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The Effect of the GekoTM Device on Post Kidney and Pancreatic Transplantation Leg Edema

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Abstract

Introduction: Kidney and pancreas transplant recipients risk thromboembolism and lower limb edema due to immobility and fluid shift after surgery. Intermittent pneumatic compression (IPC) devices + Thromboembolic deterrent (TED stockings) are used to mitigate these risks. However, they risk peroneal nerve injury, discomfort, excessive heat and sweating under the cuffs. The Geko^{TM} device, is an internally powered calf neuromuscular stimulator, shown to have beneficial effects in improving blood flow and skin capillary perfusion. Its role in transplantation has not previously been assessed. Our objective was to prospectively evaluate the effects of IPC+TED stocking and the Geko^{TM} devices on lower limb edema in renal and pancreatic transplant patients.

Methods: In a prospective, randomized, and controlled, single-center study we enrolled patients randomly to wear IPC + TED stockings or the Geko^{TM} device post-operatively until day 6 after kidney or kidney and pancreas transplant surgery.

Results: We observed a significant reduction in lower limb edema, increased urine output, and a significantly improved patient satisfaction rate with the use of the Geko^{TM} device.

Conclusion: The use of the Geko^{TM} device in the immediate post-operative period leads to an improvement in lower limb edema in kidney and pancreas transplant recipients compared to IPC+TED stockings.

Keywords:

Geko^{TM} device (neuromuscular stimulator), Intermittent pneumatic compression (IPC), Thromboembolic deterrent (TED stockings), Edema, kidney and pancreas transplant.

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Chapter 1

1.1 Introduction

Kidney Transplantation and Pancreas Transplantation

Kidney transplantation is the most appropriate solution to individuals suffering from end-stage renal disease (ESRD). However, only a few adult patients with ESRD are referred for transplantation evaluation, with a 5-year mortality rate of 70% in dialysis (Matas, et.al. 2014). Significant advancements in long-term and early graft survival and function have led to continued affordability and efficiency of kidney transplantation to dialysis. Over 500,000 transplants have been performed in the U.S, with 200,000 patients living with a functional kidney transplant as of 2015. However, an additional 151,000 patients are currently in the kidney transplant waiting list (UNOS, 2015) Additionally, the number of people being treated for kidney failure in Canada in 2010 was 39, 352 with 41% (16,164) having a functional transplant. According to Canadian Organ Replacement Register (CORR), cases if kidney transplant are on the rise with 1267 transplants conducted in 2013 alone as compared to 1196 and 1245 in 2011 and 2012.

Renal transplantation offers less cardiovascular events (Brunkhorst, et al., 2003; Ward, 2000), less hospitalization, decreased mortality (Chauveau, et al., 2009; Sezer, et al., 2004) and morbidity, and better quality of life (Baiardi, et al., 2003). The treatment costs for transplant patients are less compared to cumulative dialysis costs by at least a third (Bruno, et al., 2003). However, missing dialysis sessions comes with serious life threatening consequences among them pulmonary edema, hyperkalemia leading to arrhythmias, or coma related uremic encephalopathy.

Dialysis fails to reduce other ESRD complications like bleeding tendency, immune suppression, chronic anemia, and metabolic bone disease despite being a mandatory survival necessity to the patients.

However, there are high risks especially to patients with much comorbidity that can limit the kidney transplantation operation. There is a long list of surgical complications with a significant number of them being serious with considerable mortality or morbidity risks. Other risk factors include the immunosuppressing medications requirements whose side effects range from infections, coronary artery disease, and cancers.

Pancreas transplantation is carried out to solve insulin-dependency in patients suffering from type 1 diabetes in addition to eliminating injected insulin dependence (Wiseman AC, 2010). Approximately 1.25 million people suffered from type 1-diabetes in the U.S as of 2012. Pancreas transplantation, concurrently with a kidney graft was first successfully performed in 1966 (Sutherland, et al., April 2001). Currently, simultaneous performance of pancreas and kidney transplantations and from the same deceased donor stands at 75% of all pancreas transplants performed in North America. Additionally, pancreas-after-kidney transplantation rates stand at 15% and are performed from either a deceased or a living donor. However, single pancreas-after-kidney transplantation hold the remaining 10% with the patients who having normal kidney function, but with very labile life-threatening hypoglycemic unawareness related to problematic diabetes (Morath et al., 2008).

Successful pancreas transplantation will lead to a normoglycemia and reduced dependence on insulin by reversing the diabetic alterations seen as a result of diabetic nephropathy in recipient patients' native kidneys. Additionally, it prevents recurrent diabetic nephropathy in pancreas-kidney transplantation patients, while improving the length and quality

of life through reversing the peripheral sensory neuropathy and stabilizing the advanced diabetic retinopathy (Kuffman, 2001). The 1 year patient survival rates are 95%, 91%, and 86%, for kidney, pancreas, and kidney-pancreas transplant, respectively. Pancreas addition improves the long-term survival patient and kidney graft survival to patients with diabetes (McCullough et al., 2009). The average 1-year pancreas graft survival rate for pancreas-after-kidney transplant recipients or a lone pancreas transplant is 78-83% while that of the kidney is 77-82%.

1.2 Kidney transplantation complications (medical and surgical)

Patients who undergo renal transplantation may experience both surgical and medical complications after kidney transplantation surgery. It is therefore necessary to screen both recipient and the donor according to the U. S Centers for Disease Control and Prevention (CDC) standards in addition to United Network for Organ Sharing (UNOS), as well as local transplant work-up guidelines.

1.2.1 Surgical Complications

Being a major operation, kidney transplantation poses major organ operations complications. Surgical complications were a major cause of kidney graft loss in the past with 20% occurrence between 1960 and 1980. However, their frequency has dropped significantly due to technological and procedure advancements (Botto V, 1993; Hernandez D, 2006). As expected, surgical complications that arise after kidney transplant increase morbidity, hospitalization and costs despite the improvements (Humar A, 2005). Many of these risks are accentuated by factors such as increasing age of the recipient, obesity and concomitant vascular disease (Hernandez D, 2005).

The following is a list of some of the common complications of renal transplantation:

1.2.1a Wound Infection and Hernias

Wound infections contribute significantly to postoperative morbidity after renal transplantation (Lynch, 2009), likely due to the obligate medication regimented immunosuppression apart from the routine risk of surgical site infections arising from standard procedures.

Infection rates are high during the first year after transplantation (Sousa SR, 2010) and up to 25% of these patients require radiological or surgical intervention and with wound infections ranging from 10 to 27% (Røine E, 2010; Khoury JA, 2005; Fortun J,2010). Impaired wound healing after kidney transplantation has various risk factors such as dialysis pre transplantation, a body mass index >30, post transplantation plasmapheresis, use of thymoglobulin as induction therapy or in its use in acute rejection, mycophenolate mofetil-induced immunosuppression, use of sirolimus for maintaining immunosuppression, recipients older than 60 years, and delayed graft function (Fortun J,2010; Santangelo M,2009). Additionally, incisional hernias are a major source of postoperative morbidity as most require surgical repair at some point. However, hernia formation is more prevalent in males, older people, those participating in heavy physical labor, and previous surgery (Mazzucchi E, 2001; Knight RJ 2007). Additionally, the estimates of post kidney transplantation hernia formation range from 1.6 – 18%.

1.2.1b Vascular Complications

There might be early kidney transplant loss due to renal artery acute thrombosis which remains a devastating complication, with chances of occurrence ranging between 0.2- 7.5%. Despite being uncommon, arterial thrombosis in the early postoperative period creates surgical

emergency which should not be conducted if previously established diuresis ceases suddenly. Arterial thrombosis has often been attributed to technical factors encountered during the vascular anastomosis, use of atheromatous arteries, hypercoagulability, end-to end anastomosis and allograft malposition (Keller, 2012; Knechtle, 2008).

Despite being uncommon, renal vein thrombosis is a serious complication with incidence rates ranging from 0.9 - 4.5% and usually occurs a few days after transplantation and may lead to graft loss (Giustacchini P, 2002). Given that the transplanted kidney has no collateral circulation, venous stasis and thromboembolism often causes acute graft dysfunction.

Renal artery stenosis mainly affects 3–24 months post-transplant (Bruno S, 2004) and is common to up to 12% of transplant recipients with hypertension (Audard, 2006). Transplant renal artery stenosis risk factors include delayed transplant function, cytomegalovirus infection, organ procurement complications, and poor surgical techniques.

Another devastating complication of renal transplantation is renal arterial pseudo-aneurysm formation which occurs in approximately 1% of renal transplants. One of the causes is injury to the renal artery during procurement or preservation, excessive stripping of the artery and its vasa vasorum which cause ischemic damage, faulty suture technique, in addition to external traumatic injury. Additionally, it can result from an infected arterial anastomotic suture line from mycotic aneurysm either from bacterial or fungal pathogens (Dalla Valle, 2005; Orlando, 2009; Osman, 2009).

1.2.1c Lymphocele and Hemorrhage

Lymphocele is the accumulation of lymphatic fluid in the retroperitoneal space next to the graft and can originate either from the recipient iliac lymphatic vessels or from the allograft renal hilum. The average lymphocele occurrence rate ranges from 0.6 to 16% (Adani, Baccarani.

2007; Zargar- Shoshtari, Soleimani. 2008; Iwan-Zietek, Zietek. 2009). Inadequate ligation of the delicate system of lymph vessels overlying the iliac vessels, or present in the hilum, attribute to the etiology.

Unrecognized vessel in the donor renal hilum or surface; allograft vascular suture line disruption; inadequate preparation of the graft bed and presence of poorly ligated pelvic or epigastric vessels; or abnormal recipient coagulation mechanisms can also cause acute postoperative hemorrhage. Requirement of hemodialysis often accompanied by anticoagulation in the immediate postoperative period may also increase postoperative hemorrhage (Rabrenovic, 2007).

1.2.1d Urine Leak and Ureteric Obstruction

Urine leak or urinoma complications occur in up to 3% of patients undergoing kidney transplantation (O'Neill CW, 2002). The condition is observable in the first days/weeks after kidney transplant especially after the removal of urinary catheter. The main cause is leakage at the site of anastomosis of the ureterovesicle anastomosis as a result of poor surgical technique or ureteric necrosis. Ureteric necrosis is often caused by over-enthusiastic adventitial tissue stripping around the ureter while preparing for implantation.

Ureteral obstruction at some time after surgery will develop in approximately 1%–4.5% of renal transplant recipients (E.H. Streeter, 2002; J. Lempinen,2015) and nearly 90% probability is due to ureteral devascularization cases which leads to intrinsic stricture formation (S. Kumar,2014). Major causes of obstruction during the early postoperative i.e. during a 3 months' period include technical errors during the ureteroneocystostomy, collecting system hematoma; extrinsic compression such as hematoma, lymphocele, and abscess; kinking of a redundant

ureter, a renal stone mistakenly transplanted with the kidney, and anastomotic edema. Late obstruction during the period beyond 3 months usually results from ureteral ischemia. Additionally, vasculitis may also occur. There are a variety of treatment options for these complications ranging from radiological, endoscopic to open surgical approaches. A new systemic review showed that open management has higher success rates and fewer complications than endourological management as a primary and secondary treatment for post-transplant distal ureteric strictures (Sener et al.,2016).

