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RESEARCH ARTICLE

THE LIMFLOW SYSTEM FOR NO-OPTION CRITICAL LIMB ISCHEMIA (CLI) PATIENTS

Mohammad HAAA Alsaffar and Nawaf M.O.S Ali
Vascular Surgery Unit Department of Surgery Jaber Al Ahmad Hospital.

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Abstract

Critical limb ischemia (CLI) is a common health problem among adults. CLI is a progressive type of peripheral artery disease associated with non-healing ulceration and ischemic pain at rest. Patients with CLI may suffer from gangrene, a consequence of arterial occlusive disease. Patients with CLI have a high-risk of developing chronic health issues such as hyperlipidemia, renal failure, hypertension, and diabetes mellitus. The health and well-being of patients with CLI is low and heterogeneously complex. Patients with CLI cope with complex and chronic health issues that often require appropriate treatment and management. The newly developed Limflow system is the promising future for vascular interventions in CLI patients.

Introduction:-

Despite the availability of comprehensive treatment modalities, many patients with CLI suffer from severe form of the disease. Patients with CLI have limited therapeutic options that jeopardised their quality of life. Patients with end-stage disease suffer from occlusion of pedal arteries. Clinicians and surgeons often find it difficult to perform distal bypass to prevent the complications of pedal artery occlusion. Surgeons often fail to control the disease through conventional revascularization strategies due to the complexity of the disease. Untreated and unmanaged CLI can often be life-threatening owing to vascular complications. Patients with chronic ulceration and severe limb ischemia may undergo limb amputation despite aggressive treatment and local wound care. Patients who undergo revascularization may require amputation after a few years. An estimated 20% of patients with CLI may have no option to recover from the complexity of the disease. Some of the common factors that lead to permanent disability among chronic CLI patients include extensive co-morbidities, lack of conduit, and the presence of atherosclerotic lesions. Major limb amputation is currently the only viable option for patients with chronic CLI despite the presence of advanced endovascular and surgical techniques.

The population of patients with CLI and co-morbid conditions such as renal failure and diabetes is expected to increase exponentially. Unfortunately, the number of patients with no option for reconstructive or salvage surgery would be forced to undergo limb amputation. The quality of life (QoL) of patients is a major concern for clinicians and healthcare professionals. In a recent report, the QoL of patients who had no endovascular treatment or surgical procedure had a lower quality of life as compared to patients who underwent some form of salvage treatment. Chronic pain and physical dysfunctionality were common among patients with severe forms of CLI. Patients with co-morbid conditions often suffered from severe form of CLI with lower quality of life as compared to those with mild form of the disease (Sprengers et al. 2010).

Corresponding Author:- Mohammad HAAA Alsaffar
Address:- Vascular Surgery Unit Department of Surgery Jaber Al Ahmad Hospital.

Although below-the-knee amputations adversely affect the quality of life of CLI patients, there is scope to improve physical function and household mobility. As per a recent report, more than 50% of patients who undergo BTK amputation can regain physical function and mobility within the house. An estimated 25% of patients may regain mobility for activities outside their house (Davies &Datta 2003). Patients who undergo limb amputation have a high-risk of mortality. The overall risk of mortality increases from 25% at 1 month to 50% after a year, and over 75% over 5 years (Fortington, Dijkstra, Geertzen 2013). Based on current evidence, limb salvage remains an essential component of modern treatment for CLI (Sprengers et al. 2010).

Background:-

Surgeons, clinicians, and allied healthcare professionals have cited the need for advanced treatment to prevent and control the complications of CLI. The LimFlow percutaneous deep vein arterialization (pDVA) is developed to treat chronic and complicated cases of CLI. LimFlow is based on the principle of venous arterialization. The procedure is widely known among surgeons and has been used for several years. The first surgical cases of venous arterialization were reported in the 20th century (Francois-Franck 1896 and Halstead & Vaughan 1912).

Several clinical trials on venous arterialization as a primary surgical approach for CLI have been published. A recent meta-analysis was published summarizing the benefits and challenges of venous arterialization. Although the initial findings for limb salvage were prosing in context to the quality of life and decrease in overall morbidity, venous arterialization has not been widely accepted due to technical limitations and risk of morbidity (Schreve et al. 2017). The need for a robust, comprehensive, effective, and efficient surgical approach has been cited by several researchers and surgeons.

