years had a higher AFS (53 % vs. 44.9 %, P = .005) and bypass surgery was an independent factor in decreased AFS (RR 1.55, 95 % CI 1.24–1.93). However propensity scoring did not take into account the extent of disease, occlusive vs. stenotic lesions, lesion length, and TASC II making direct comparison difficult.

Quality of Life

Healthcare QOL was assessed using the Vascular Quality of Life Questionnaire (VascuQol) that specifically assesses pain, symptoms, activities, social, and emotional wellbeing. The generic Short Form 36 (SF-36) health survey and utility scores from the EuroQoL 5-D (EQ-5D) were also used. The BASIL trial did not find

significant differences in the QOL between the two treatment strategies [9]. The methodology of the BASIL trial has been criticized on numerous fronts [16]. First, the trial limited allowable procedures in their endovascular cohort to angioplasty alone, which does not represent current management strategy. Exclusion of tools in the armamentarium of the endovascular specialist, such as stents, both biases the trial results and severely limits their generalizability. Second, AFS is significantly flawed as a primary endpoint to compare revascularization strategies as it both overemphasizes non-treatment-related mortality and underemphasizes limb-related events specifically attributable to treatment modality. Third, the study did not address the influence of anatomic patterns of disease on outcome. Fourth, the trial did not include any assessment of the hemodynamic success or failure of the treatment arms, a significant omission given the importance of objectively measuring treatment-related changes in perfusion in patients with CLI [9, 11, 14, 15].

Vogel and colleagues looked at changes in functional status in elderly patients treated with bypass and endovascular interventions by linking Medicare inpatient claims with nursing home assessment data [10]. A functional impairment score, based on need for assistance with activities of daily living, was calculated pre-procedurally, post-procedurally and at 6 months. Both patient groups demonstrated a decrease in their functional status, corresponding to the severity of their disease, in the immediate post-operative period. The less invasive endovascular procedure did not result in less impairment of functional status. Other factors that impaired long-term functional status post-procedure were female gender and poor baseline cognitive and functional ability. Recovery rates at 6 months were higher in the bypass than in the endovascular group. This is an analysis comparing large administrative databases and has limitations. Although the pre-operative functional status was similar, the severity of disease and details of the reconstruction were unclear. Furthermore, patients who were readmitted and those who had concurrent amputations were excluded.

When looking at QOL broken down into different categories, a retrospective survey sent out to patients after open and endovascular interventions revealed no difference between endovascular and open surgery post-procedure in patients [4]. However, compared to age and gender matched cohorts, patients undergoing open vascular surgery overall scored considerably lower for every variable. The largest differences seen in mobility, breathing, sleeping, discomfort, vitality, and sexual activity. Surgical patients were also less likely to have social support, more likely to have walking limitations, worse Geriatric Depression and Life Satisfaction scores, and a poorer perception of health.

A Personal View of the Data

Data reviewed herein suggest that those patients with CLI who are expected to live more than 2 years may benefit from open revascularization over endovascular therapy. In addition open vascular revascularization is associated with higher

Table 14.2 Data comparing open vs. endovascular treatment of critical limb ischemia

Author (year)	N endo	N bypass	Limb salvage	Quality of life	Disease extent compared?	Type (quality of evidence)
Bradbury (2010) [14]	224	228	Favors open surgery	No difference	No	Randomized, prospective, multicenter (moderate)
Remes (2010) [4]	131	100	N/A	No difference	No	Retrospective, single center (low)
Arvela (2011) [16]	277	307	Favors endovascular	N/A	No	Retrospective, single center (low)
Korhonen (2011) [17]	517	341	Favors open surgery	N/A	No	Retrospective, single center (low)
Dosluoglu (2012) [13]	363	151	No difference	N/A	No	Retrospective, single center (low)
Soga (2013) [12]	223	237	No difference	N/A	No	Multicenter, retrospective (low)
Vogel (2014) [10]	350	352	N/A	Favors open surgery	No	Medicare database (low)

post-procedural morbidity than endovascular therapy. Little else can be definitively concluded from these data (Table 14.2).

There are few areas of medicine that have as little consensus to support treatment strategy as does the management of CLI. The decision to recommend surgical or endovascular revascularization varies significantly among providers and is based on a range of factors, including disease pattern, availability of autogenous conduit, training, surgical and endovascular skill sets, access to an appropriate procedural environment, and perhaps most importantly, disparate treatment biases. There is general agreement that some patients considered poor candidates for surgery are well served by endovascular revascularization. What is presently not known is which therapy is more suitably offered to patients who are candidates for both open and endovascular treatment. This lack of clarity in current treatment algorithms for CLI has led to a blurring of the standard of care, inevitable misapplication of technology, and likely increased health care expenditure.

Persistent clinical equipoise in combination with a paucity of comparative effectiveness data to guide treatment of CLI has led to a multidisciplinary effort to organize the BEST-CLI Trial, a prospective, randomized, multicenter, controlled trial to compare Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischemia. This trial is funded by the National Lung Heart and Blood Institute (NHLBI) of the National Institutes of Health and aims to enroll 2,100 patients with CLI at 120 sites in North America over the course of 4 years. The aim of BEST-CLI is to compare treatment efficacy, functional outcomes and cost in patients with CLI undergoing best open surgical or best endovascular revascularization [19]. The BEST-CLI trial started enrollment in

September of 2014 and promises to comprehensively answer many questions that remain unanswered with regard to the management of patients with CLI and infrainguinal PAD. Its multidisciplinary structure is specifically designed to welcomes all stakeholders across the United States and Canada. This effort aims to define practice in the field.

Recommendations

- We recommend for patients with a high likelihood of long-term survival that they should undergo bypass surgery for critical limb ischemia (**evidence moderate, recommendation weak**).
- We recommend for patients with poor long-term survival should that they should undergo endovascular intervention (**evidence moderate, recommendation weak**).

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