1.2.2 Medical Complications

Graft loss arising from rejection has significantly been reduced as a result of better immunological cross matching techniques and selection of induction immunosuppression after renal transplantation, all of which have increased the success rates of long term graft function. However, more elderly patients and the number of patients with multiple co-morbidities receiving renal allografts are on the rise, thus consequently their risk of medical complications and transplant-related spectrum of complications as a result of the immunosuppression, their underlying disease or the previous uraemia state are a concern.

Rejection is most commonly due to T cell mediated processes but can also be attributable to B-cell mediated rejection and is dependent upon induction regimens, tissue cross matching and patient alloreactivity.

Acute cellular rejection occurs in a 25% of all patients normally within the first 1-3 weeks which can extend to 3 months. Signs include fluid retention, high blood pressure, and rapid increase in serum creatinine. Lastly, chronic rejection is observed late after transplantation and is associated with hypertension, excretion of protein in urine and gradual rise in serum

creatinine. Unlike other forms of rejection, chronic rejection is inevitable and cannot be acutely remedied with immunosuppressive therapies.

There is a lower risk of fatal and nonfatal cardiovascular events in transplant recipients in relation to wait-listed patients on dialysis (Lentine KL, 2005; Meier-Kriesch, 2004). However, they face a much higher risk compared with the general population (Jardine, 2011). Cardiovascular disease is one of the common risks and the most common cause of death in graft function after transplant patients and accounts for 30 percent of graft loss from death overall, with early after transplant facing the highest risk. On the other hand, hypertension and transplantation are closely related and the risk of their association may promote impaired graft and overall survival (Kasiske, 2004**).** High blood pressure frequently occurs early after kidney transplantation due to saline loading and its interaction with initial high-dose immunosuppression when they are present. However, it is observed in 50–80% of transplanted patients since calcineurin inhibitors started being used (Vella, 2009).

New-onset diabetes mellitus (NODAT) is a serious long-term transplantation complication known since the past and various clinical studies demonstrate that it is associated with low survival rates in both patient and graft. A research reported that every patient with pre-transplantation diabetes and 87% of those without it had evidence of hyperglycemia (bedside glucose above 200 mg/dL or physician-instituted insulin therapy) during recovery or initial hospitalization post transplantation (Chakkera, 2009). NODAT development is associated with a number of factors including deceased kidney donor, age of the recipient, presence of hepatitis C, polycystic kidney disease (ADPKD), rejection, and using tacrolimus in place of cyclosporine. NODAT reduction is associated with incidence of withdrawal or avoidance of steroid and statin therapy (Pascual, 2009).

Long-term risk of malignancy overshadows improvements in renal recipient and graft survival rates in transplantation. The nature and intensity of immunotherapy and its relationship to subsequent malignancy has been extensively reviewed (Vella, 2008). However, the most common malignancies in adult kidney transplant recipients are skin and lip carcinomas which, by far, account for between 40% and 53% of the total transplant patient malignancies (Kasiske BL, 2000).

Depression is another complication which occurs early after transplantation in the kidney transplant population and has been associated with the use of prednisone immunosuppression. It is occurring in over 45% of recipients. With one particular study reporting a suicide rate of 24 per 100,000 patient-years in kidney transplant recipients which is 84% higher than the general population (Kurella et al., 2005).

Many post renal transplantation infections remain a significant cause of morbidity and mortality among kidney transplantation recipients. Additionally, augmented immunosuppression may occur after graft dysfunction or chronic rejection consequently increasing the risk for viral infections. Infections are the second to cardiovascular events in the common causes of death in renal transplant recipients despite prophylactic therapy against common pathogens. The U.S. Renal Data System (USRDS) indicate that infections occurred at a rate of 45 per 100 patient-years in initial 3 years' post transplantation (Snyder et al., 2009).

1.3 Lower Limb Edema after Kidney Transplantation

Edema is defined as the swelling that is caused by accumulation of fluid in the spaces around various tissues and can occur nearly anywhere in the body after kidney transplantation. Some of the most common forms of edema include the peripheral edema which affects the upper

or lower limbs, intraabdominal ascites, pleural effusion around the lungs and lastly pulmonary edema. Peripheral edema is uncomfortable to most patients and may lead to more severe conditions after kidney transplantation. (Richard, 2016).

1.3.1 Pathophysiology

Water and solutes of low molecular weight such as salts move between the intravascular and interstitial under the primary control of plasma colloid osmotic pressure and the opposing effect of vascular hydrostatic pressure. The outflow of these fluids from the microcirculation arteriolar end into the interstitium is nearly balance to inflow at the venular end. However, the interstitium may be left with a small residual amount of fluid which drains into the lymphatic vessels to return to the bloodstream through the thoracic duct (Dongaonkar et al., 2009) (Figure1).

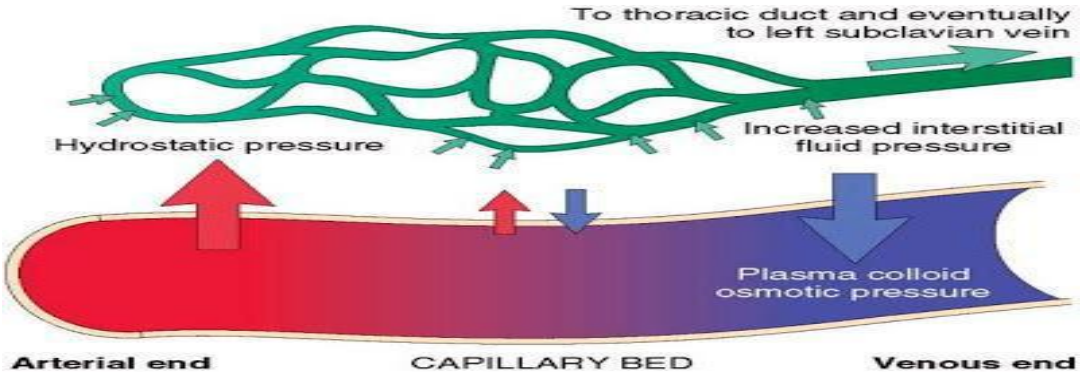

Figure 1: Either increased capillary pressure, diminished colloid osmotic pressure or inadequate lymphatic drainage can result in an abnormally increased interstitial fluid i.e. edema.

Source: www.medicinehack.com/2012/10/edema-definition-pathophysiology-causes.html?m=1

1.3.2 Causes of Edema after Kidney Transplantation

Lower limb edema after a kidney transplant is commonly experienced by post- kidney transplant surgery patients. Most patients experience edema at their ankles and legs after kidney transplant because they are exposed to large fluid volume infusions. After a successful kidney transplant, it takes the patient's body time to adjust to the new kidney. Also, the lower limb edema, which is usually located on the side similar to the renal transplant, results from the action of renal transplant through the compression of iliac vein in combination with the collection of peri-renal fluid and potential obstruction from ligated iliac lymphatic trunks.

1.4 Intermittent Pneumatic Compression Device and Compression Stocking (And Their Role in Deep Vein Thrombosis and Lower Limb Edema)

Deep vein thrombosis prophylaxis mechanical methods have gained extensive acceptance over the last three decades for surgical patients and are becoming more popular across various geographical locations (Prandoni, 2004). However, intermittent compression devices exist in a great range of forms, but they lack broad understanding of the relative efficiency of specific systems. However, all systems depend on periodical deflation and inflation of a pump in form of air bladders within cuffs that are wrapped around the limb. The cuffs can either wrap the calf, the feet, or a whole limb and will inflate uniformly or sequentially according to the specified pressures that determine if rapid or moderate inflation rates are to be followed. These different attributes naturally have cost implications, and, more importantly, possible influences on patient compliance, which is critical with these methods of prophylaxis; the longer they are used, the better the protection. Therefore, it is important, when choosing a system for patient care, to understand the hemodynamic reasoning behind its attributes, the validity of those claims, and any medical implications, before cost and compliance are considered (Geerts, 2001).

The cuff and pump borrow innovations and design from fluid dynamics and blood flow analysis. The link between DVT and blood flow velocity and the comprehensive studies in the field date a century and a half back since the ages of Rudolf Virchow who initially defined blood flow velocity and the subsequent pulmonary embolism risk, in addition to offering a description of the causal factors afterwards. Additionally, the hypercoagulability, vessel damage, and stasis are still among the recognized thrombogenesis influences. However, stasis prevention was the ultimate lead to the intermittent compression for prophylaxis of the development of deep vein thrombosis (Wicklin, 2011).

The main purpose of all intermittent compression systems is to squeeze blood from the underlying deep veins that will be displaced proximally assuming that the valves are competent. The veins refill during cuff deflation and the intermittent nature of the system and adequate supply will guarantee periodic blood flow through the deep veins. Doppler ultrasound easily determines the peak velocity, percentage augmentation, and duration; which are pulse of flow properties, are a source of competition between compression devices.

A study by Wilson, et al. (2005) demonstrates the effectiveness of intermittent pneumatic compression (IPC) devices as thromboprophylactic devices. The study further revealed that IPC and TED stockings are important in edema and deep vein thrombosis management. Most pneumatic compression devices are designed in form of plastic sleeves enclosing the whole limb or foot which leads to compliance and comfort challenges (Comerota, Katz, & White, 1992). In addition to requiring a pump, the device weight, size, an external power source, and attached tubing also limit the IPC devices application (Wilson et al., 2005).

Imaging studies demonstrate a rate between 4.5% and 43% despite the risk for clinically relevant thrombosis in a cast not being established clearly the past literature studies in which

case prophylaxis must be considered (Testroote, Stigter, de Visser, and Janzing, 2008). However, the most appropriate prophylaxis is yet to be established and a chemical agent may have to be applied over time in the plaster especially when there are signs of effect (Roberts, 2012). Mechanical methods would be more appropriate for patients with a risk of bleeding, especially soon after surgery or injury; on the other hand, traditional mechanical methods are not practical for patients in a plaster cast.

Most modern intermittent devices pump blood from lower-extremity vessels in an automated mode with sequentially deliverance of compression up the limb, producing a wavelike milking effect to evacuate leg veins with regular compression cycle. A microprocessor controls air pressure and direction into segmental diaphragms secured around the leg for a fixed period of time (Kendall Healthcare Products Company, 1995). However, various reports consistently show that all IPC devices produce changes in femoral vein velocity. The typical maximum velocities achieved following the compression of calf and/or thigh at pressures around 40 mm Hg would be 35–60 cm/s with maximum compression velocity compared with maximum velocity stabilizing at a range of 50–250% (Whitelaw et al., 2001) (Figure 2).