The first clinical studies based on the use of LimFlowpDVA were performed in October 2016. Patients with CLI who had no option for salvage were recruited in the study. The clinical sites were based in Europe and Singapore as the CE mark was granted by local health authorities. The initial results of the study showed promising results among high-risk patients with CLI. Clinical improvement was reported in 60% of the patients and the 6-month improvement rate (limb salvage) was 86% (Giudice et al. 2018 and Kum et al. 2017). The initial findings of the study showed promising efficacy and safety results. As per Kum et al. (2017), the early feasibility study was launched based on the Food and Drug Administration's approval in the United States. The early experiences of the LimFlow system were reported and published (Mustapha, Saab, Clair, & Schneider 2019).

The LimFlow System

The LimFlow system is a newly developed and approved system to treat and manageno-option chronic limb ischemia patients. The LimFlow system is based on conventional surgical approaches with a modern technological system. The purpose and advantages of the LimFlow system can be assessed based on the technique and components involved in the procedure. The LimFlow System is based on five primary components: (a) Ultrasound system, (b) Extension cable set, (c) Arterial and venous catheter set, (d) Valvulotome, and (e) Stent grafts

Ultrasound system

The LimFlow ultrasound system comprises of a transceiver box, a laptop, and a power supply. An electrical pulse is applied via the catheter using the powered source. The catheter helps in amplifying, filtering, and digitalizing the electrical pulse. The filtered signal is projected on the laptop screen as a waveform. The process enables the reader to visually determine the strength of the electrical pulse. The orientation of the catheters is based on the strength of the pulse received. A software within the laptop enables the user to adjust technical parameters and receive/divert signals based on the need of the patient.

Extension cable set

The LimFlow system comprises of an extended cable set that supplies power to the venous and arterial catheters. The cable set is a simple wired system that enables efficient power supply.

Arterial and venous catheter set

The arterial catheter is around 100 cm in length with a 6.5-Fr catheter. The ultrasound arterial catheter is placed over a 0.014-inch guide wire. The catheter is guided via a sheath within the femoral artery. The wire is then taken to the arterial occlusion via the tibial artery. The ultrasound sound catheter in the artery has two primary functions: (a) Identifying and locating the neighboring veins: The handle-like design is beneficial for the surgeon to generate torque. It also helps in pull-push function that enables the surgeon to identify the correct location. The ultrasonic

transmitter within the arterial catheter tip allows the surgeon to identify the venous catheter within the neighboring vein. (b) Connecting to the adjoining vein via a cross-linked needle: The catheters are placed with a pusher ring that passes through the crossing needle via the artery to the vein. The needle is placed within the catheter shaft. As the catheter is placed within the artery, the needle retracts from the shaft. The wire is also known as the 'Crossingwire' that is placed over a standard 0.014-inchu guard wire. (Schreve et al. 2019).

The venous catheter comprises of an ultrasound receiver. The presence of the receiver helps the surgeon to target the site within the vein to align the needle of the arterial catheter. The tip of the venous catheter comprises of a 360° ultrasonic sensor that helps in identifying the arterial catheter. (Schreve et al. 2019). The venous catheter can detect the arterial catheter at any circumference angle. The venous catheter is about 100-cm in length with a 5-Fr catheter. Like the arterial catheter, the venous catheter is also placed over a 0.014-inch guide wire. (Schreve et al. 2019). The catheter is placed through a sheath via the femoral vein. It is routed through the tibial vein and placed parallel to the arterial catheter. The venous catheter is placed on the left side as the arterial catheter is rotated around in a longitudinal position. The arterial catheter is rotated to obtain the desired ultrasound signal to indicate the alignment of the needle with the venous catheter. The placement of the venous and arterial catheter is based on the procedure used, while the venous catheter is placed within the tibial vein. Patients who consent for fluoroscopy-guided procedures require arterial and venous catheters for catheterization in laboratory-controlled settings. The arterial and venous catheters are meant single use only. They are removed at the end of the procedure. All catheters are sterile and provided to patients at the time of surgery for a one-time use only (Schreve et al. 2019).

Valvulotome

The valvulotome is an essential component in the LimFlow system to disable the venous valves. The valvulotome is placed over the crossing wire and passed through a section within the venous vessel. The distal tip of the valvulotome comprises of a nitinol cutting basket that has a push-pull mechanism. The distal tip or the cutting component is placed within the venous vessel at a maximum 4.5 mm diameter. The cutting blades have a lower diameter as it helps in cutting the valves as they are pushed through the veins. As the diameter is lower than that of the maximum diameter, the venous vessels remain intact. The total diameter of the valvulotome is 4 Fr. The valvulotome is provided for single-use only and supplied sterile (Schreve et al. 2019).