Notably, the venous blood flow is *variable* and resting blood flow in the femoral vein varies between different people (Fronek et al., 2001) in addition to varying in a single subject over time as a result of natural limb inflow fluctuations (Lewis et al., 1986). The flow pattern will change with respect to the particular physiology and posture. However, breathing and the cardiac cycle modulate the flow to differing extents (Abu-Yousef et al., 1997). In addition, venous blood pressure varies chronologically which means that the velocity results from a particular pump and for a particular individual will also vary over time.

Improper fitting, inappropriate use of device, peroneal nerve injury, discomfort, excessive heat and sweating under the inflatable cuffs are some of the limitations of IPC devices. Furthermore, the device size, weight and external power source requirements contribute to poor compliance and fall risks due to attached chords which limit the efficacy of IPC devices (Wright et al., 2010).

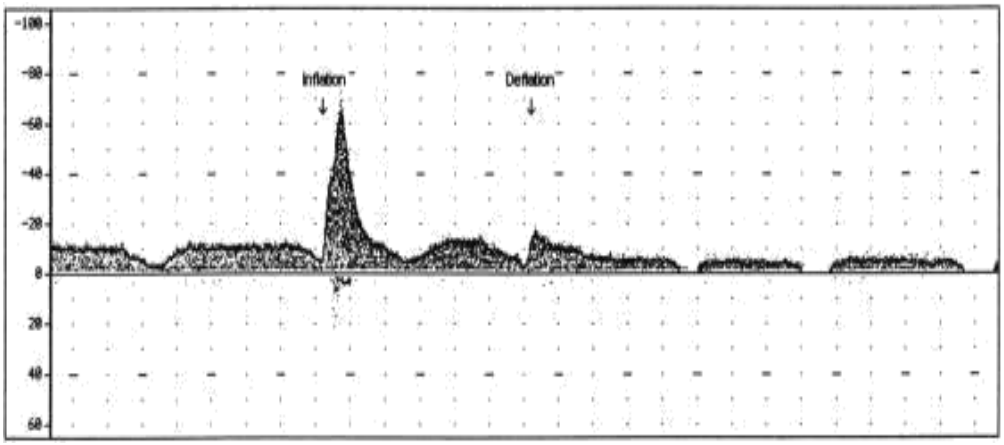

FIGURE 2: Venous blood flow velocity in the femoral vein during compression by a two-bladder graduated sequential thigh-length cuff (velocity [cm/s] vs. time [1 second per vertical dotted line]. Source: www.medscape.com

1.5 Compression Stockings

These are specialized hosiery wearable stockings which help in prevention of, and reduction of further progression of venous disorders such as phlebitis, edema, and venous thrombosis (Miramar, 2004). These elastic garments are worn around the lower limb with an intention to compress it thus reducing the diameter of distended veins while simultaneously raising venous blood flow velocity and valve effectiveness. Compression therapy helps in decrease venous pressure and consequently preventing venous stasis and venous wall impairments while relieving pain and perceived weight of the legs (Meissner et al., 2007). They are tightest at the ankles with gradual constrictive reduction toward the knees and thighs. They force circulating blood through narrower channels through compressing the surface veins, arteries and muscles. Consequently, the pressure of the arteries carrying blood to the heart increases than that of blood flowing through the limbs. This increases the blood flow to the heart. Compression stockings exist in two forms; anti-embolism and gradient.

Gradient Compression Stockings

Gradient compression stockings are designed to reduce and manage impaired "musculovenous pump" performance which results from incompetent limb vein valves. They are designed in such a way that the compression level is the highest around the ankle with gradual decrease towards the top of the hose. They are recommended for people prone to leg edema, blood clots, and blood pooling in the lower limbs and feet as a result of prolonged sitting or inactivity periods. These stockings often address lymphedema, thrombosis, cellulitis, and other post-transplant complications (Blattler et al., 2008).

Prior to using compression stocking cautionary steps need to be taken. A patient's ankle brachial pressure index (ABPI) must be greater than 1.0 per limb; otherwise the stockings may

interfere with the patient's arterial flow. The ankle brachial pressure indicates the level of unobstruction on the patient's limbs' arteries (Marston et al., 2003). It is also necessary that compression stockings are properly sized in relation to limb size. The compression should gradually reduce from the highest compression at the ankle's lower section to ultimately obtain a 70% reduction of pressure just below the knee (Partsch et al., 2008).

Anti-Embolism Compression Stockings

These stockings are commonly referred to as Thromboembolism Deterrent (TED) stockings hose that are used for venous and lymphatic drainage support and that are intended to exert mild pressure on lower limbs to prevent blood clotting and often support the venous and lymphatic drainage systems within the lower limbs. Anti-embolism stockings exert a distributed compression force at the ankle and up the leg in the same way as gradient compression stockings. When combined with the calf's muscle pump effect, this compression aids in circulating blood and lymph fluid through the lower limbs especially in non-ambulatory patients (Blattler et al., 2008). The compression degrees or levels are divided into Mild <20 mmHg, Moderate ≥20–40 mmHg, Strong ≥40–60 mmHg, And Very strong >60 mmHg (Partsch et al., 2008).

Table 1 below gives a general guide to the recommended amount of compression for various indications. Patient factors and the underlying disease process determine the ideal sub-bandage pressure (mmHg) required for therapy. The stocking pressure is directly related to the number of layers applied the tension while indirectly related to the leg circumference and the bandage width (Thomas S, 2003). The application technique and the sub-bandage pressure are dependent on both the skill of the person applying the bandage and the bandage type. The final sub-bandage pressure, however, depends on the tension of application.

Degree of Compression	**Indication (Use)**
<20 mmHg	• Prevention of deep vein thrombosis (graduated compression stocking) • Treatment of mild edema • Relief for tired, aching legs (occupational leg symptoms)
20–30 mmHg	• Treatment of mild varicose veins • Treatment of mild to moderate edema • Relieving fatigue after long-haul flights (>4 hours, high-risk patients for deep vein thrombosis) • Treatment of varicose veins during and after pregnancy
30–40 mmHg	• Treatment of venous ulcers (including healed ulcers) • Treatment of deep vein thrombosis • Treatment of superficial thrombophlebitis • Following venous surgery and sclerotherapy • Treatment of varicose veins with severe edema and/or skin changes • Treatment of post-thrombotic syndrome • Treatment of mild lymphedema
>40 mmHg	• Treatment of severe lymphedema • Treatment of severe chronic venous insufficiency

Table 1: Guide to recommended compression for various indications.

Adopted from www.nps.org.australian-prescriber/articles/compression-therapy-for-venous-disease

If the calf muscle pump is ineffective or ankle mobility is limited, then the effect of compression therapy is limited irrespective of the compression method. The variable ankle mobility and calf muscle function have a likelihood of accounting for much of the variability in the compression therapy success (Bolton L, 2008).

1.6 Summary

Numerous currently available systems can utilize a wide range of various compression sequences and techniques in despite intermittent pneumatic compression (IPC) being is an established method of deep vein thrombosis (DVT) prophylaxis and edema treatment in the legs. However, overall system performance and the physiological effects of specific variables should be critically and objectively analyzed in order to make suitable choices that will provide the maximum patient protection.

1.7 Neuromuscular Stimulators and Their Role in Deep Vein Thrombosis Prevention in Lower Limb Edema

National Institute of Clinical Excellence (NICE) has approved the NeuroMuscular ElectroStimulation (NMES) for prophylaxis against deep vein thrombosis (DVT). According to various credible evidences, neuromuscular stimulators and electrical stimulation have been found to be very clinically effective in reducing the incidence of deep-vein thrombosis (Kaplan, Czyrny, Fung, Unsworth, & Hirsh, 2002; Browse & Negus, 1970; Lindström, Holmdahl, and Jonsson et al., 1982). However, the considered studies which involve direct electrical muscle stimulation do not necessarily lead to the adoption of effective and easy to use devices that

would enhance blood flow in the lower limb. The high intensity discomfort levels experienced by many patients who use the direct electrical stimulation devices to the muscle attribute to the high levels of failure to adopt Electrical stimulation. Their batteries for are irreplaceable and last slightly over 24 hour's thus requiring daily replacement of the device. The cost of the devices, is approximately $20 USD and its daily replacement, is also a challenge to many low-income individuals. Such devices are often rather cumbersome, and may require chords, and they may be incompatible with use of a normal plaster cast or ambulation as is the case with Intermittent Pneumatic Compression (IPC) devices in edema management (Sluka & Walsh, 2003). Studies show that the electrical stimulation of the lower limb muscles is effective in improving the flow in the legs (Sluka et al., 2003).

1.8 Geko™ Device and Its Role in DVT Prevention and Lower Limb Edema

Promoting venous blood flow is necessary in treatment of the leg edema but may it be difficult to conduct in patients with comorbidities through the use of traditional mechanical compression devices or limb elevation. The Geko™ device is a self-powered neuromuscular stimulation device that is attached above the skin over the common peroneal nerve in the legs (Figure 3). Geko™ device emits low-voltage that creates stimulus which in turn activates the lower limb musculature thus improving superficial femoral vein velocity and blood flow (Figure 4). Chronic wound healing and pain reduction is also achieved through its use. Despite being expensive, Geko™ has relatively welled toleration rates and can be used to provide alternative treatment for edema. The Geko™ device has no known side effects when used according to instructions apart from minor skin irritation and rash.

Improving venous blood flow an effective method of treating leg edema and can be achieved through limb elevation irrespective of the etiology (Abu-Own A et al., 1994), activation of the leg's calf muscle pump (Kan et al., 2001), regular ankle plantar flexion exercise (Padberg FT et al., 2004), and intermittent pneumatic compression (IPC) devices as well as other traditional mechanical devices like compression garments (O'Meara S et al., 2009).

Unfortunately, patients suffering from contraindications to adequate compression such as peripheral arterial insufficiency, those having skin infections, as well as patients with comorbid conditions that limit movement of the legs cannot benefit from these treatment methods (Partsch et al., 2008). It is notable that current mechanical compression devices may induce discomfort in addition to their difficult application procedures which decreases compliance (Comerota AJ, 2011)

Transcutaneous direct muscular stimulation method can be used in treating edema by improving venous blood flow (Clarke et al., 2012). Transcutaneous direct muscular stimulation device promotes venous blood flow and stimulate the calf muscle pump by creating electrical stimulation by use of electrodes applied to the skin (Kaplan et al., 2002). However, results may vary in relation to voluntary ankle contraction (Breen PP et al., 2012). These devices are not popular in routine clinical use due to discomfort created by their high voltage. However, Geko**TM** device has gained popularity as an alternative to direct electrical muscle stimulation (Tucker A et al., 2010). Geko**TM** device delivers a low-voltage stimulus at a low frequency (1 Hz), which activates the musculature of the legs with little discomfort. Additionally, it considerably increases blood flow and velocity in the superficial femoral vein (Breen PP et al., 2012) while providing a possible tolerable and safe method for lower limb edema treatment.

The Geko™ device is greatly advantageous over other stimulation devices due to its compactness, portability, ease of application, and an in-built power source lasting over 24hours. Its tolerability and potential clinical utility is well assessed in cohorts of healthy volunteers (Broderick BJ, 2010), including use by individuals wearing below-knee plaster casts, and has shown potential for use limited space conditions where other IPC devices fail to apply.

1.8.1 Mechanism of Action of the Geko™ Device

Geko™ device is a non-invasive On-Pulse™ technology powered device that works by stimulating patient's calf muscles to increase blood circulation. It activates the muscle pumps of the lower limb through creating a small electrical impulse that in turn triggers the common peroneal nerve which improves pumping of blood in veins leading back to the heart. Geko™ device is a self-adhesive and well-designed device which can be wrapped around the leg, below the crease of the knee. It is ideal for person requiring reduction of blood stasis and increased circulation on the legs. The device improves the flow of blood while prevents venous thrombosis through direct post-surgical stimulation of the leg muscles.

1.8.2 Benefits

The device lowers venous thromboembolism risk by managing venous stasis. It also aids in good patient adherence due to the ease of application thus facilitating faster surgery patient recovery. Due to its comfort and ease of application, patient will retain their mobility and independence which ensures self-sufficiency and wellbeing. It observes minimum skin contact which reduces cases of skin breakdown, irritation, and unnecessary sweating. It delivers venous thromboembolism prophylaxis experience to patients who have a challenge in using the normal

venous thromboembolism prophylaxis. Its increased speed of patient recovery potential helps in eliminating lengthy hospital stay through reduction and prevention of subsequent complications such as edema (Broderick, O'Briain, Breen, Kearns, & Olaighin, 2010; Breen, Galvin, Quondamatteo, Grace, & ÓLaighin, 2012).

Figure 3: Geko**TM** device (left), with the device in use on the right. Source: *www.geko*[TM]*devices.com/enun/technology/specifications/neuromuscularstimulations-geko*[tm]*-t-1/*

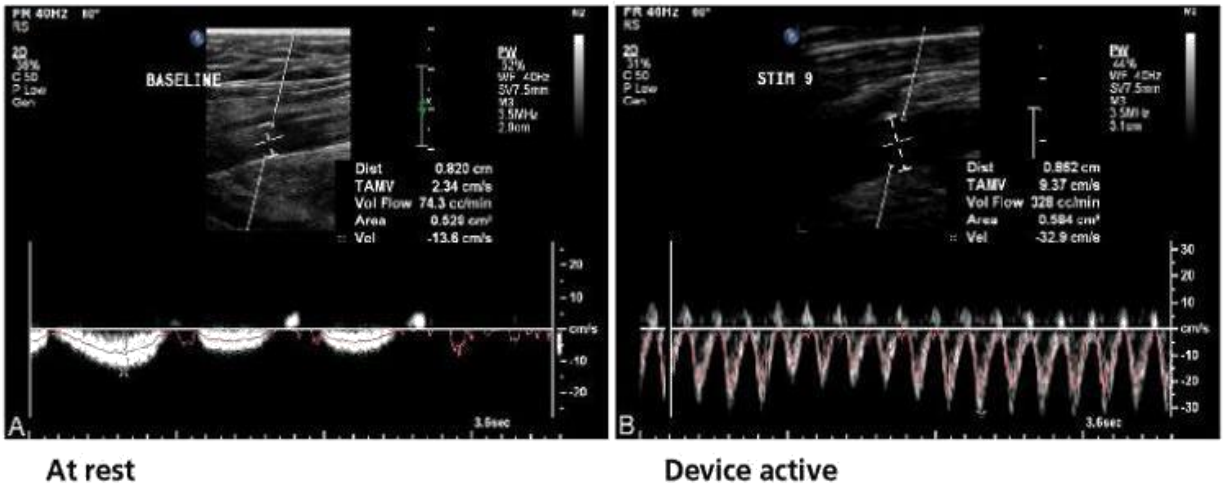

Figure 4: Ultrasound comparison showing the superficial femoral vein at rest and with the device active at 1Hz. *Source: www.geko™ devices.com/en-us/studies/neuromuscular-electrostimulation-dvt-prophylaxis–nmes-studies-and-trials/blood-supply-augmentation-in-the-leg/*

1.9 Rationale for the Proposed Study

Numerous complications such as edema are associated with kidney and pancreas transplantation. Additionally, intermittent pneumatic compression devices (IPC) used in deep vein thrombosis and lymphedema treatments are not yet fully understood. However, their use is promoted by their undisputed hemodynamic effects. However, it is evident that IPC devices cause increase of velocity and volume of the venous flow through the femoral and/or popliteal veins. There is a further significant increase in the flow within the popliteal artery which has been previously reported while using IPC devices on patients suffering from critical limb ischemia. However, there are limitations of using the IPC device which include probable peroneal nerve injury, difficulty in fitting around the designated limb, inappropriate use of device, discomfort experienced by the patients, and unnecessary sweating and rise in temperature under the inflatable cuffs. Additionally, its weight, size, and external power source requirements and additional chord requirements contribute to poor comfort levels, acceptability, lack of proper compliance, and risk of falls which limits the efficacy of IPC devices.

Electrical stimulation of the calf muscle pump has been proved to effectively and significantly reduce the perioperative and postoperative deep venous thrombosis (DVT) risk while simultaneously lowering the limb edema. Nevertheless, high currents applied to induce mechanical stimulation of the muscles leads to induction of pain which limits its practical use and reduces comfort.

In this regard, a new improved, portable, easy to use, and internal-powered calf stimulator known as the Geko^{TM} device (Firstkind Ltd, Sky Medical Technology, and Cheshire, United Kingdom) was developed to address the problems of the traditional stimulators. It is comfortable, easy to apply and use and its reduced discomfort and pain improve patient

compliance and acceptance. Past hemodynamic research indicates that the device provides a significant increase in volume flow and velocity of blood and enhanced skin capillary blood flow. The significant increase in comfort, acceptability, and satisfaction level of patients, in addition to ease of use, enhance its preference and potential use in clinical settings such as kidney and pancreatic transplantation, where patients are prone to severe lower limb edema from the infusion of large volumes of fluid following transplantation. Edema management has traditionally been carried out by walking and workouts. However, challenges occur in cases of bedridden or minimally mobile patients where the natural, traditional therapy cannot apply.

Although various studies have shown that the Geko ^{TM} device leads to an increase in flow of blood in the lower limbs equivalent to 60% of the levels which would be seen in continuous walking, no study has evaluated its efficacy compared to standard TEDS and SCD in transplantation.

1.10 Aim of the Study

The study aimed to examine the effect of Geko^{TM} device on post kidney and pancreatic transplantation leg edema. It was being conducted in a randomized controlled trial which involved kidney and pancreas transplant patients from the onset of the transplant through the recovery process. Patients were been randomized to one of the two groups; group 1: standard of care IPC and TED stockings to aid in blood circulation after the transplant, while group 2 will fitted with the Geko^{TM} device post-transplant. Various components of patient clinical outcomes and satisfaction were then evaluated and compared between the two groups.

1.11 Research Question

The following research questions were posed in conducting the study:

1. What is the effect of Geko^{TM} device on post kidney and pancreatic transplantation leg edema?
2. What are the clinical outcomes observed between patients who receive routine medical therapy with IPC/TEDS versus the Geko^{TM} device?

1.12 Hypothesis:

We hypothesized that the use of the neuromuscular electric stimulation device (Geko$^{\mathbf{TM}}$) will achieve decreased lower limb edema, improved clinical outcomes and better patient satisfaction scores compared to standard IPC and TED stockings following transplantation.

Chapter 2

2.1 Study Design and Methodology

The current study employed a prospective, single-centered, controlled, and randomized investigator-initiated design in evaluating clinical outcomes on patients using either the Geko^{TM} device or standard TEDS and SCD following kidney and kidney/pancreas transplantation. Patients were first supplied with written consent before being enrolled into the study and enrolled prior to the transplant operation and randomized to either treatment group (Figure 5). The randomization process is carried out by flipping a coin to ensure equal chances of placement within either group with those falling under the tail outcome being placed in the Geko^{TM} device group while those falling under the head outcome shifting to the IPC+TED group. Patients were assigned numbers, and the list stored in a centralized location in our research office indicating the assigned group of the patient. At the time of surgery, both groups of patients were placed on TEDs and SCD. On post-operative day 1, patients were placed in their assigned groups: patients randomized to the Geko^{TM} arm were fitted according to manufacturer's instructions. If patients fell into the standard TEDS and SCD arm of the study, they were left earing them. However, if patients adversely responded to the Geko^{TM} device, they were transferred to the IPC+TED stockings group at the initial stage. The Geko^{TM} device was removed and replaced daily in patients. Both groups of patients were followed following surgery for six days after surgery on daily basis and at precisely the same time. Patients were normally discharged on the sixth day.

The inclusion criteria for the study included patient's written consent, age (where a patient should be above 18 years), and Body Mass Index (BMI) which should be between 18 and 34. Additionally, the patients should be recipients undergoing either pancreas or kidney transplant, and there should be no known peripheral vascular ailments.

The exclusion criteria were as follows: age younger than 18 years, patients with history of deep vein thrombosis, contraindications to use of the device as listed on the manufacturer's safety sheet, patients who have previously undergone leg amputation and patients with intra cardiac defibrillators. In addition to these, the patient could be excluded for having a BMI of more than 36, possessing neurological disorder history or any ailment potentially hindering proper assessment, having presence of stimulators such as implantable brain, or inability to tolerate Geko^{TM} device stimulation.

2.2 Ethics approval

The research was approved by the University of Western Ontario Research Ethics Board. Every recruited patient was served with a written informed consent and made aware of freedom to withdraw from participation at any time and were assured that it would in no way affect the management or care they received.

2.3 Primary and Secondary Endpoints

2.3.1 Primary end points

The primary intent of the study is to assess patients' lower limb edema after surgery and patients` satisfaction with the Geko^{TM} device and IPC+TED stockings following transplantation. Measurements were made with a measuring tape whereby the thigh and calf circumference within 15cm above or below patella's midpoint were evaluated in order to assess lower limb edema. The difference in circumference between the 1st and 6th days reflects lower limb edema assessment from admission to discharge day were recorded for further analysis.

In regard to this assessment,

- Change in circumference = difference in leg (below the knee) circumference between 1st and 6th days.

- Difference in thigh circumference = difference between 1st day and 6th day thigh circumference (above the knee)

The following one page questionnaire was used to assess patient satisfaction with the use of the devices on the 6th day post-transplant. There are six questions which relate to leg swelling, device comfort during the period, the intent to use the device in case of future surgeries, and the influence of the devices on mobility and sleep.