Stent grafts

Stent grafts were made to facilitate blood flow within an artery or a vein. The LimFlow system comprises of crossing of the artery to a vein to facilitate blood flow. Stent grafts can facilitate constant blood flow across the cross-over created from the artery to the vein. The size and shape of stent grafts are based on the physiological needs of the patients. The LimFlow system comprises of a comprehensive product line for stent grafts. The stent grafts are crafted to perfection to facilitate normal physiological function. The size of the stent grafts is checked for compatibility. The LimFlow system is based on a nickel-titanium alloy (nitinol) that is cut through laser-like precision. The nitinol-based stents form the foundation for encapsulation procedures. The nitinol-based stents help in developing customized and functional stent grafts for the patient. The delivery system is based on an inner tubing made of flushing lumen and a 0.018-inch guide wire. The guide wire is accessible through a valve. The design of the stent graft delivery system requires a 7-Fr sheath to ensure computability during the procedure. The shaft is designed based on brain pattern to achieve functional and mechanical properties. The distal end of the delivery device comprises of two distinct radiopaque markers. The design of the delivery device prevents unintended movement during the procedure such as sheath retraction (Schreve et al. 2019).

Current evidence on LimFlow systems

The LimFlow system has emerged as a safe and effective treatment approach to reduce the morbidity and mortality rates among patients with CLI. (Mustapha, Saab, Clair, & Schneider 2019). In one of the early-stage clinical trials comprising of 10 patients with no option for salvage, a team of researchers assessed the safety and feasibility of the LimFlow system. A total of 10 patients were recruited in the study. The patients were categorized based on the Rutherford class. All participants were Rutherford class 5 or 6 patients and were deemed ineligible for surgical or endovascular procedures. 80% of the patients were classified based on high-risk for amputation (Stage 4) as per the Society for Vascular Surgery wound, ischemia, and foot infection (SVS WIfI) scoring index. Amputation-free survival (AFS) was the primary end point at 30 days. The secondary end point was evaluated as AFS at 180 days (6 months). AFS for 30 days and 180 days was 100% with no above-ankle amputations and deaths. The technical success rate of LimFlow was 100% with no complications reported during the procedure. The patency rates at 30 days was 90% while it was 40% at 180 days. An estimated 30% of patients required reintervention. Complete

wound healing was reported in 30% of the patients after 180 days. Nearly 50% of the patients reported 85% to 93% wound healing. This was the first exploratory study to document the safety, efficacy, and feasibility of the LimFlow system. The use of the novel approach reduced amputation and showed promising results in lowering mortality among high-risk patients (Mustapha, Saab, Clair, & Schneider 2019).

The mid-term outcomes of the LimFlow system was assessed based on a multi-site retrospective study. A total of 32 patients were recruited in the study. Participants were based from 4 clinical centers. Patients had several comorbid conditions such as diabetes (66%), immunosuppression (25%), and renal failure (28%). Nearly 78% of patients were considered high-risk for amputation. The primary end point of the study was AFS at 180 days. The secondary end point was survival, limb salvage, and wound healing at 180 days, 12 months and 2 years respectively. The technical success rate was 96.9%. The AFS was 83.9% at 180 days, 71% at 12 months, and 67.2% at 24 months. Limb salvage was 86.8% at 180 days, 79.8% at 12 months, and 79.8% at 24 months. Complete wound healing was reported at 36.6% at 180 days, 68.2% at 12 months, and 72.7% at 24 months. The median time for complete wound healing in all participants was 4.9 months. The median time for occlusion in all patients was 2.6 months. A total of 17 patients required reintervention due to occlusion. It is one of the largest studies that assessed the safety and efficacy of the LimFlow system for patients with CLI (Schmidt et al. 2020).

The quality of life of patients with CLI is worse than those of patients with chronic health issues such as cancer, chronic heart disease, and chronic kidney disease. The physical composite score of patients with CLI was 30.8 (Fig 1). An estimated 35% to 45% of patients opt for limb amputation without confirmation of CLI diagnosis (LimFlow 2020). An estimated $794,000 is spent in a lifetime once a patient is diagnosed with CLI. A patient with CLI has an average 19 admissions or hospital visits per year (Fig. 2). An estimated 30% of patients with CLI undergo amputation, 25% of patients die due to complications, 20% develop chronic complications, and 25% of patients resolve completely (Fig. 3). The risk of morbidity and mortality is high among patients with CLI despite advancements in treatment options (LimFlow 2020).