1. To which random group where you placed

-IPC+TED stockings - Geko^{TM} Device (Check one)

2. How comfortable are the devices

- Extremely comfortable
- Moderately comfortable
- Average
- Moderately uncomfortable
- Extremely uncomfortable

3. What is the extent of the leg swelling

- Extremely increased
- Slightly increased
- No change
- Slightly reduced
- Extremely decreased

4. What was the device's influence on sleep patterns

- Extremely positive
- Moderately positive
- No effect
- Moderately negative
- Extremely positive

5. What is the device's mobility after surgery

- Extremely difficult
- Moderately difficult
- No change
- Moderately easy
- Extremely easy

6. Would you want to use the same device if you had another surgery

- Yes
- No

Table 2: Questionnaire to assess patient satisfaction with the use of the various devices.

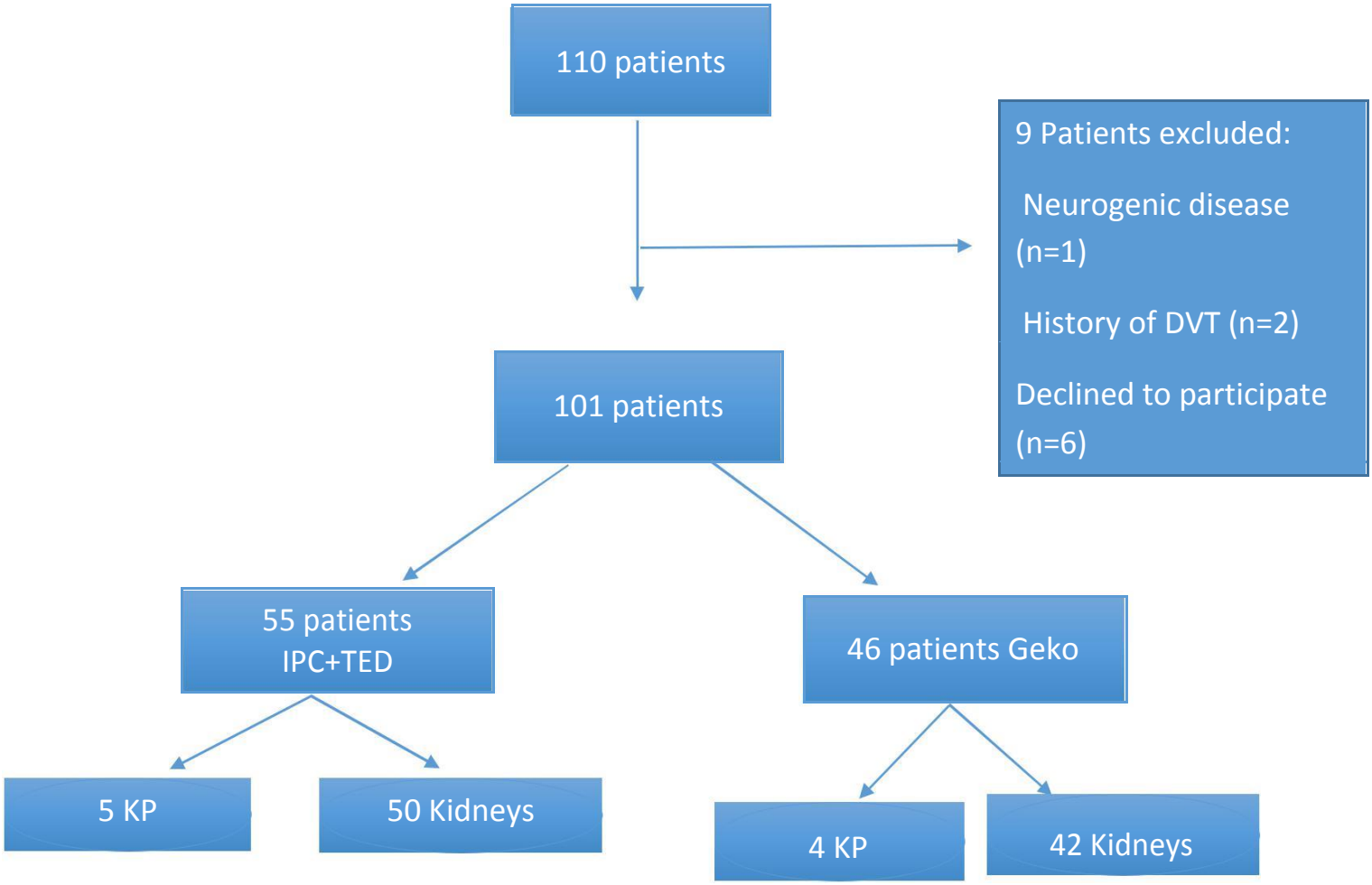

Figure 5: Flow diagram of participants in the study. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent; KP: Kidney and Pancreas; DVT: Deep Vein Thrombosis.

2.3.2 Secondary Endpoints:

A number of secondary endpoints were carried out including assessing post-transplantation weight by evaluating weight changes from day of admission through to discharge day. Every patient also underwent screening for subclinical deep-vein thrombosis (DVT) through ultrasound of the legs at the fifth day following transplantation. Total daily urine output was measured and recorded across every patient individually from transplant day to discharge day. Kidney functionality was assessed through serum creatinine and eGFR assessments at discharge day and at 21 days following transplantation. Doppler ultrasound was used to measure velocity at the femoral veins on day 5 post-transplant. Lastly, Doppler ultrasound was used to measure resistive index of transplanted kidneys at day one and five after transplant to evaluate whether or not there was an increase in renal capillary perfusion parameters with either technique.

Of note, two actions occur to promote blood flow using the Intermittent Pneumatic Compression (IPC) by inflation and deflation. Inflation increases the pressure on the limb which forces blood and other fluids out the blood vessels towards to heart, whereas deflation lowers pressure on the leg which facilitates the refilling of the vascular fluids in the leg vessels.

A Doppler ultrasound scan was conducted when the patient is not in motion and it revealed blood movement as a wave of peaks and troughs relative to the breathing pattern of the patient. Compilation of these scans and plotting them with the help of the built-in software gave us a pattern that was used to compute the average flow of blood during a particular duration by calculating the area under the curve. The IPC device takes about a minute to inflate and deflate which is too long for the instrument to make a single calculation over a single measurement. In this regard, two recordings were made with one being the flow of blood during inflation, labelled

F1, with the time it takes for the flow denoted as T1. The second recording which is in the opposite cycle involves measuring blood flow during deflation which is labelled F2 and the duration denoted T2. Summated values during the flow are obtained through making the following calculation:

$$\text{Total blood flow} = \{(T1/BT \times F1)\} + \{(1-(T1/T2)) \times F2\}$$

2.4 Statistical Analysis:

GraphPad Software was used to conduct a statistic analysis using a Students' T-test for independent groups where $p < 0.05$ representing the point of statistical significance. Additionally, all data in the following figures is reported as mean +/- standard deviation (SD).

Chapter 3

3.1 Results

The duration of recruitment took one year and involved a total of 101 patients. However, nine of the patients were excluded for failing the inclusion policy stated above. Of the excluded patients, one patient suffered from a neurological disorder; two had histories of venous thromboembolism, while six of them were not explicitly willing to participate in the study.

Characteristic	**Intermittent Compression Device + TED Stocking**	**Geko Device**
Number of Recipients	55 Patients	46 Patients
Age (Years)	46.2±12	47.7±13
Gender: Male Female	33 22	25 21
Body Mass Index	26.2±4	25.4±6
Weight	88.3±6	87.5±4
Type of Dialysis: HD PD Preemptive	41 10 4	37 4 5
Type of Surgery Kidney+Pancreatic Kidney	 5 50	 4 42

Types of Donors		
LD	14	13
NDD	26	19
DCD	15	14

Table 3: Patient characteristics. LD: Living donor; NDD: Neurological determination of death DCD: Donation after cardiac death; HD: Haemodialysis; PD: Peritoneal Dialysis.

3.2 Primary End Point Results:

3.2.1 Lower limb edema:

Transplantation led to an overall increase in the circumference of the lower legs of both groups of patients due to significantly increased fluid administration. However, this increase was significantly greater in the IPC+TED stockings group by an average of 2.3 +/- 2.1 cm, whereas the Geko^{TM} group had an increase of 0.25 +/- 1.2 cm ($p<0.001$). Additionally, the thigh circumference increased by 2.5 +/- 2.3 cm in the IPC+TED stockings group and by 0.5 +/-0.8 cm in the Geko^{TM} groups ($p<0.001$), respectively (Figures 6 and 7).

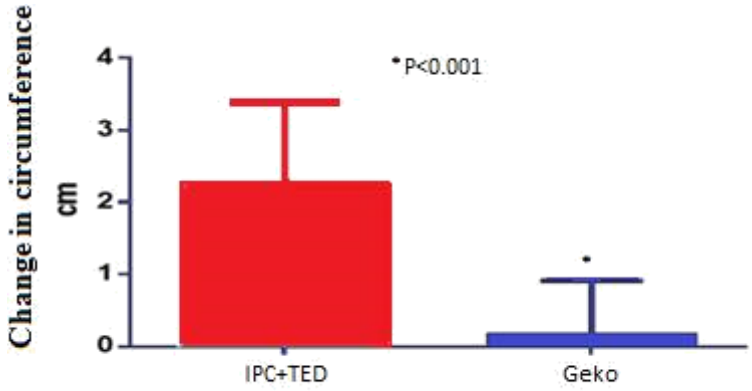

Figure 6: Change in lower leg circumference following transplantation using IPC+TED or the Geko^{TM} device for 6 days following transplantation. Data are expressed as mean +/- standard deviation with *p<0.001. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

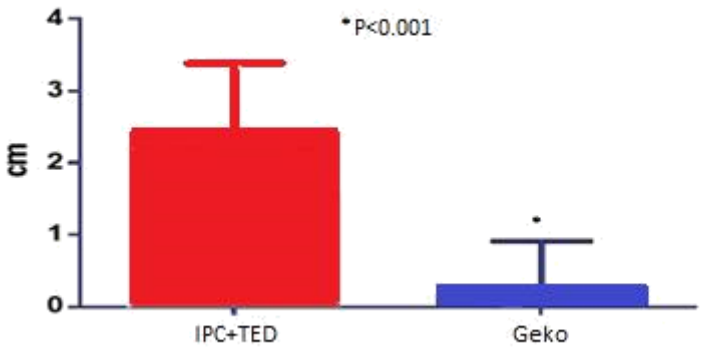

Figure 7: Change in thigh circumference following transplantation using IPC+TED or the Geko™ device for 6 days following transplantation. Data are expressed as mean +/- standard deviation with *p<0.001. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

3.2.2 Patient satisfaction:

The answers from patients in both arms were recorded and presented as follows:

Question 1: How comfortable are the devices?

Of the 101 participants, 55 took part in the IPC+TED study while 46 were fitted with Geko^{TM} device. When level of discomfort was evaluated in TED+IPC patients, 57% reported some level of discomfort, 29% reported no effect on comfort and 14% reported comfort. In contrast, the reports were skewed towards being more comfortable in the Geko^{TM} arm with 13%, 23%, and 64%, being responses for discomfort, no effect on comfort, and comfortable, respectively. The Pearson Chi-square showed that there is a significant difference in comfortability between the two groups ($P<0.003$).

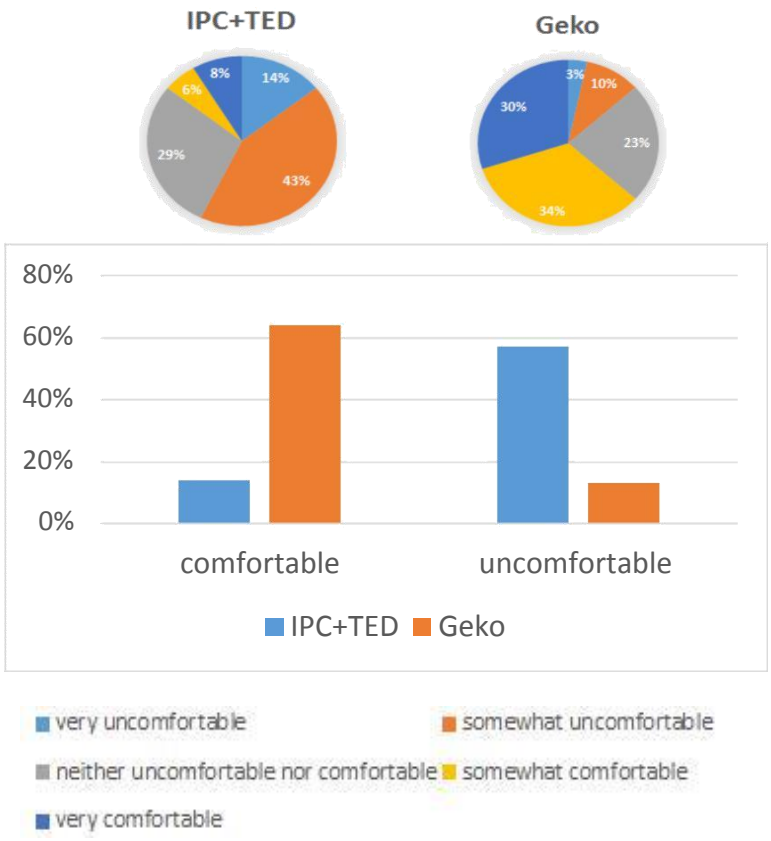

Figure 8: Comfort level following fitting of IPC+TED or the Geko ^{TM} device for 6 days post transplantation (P<0.003). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent

Question 2: What is the extent of the leg swelling?

When perception of leg swelling was evaluated, 52% of IPC+TED patients had an increase in leg swelling, 17% had no change, and 31% recorded a decrease in swelling while Geko^{TM} device participants recorded 22%, 30%, and 48%, respectively for the same questions. This suggests that patients who wore the Geko^{TM} device had the perception of improved leg edema compared to those patients who were on standard therapy. The Pearson Chi-square showed that there is a significant difference in the leg swelling between the two groups ($P<0.001$).

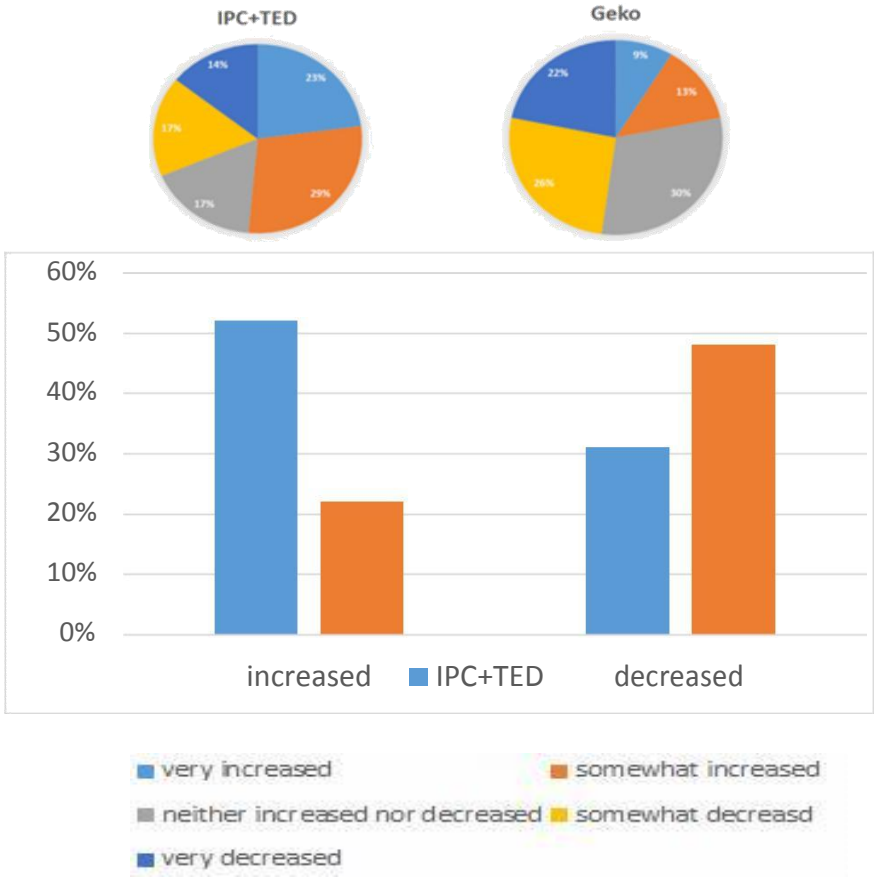

Figure 9: Extent of swelling following fitting of IPC+TED or the Geko ^{TM} device for 6 days post transplantation (P<0.001). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

Question 3. What was the device's influence on sleep patterns?

When asked about their sleep patterns, 49% of IPC+TED participants indicated no change in sleep patterns compared to 50% in the Geko™ arm. However, 31% reported a negative change in the IPC+TED compared to only 16% in the Geko™ group. Interestingly, 20% of patients reported that they had an easier time going to sleep in the IPC+TED group whereas this number was 34% in the Geko™ arm. The Pearson Chi-square showed that there is a significant difference in device's influence on sleep patterns between the two groups ($P<0.02$).

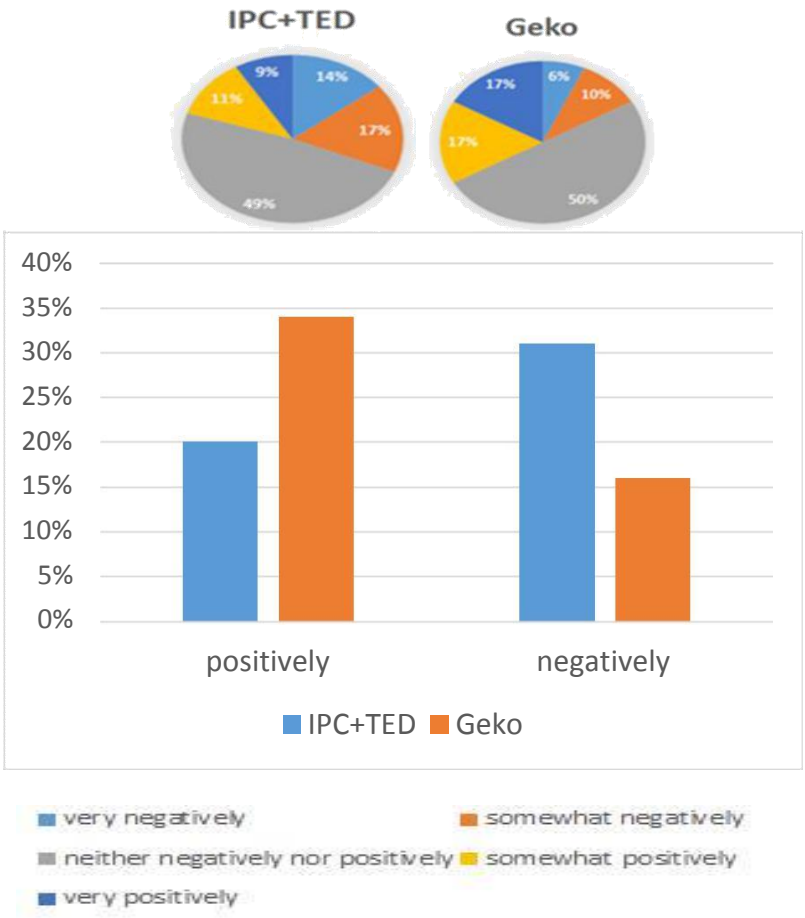

Figure 10: Influence on sleeping pattern following fitting of IPC+TED or the Geko ™ device for 6 days post transplantation (P<0.02). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

Question 4: What is the device's mobility after surgery?

After undergoing surgery, 29% of patients fitted with IPC+TED reported no effect on mobility while 28% and 43% reported difficulty and improvement in mobility, respectively. On the other hand, Geko^{TM} device created a 10% mobility difficulty with 17% reporting no change effect and 73% reporting a free and improved mobility. This becomes increasingly important in patient mobility after major surgery and could have a significant impact on patient convalescence and length of stay in hospital. The Pearson Chi-square showed that there is a significant difference in mobility after surgery between the two groups ($P<0.001$).

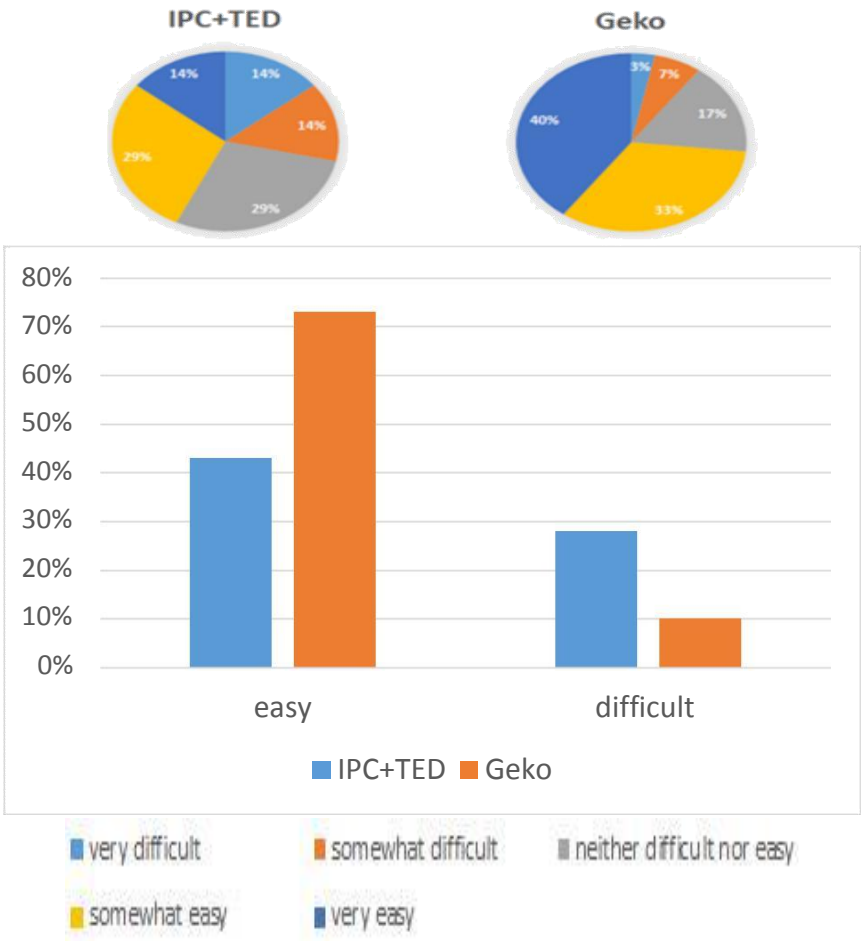

Figure 11: mobility level following fitting of IPC+TED or the Geko ^{TM} device for 6 days post transplantation (P<0.001). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

Question 5: Would you want to use the same device if you had another surgery?