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Appendix:-

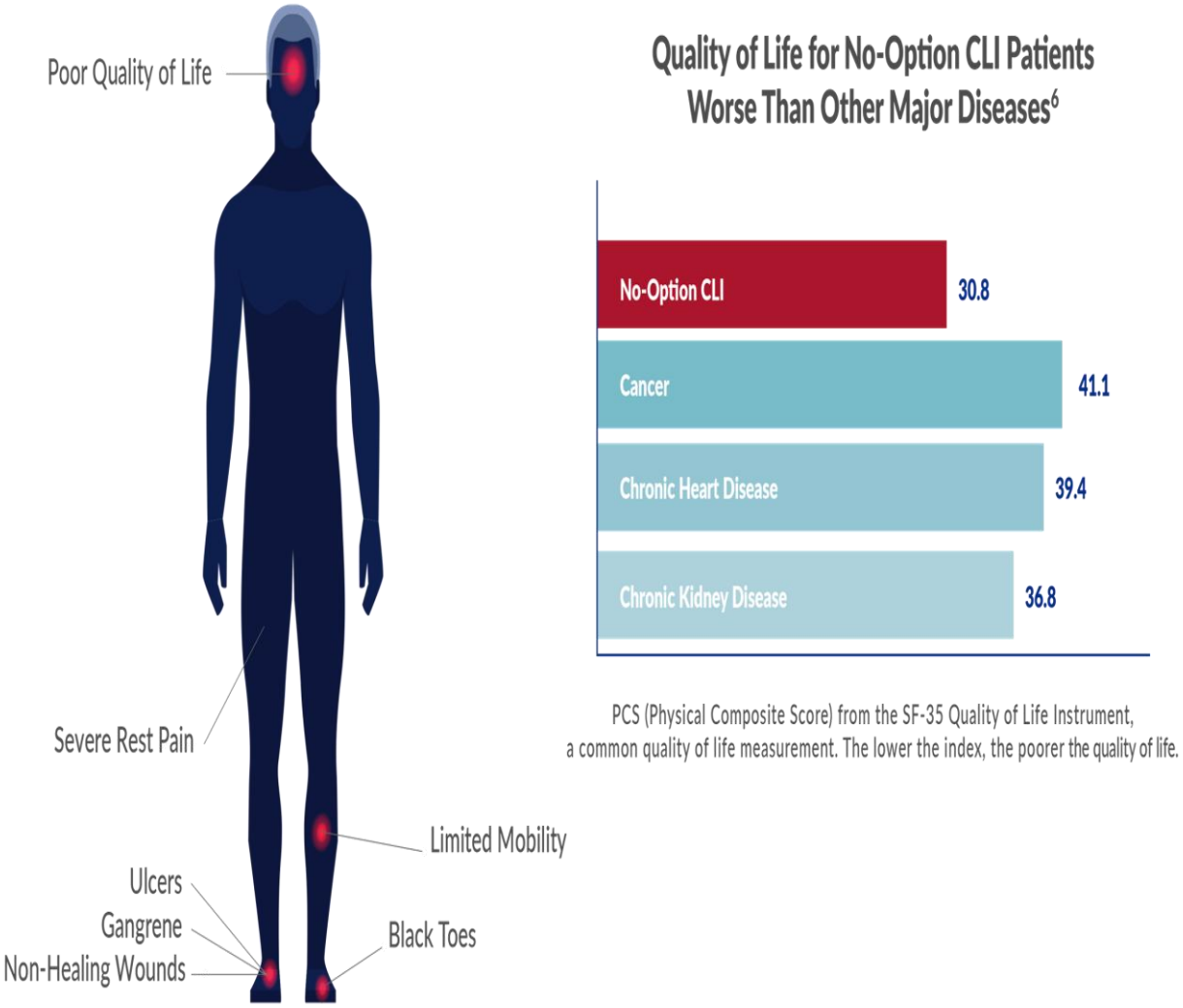

Figure 1:- Poor Quality of Life in patients with Critical limb ischemia (CLI) (LimFlow 2020).

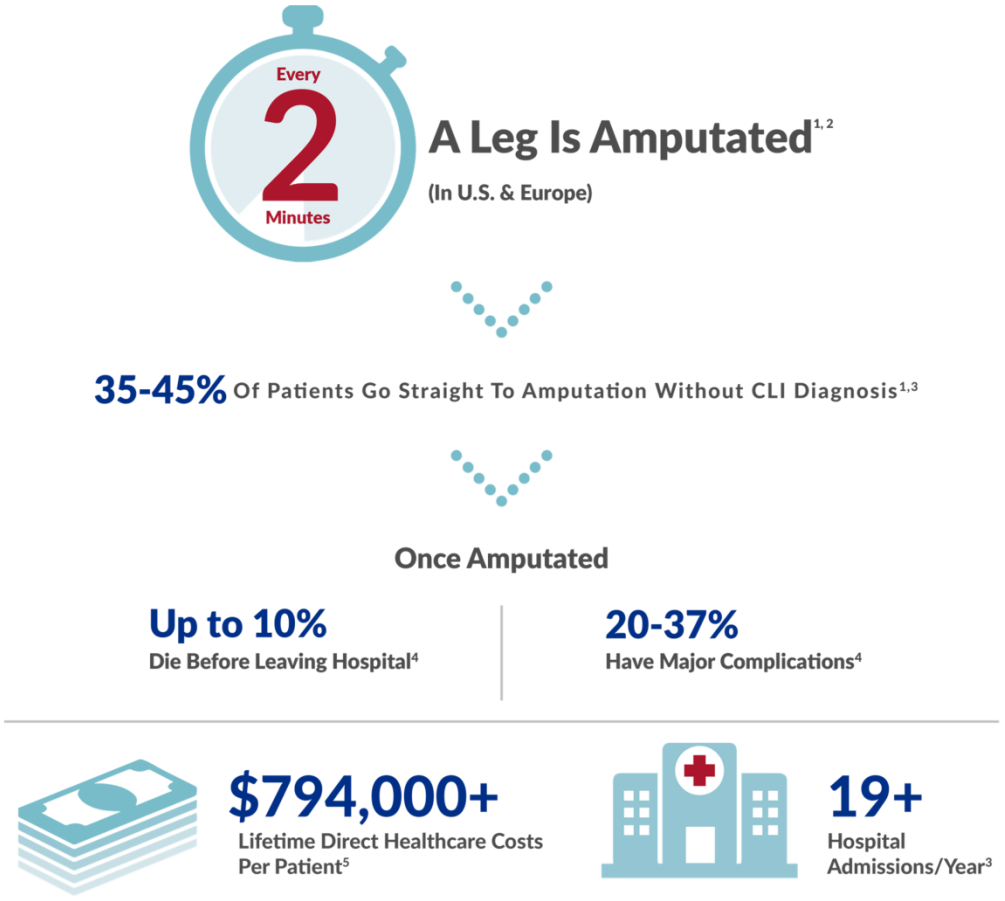

Figure 2:- Statistics on the burden of CLI (LimFlow 2020).

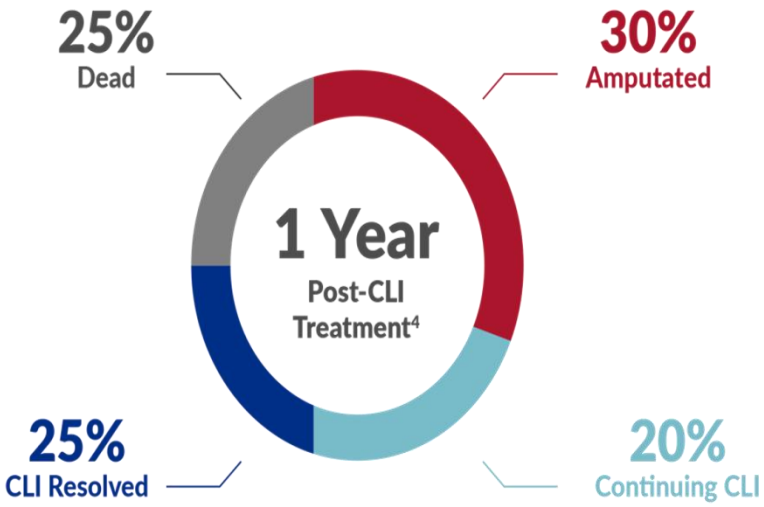

Figure 3:- Treatment outcomes for CLI (LimFlow 2020).