Interestingly, when asked about whether or not patients would like to use the same modality of treatment for another operation, only 57% of IPC+TED participants acknowledged that they would use it in comparison to Geko™ device whose participants gave it 83%.

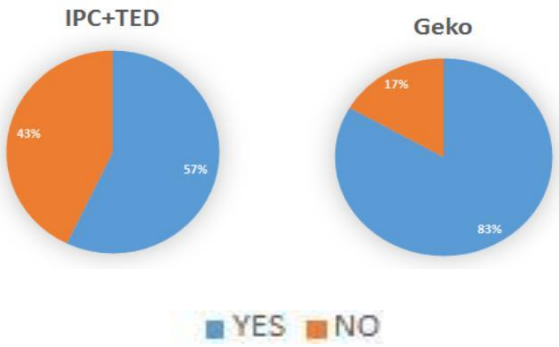

Figure 12: Chances of future use of IPC+TED or the Geko™ device for 6 days post transplantation. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

3.3 Secondary End Point Results:

3.3.1 Femoral vein velocity:

When we evaluated femoral vein velocity on day 5 following transplantation, we observed a 21 +/- 7 cm/s mean femoral vein flow velocity in the IPC+TED arm. In comparison, we saw a significantly higher velocity in the Geko^{TM} group with a value of 28 +/- 8 cm/s ($p<0.04$, Figure 13).

3.3.2 Total urine output:

Urine volume was collected and recorded daily for total of 6 days from the patients. The mean urine output being 8800 cc with a standard deviation of +/- 8 in the control arm in relation to 17900 cc and a standard deviation of +/- 10 in the Geko^{TM} arm. There was statistically significant difference between the IPC+TED arm and Geko^{TM} arm ($P<0.05$, Figure 14).

3.3.3 Measurement of intra-renal resistive index:

We evaluated intrarenal resistive indices in the two groups to determine whether there would be a difference in renal perfusion. We found that neither on post-operative day 1 or on Day 5 was here an observable difference in the resistive index between the control arm and Geko^{TM} arm (Figures 15 and 16).

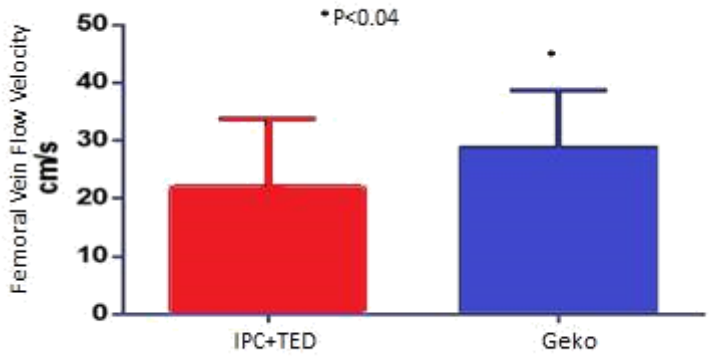

Figure 13: The flow velocity in femoral vein following transplantation using IPC+TED or the Geko^{TM} at day 5 following transplantation. Data are expressed as mean +/- standard deviation with *p<0.04. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

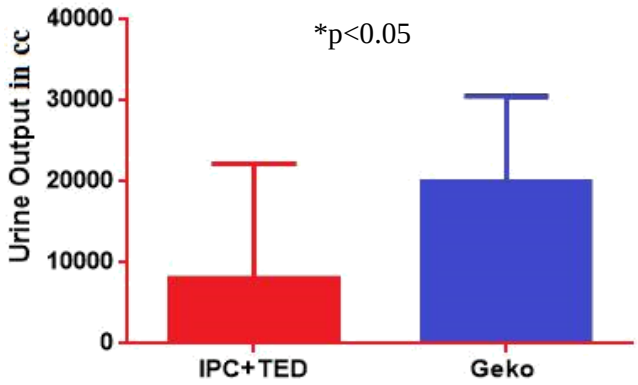

Figure 14: The total urine output following transplantation using IPC+TED or the Geko^{TM} device between 1st and 6th day following transplantation. Data are expressed as mean +/- standard deviation with *p<0.05. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

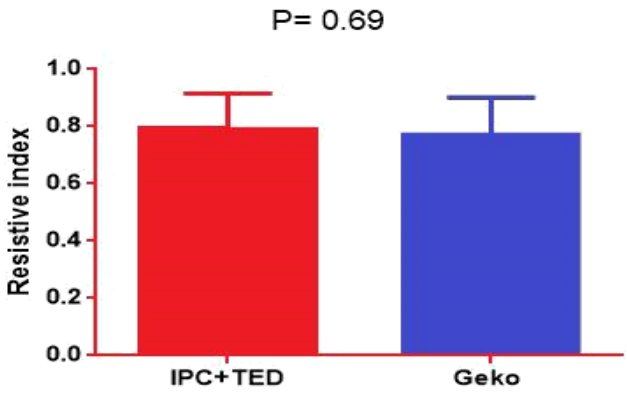

Figure 15: Resistive index following transplantation using IPC+TED or the Geko^{TM} device at day 1 following transplantation. Data are expressed as mean +/- standard deviation with p=0.69. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

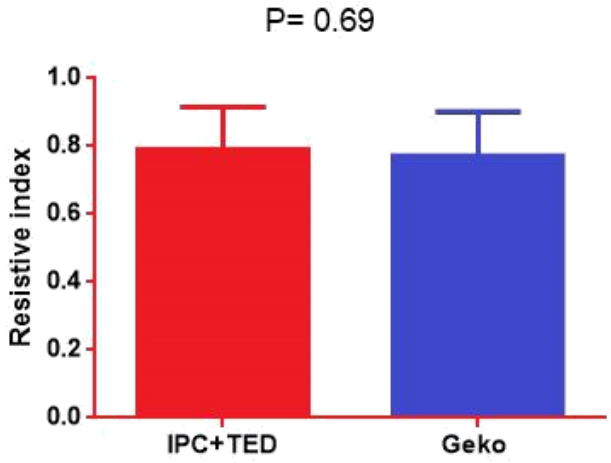

Figure 16: Resistive index following transplantation using IPC+TED or the Geko^{TM} device at day 5 following transplantation. Data are expressed as mean +/- standard deviation with p=0.69. IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

3.3.4 Weight change, kidney function, and subclinical DVT:

Recordings were made concerning changes in weight after transplant, subclinical deep-vein thrombosis (DVT) presence, and kidney functionality 6 and 21 days post transplantation. There was less weight gaining in the Geko^{TM} arm than the control arm (average weight change: +2.5 kg vs +6 kg) but it was not statistically significant (Figure17, p=0.09).

There was a trend of lower creatinine level in the Geko^{TM} arm than the control arm at day 6 in the DCD group (240±36.1 umol/l vs 270±29 umol/l), but it was not statistically significant.

There was no difference in Estimated Glomerular filtration rate (eGFR) at the 6th day between the control arm and Geko^{TM} arm (Figure 18, p=0.98). Also, there was no difference in eGFR after 21 days between the control arm and Geko^{TM} arm (Figure 19, P=0.97). There was no subclinical DVT in both IPC+TED group and Geko^{TM} group.

P=0.09

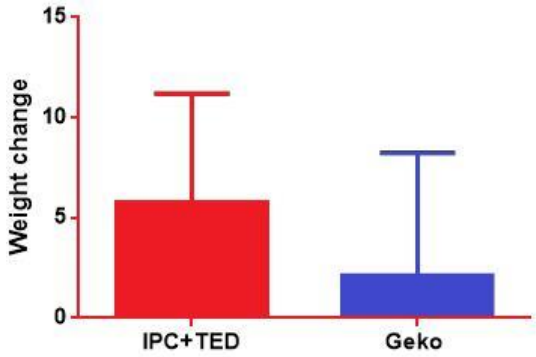

Figure 17: The weight difference between IPC+TED arm and Geko^{TM} arm. There was no statistical significance difference between the Geko^{TM} arm and the Control arm. Data are expressed as mean +/- standard deviation (p=0.09). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

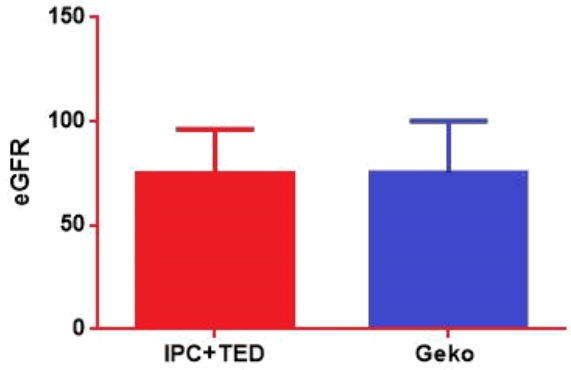

Figure 18: The eGFR at 6th day between the control arm and Geko^{TM} arm. There was no statistical significance difference between the Geko^{TM} arm and the IPC+TED arm. Data are expressed as mean +/- standard deviation (p=0.97). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

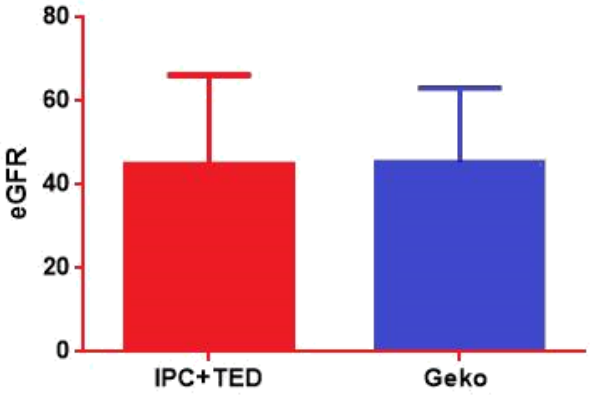

Figure 19: The eGFR 21 days after transplant in the control arm and Geko™ arm. There was no statistical significance difference between the Geko™ arm and the IPC+TE. Data are expressed as mean +/- standard deviation (p=0.96). IPC: Intermittent Pneumatic Compression; TED: Thrombo-Embolic Deterrent.

Chapter 4

4. Discussion:

The results of the current study are the first to show a direct comparison between standard IPC + TED treatment versus the Geko™ device a novel technology adopting wearable neuromuscular stimulation in transplantation. We show, for the first time, that the use of the Geko™ device in the immediate postoperative setting following a kidney or kidney and pancreas transplant results in a significant reduction in lower leg and upper thigh circumference, increased urine output and a concomitant increase in femoral vein velocity suggestive of improved circulatory blood flow. It was noted that Geko™ device improved led to increased venous blood velocity which signifies an improvement in blood circulation and consequently a rise blood flowing through various organs; including the renal, thus leading to the increase in urine output. In addition, we demonstrate that patients had much higher satisfaction scores wearing the Geko™ device compared to the IPC+TED, especially in terms of improved comfort, perception of decreased edema, improved post-operative sleep hygiene, and enhanced early mobility.

It was showed in the study that the creatinine is lesser at day six in the DCD group in the Geko™ arm than the control arm, but it was not statistically significant. This result needs to be further studied with more powerful studies.

The randomization of the patients and the balanced nature of the two groups with respect to gender whether or not the donor kidney was from a living or deceased donor all ensure to limit the bias in the reported findings.

The present work demonstrates successful control and management of edema in complex surgery patients. Interestingly, the results were evident as early as 1-2 days after surgery and

definitely within six days of treatment commencement which was immediately after surgery. The Geko^{TM} device was also well tolerated with minimum recorded discomfort, immobility, and adverse effect on sleep. In operational matters, the devices work by stimulating muscles which promote the blood flow and consequently reducing the chances of edema and thrombosis which are rampant in transplant/surgery patients. This observation is supported by various studies that reveal improved blood flow in both limb blood vessels and consequently the other body organs. According to this research, Geko^{TM} device proves more successful than the IPC+TED stockings devices. Geko^{TM} device creates a direct muscular stimulation mechanism that promotes good blood flow to prevent edema. However, this method is much appropriate in preventing venous thrombosis by promoting flow of blood within the veins. Despite the absence of deep-vein thrombosis cases in this study, the muscle stimulants are known to act deep within the skin and help in improving action within blood veins of patients thus creating reducing chances and effects of deep-vein thrombosis. The other methods which involve nerve stimulation with no direct stimulation of the muscles act closer to the surface and, despite their history of pain reduction through action on sensory nerves; they prove lesser effective on such complex cases especially thrombosis-related ones. Although we did not notice any changes in rates of DVT between the two groups (we did not expect to see this effect due to the lower incidence of DVT in this population), we predict that in a larger cohort of patients, we may be able to tease out this effect.

With regard to the changes in leg circumference, the recorded changes are positive and significantly better than those of the control with recorded increase in leg circumference for patients in the IPC +TED arm being higher than that of Geko^{TM} cohort. In reference to answer to the question on leg circumference change (Question 2), it is notable that the percentage under the

"Very increased" check box was 23% for IPC+TED against Geko's 9%. Additionally, the percentage of Geko ^{TM} device's patients who recorded large decreases in circumference was 22% against IPC+TED's 14%. With these significant differences between the two groups, it is clearly evident that the Geko^{TM} device may be an important contributor to patient recovery post transplantation. The relative positive changes recorded on patients fitted with the Geko^{TM} device was as a result of muscle and venous stimulation which improved flow of blood and consequently improved lymphatic drainage leading to a reduction in swelling.

When patients undergo surgery or transplant (especially kidney and pancreas), they face the risk of swelling of their limbs as a result edema arising from buildup of body fluids. The cases are worse in patients whose bodies tend to reject the transplants. It is, therefore, necessary to conduct elaborate tests to ensure that patients are properly matched to their donors in order to reduce such cases. Additionally, thrombosis is known to occur in the blood vessels prompting swellings and pain in adverse cases as a result of the rise in blood pressure within the blood vessels. The Geko^{TM} device works as a stimulant to the muscle cells in areas where it is fitted which lead to improved results both at the immediate section and the other parts of the body as a result of the smooth flow of body fluids and the assistive aspect in muscle cells. The research outcomes demonstrate the positive changes that can be achieved with the correct application and monitoring of the device.

Patients, especially those recovering from surgeries, are delicate and require good handling to guarantee their comfort and reduce any chances of interfering with the recuperation process. To validate the Geko^{TM} device's appropriateness and effectiveness, it is necessary that the device has to pass the comfort test and preferably outperform the control set and other available devices. However, Geko^{TM} device had a cumulative positive comfort feedback of 64% against IPC+TED's

14%. Additionally, the discomfort percentage for Geko^{TM} device was 13% against IPC+TED's 57%. In this regard, Geko^{TM} device is designed to offer very high comfort levels of comfort to the patients. The device, therefore, proves that it is ideal for such sensitive and delicate cases involving vulnerable patients. This study further notes that the device has clear instructions on use which, coupled with the strictness in the experience and mandatory training of the staffs involved in the fitting and replacement process, assisted in realization of the satisfactory comfort levels. The edema challenge affects a huge section of the patients which means that any stimulating device with best results is a necessary factor in the recovery process. The comfort of these devices should be paramount to ensure that they appropriately solve the problem without necessarily creating further complications for the patients.

The Geko^{TM} device recorded higher mobility rates which cumulated to 73% by adding the "somewhat easy" and "very easy" responses in relation to IPC+TED's 43%. With discomfort patients accounting for 10%, this indicates that most of them could move easily without any negative effect from the device. The "very difficult" group accounted for 3% which quite a small number. The positive feedbacks realized in relation to effect on sleep pattern and future use in case of requirements (83% against 17%) indicate a high acceptability ration from the patients. This high positive feedback is congruent to the higher leg circumference reduction ratio which is a relief to the patients. The effect on sleep patterns and mobility was also seen to improve which is one of the attributes to the high acceptability ratio in cases of future requirement. Various studies support this outcome by showing both improvement in blood flow and a high patient satisfaction rate ((Tucker A et al., 2010); Breen PP et al., 2012; Broderick BJ, 2010).

With regard to the changes in leg circumference, the recorded changes are positive and way better than those of the control with recorded increase in leg circumference for patients under the IPC +TED being higher than that of Geko^{TM} plan. In reference to answer to the question on leg circumference change (Question 2), it is notable that the percentage under the "Very increased" check box was 23% for IPC+TED against Geko's 9%. Additionally, the percentage of Geko^{TM} device's patients who recorded huge decreases in circumference was 22% against IPC+TED's 14%. With these huge differences, it is evidently clear.

The above case study is a demonstration of successful control and management of edema in surgery patients. Interestingly, the results were evident within six days of treatment commencement which was immediately after surgery. The Geko^{TM} device was also well tolerated with minimum recorded discomfort, immobility, and adverse effect on sleep. In operational matters, the devices work by stimulating muscles which promote the blood flow and consequently reducing the chances of edema and thrombosis which are rampant in transplant/surgery patients. According to this research, Geko^{TM} device proves more successful than the IPC+TED stockings devices. Geko^{TM} device creates a direct muscular stimulation mechanism that promotes good blood flow to prevent edema. However, this method is much appropriate in preventing venous thrombosis by promoting flow of blood within the veins. Despite the absence of deep-vein thrombosis cases in this study, the muscle stimulants are known to act deep within the skin and help in improving action within blood veins of patients thus creating reducing chances and effects of deep-vein thrombosis. The other methods which involve nerve stimulation with no direct stimulation of the muscles act closer to the surface and,

despite their history of pain reduction through action on sensory nerves; they prove lesser effective on such complex cases especially thrombosis-related ones.

In reference to the physical nature and patient satisfaction, the Geko device is lightweight and requires no additional power connections as it is self-powered. Its battery power is sufficient to maintain it for the 24-hour stipulation period.

This study followed clearly set guidelines in delivering its results. As with every other research, however, the study leaves room for future and further studies. The guidelines included an inclusion and exclusion clause that excluded patients who had known past complications such skin problems, ECG electrode requirement, hematological disorders, BMI index ratings exceeding 36, and leg amputation among others.

Limitations of the Study

The results achieved, and the conclusion deduced are only valid for patients who match the medical aspects of the inclusion criteria. Therefore, this calls for future research which should address the groups not covered in this section. Additionally, there is a necessity to address the compatibility of Geko^{TM} device with patients using brain stimulators and the effect that it can pause to such patients. Despite its high acceptability ratio, it is necessary to address the small percentage reporting adverse issues to ensure that patients have equal chances of benefiting from the device since, as derived above; it possesses excellent benefits on patients on post kidney and pancreatic transplant and leg edema patients.

Notably, Geko^{TM} device requires daily replacement on patients. The cost of replacing the device on a daily basis further increases its costs, and it might prove too expensive to afford for patients especially from the low-income backgrounds. In order to ensure exhaustive results,

complete acceptability, and utilize all its beneficial aspects as evaluated within the research findings, there is a necessity to include the economic variable in future research.

Lastly, although the numbers in each group are matched, there are subgroups within each of our categories including various types of donor populations which may be important to tease out when considering the data. For the purposes of our study, these were grouped together when evaluating the final data, however, it was evident from our subgroup evaluation that the DCD group may benefit to a greater extent from the Geko^{TM} device in turns of early urine output and edema, however the numbers are too small to make any concrete inferences. These subgroup evaluations should be carried out in larger cohorts.

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6. Appendices

6.1. Research Ethics Board Letter

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Alp Sener
Department & Institution: Schulich School of Medicine and Dentistry\Microbiology & Immunology,Western University

Review Type: Full Board
HSREB File Number: 103618
Study Title: The Effect of Neuromuscular Stimulation on Post-Transplant Leg Edema (GOCART: Geko for Oedema versus Compression After Renal Transplantation)

HSREB Amendment Approval Date: February 29, 2016
HSREB Expiry Date: March 19, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Patient Questionnaire	2015/12/15
Instruments	Questionnaire	2015/12/15
Instruments	Questionnaire	2015/12/15
Revised Western University Protocol	version: Feb/2016	
Letter of Information & Consent	version 10	2016/02/26

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

6.2 Curriculum Vitae

Personal data:

- Name: Bijad Atqan Alharbi
- Date of birth: 12/July/1982
- Nationality: Saudi
- Work address:
    - University of Western Ontario, LHSC, Surgical Department, Urology Division.
    - King Abdulaziz Medical City(NGH), Surgical department, Urology Division, Riyadh, Saudi Arabia.

- Qualifications:
    - MBBS, Faculty of Medicine, Taibah University, Saudi Arabia (2006).
    - Saudi Board of Urology (2013).
    - Master of Science in Surgery in western Ontario (2015-now).
    - Kidney transplant Fellow (2015-now).

- Employment history:
    - Graduated from Taibah university (medical college) in Saudi Arabia (2006)
    - Internship House Officer: (2006-2007):
      3 months in department of surgery
      3 months in department of medicine
      2 months in department of pediatrics
      2 months in department of obstetrics and gynecology
      1 month in department of emergency medicine
      1 month in department of urology
    - Urology service resident, King Fahad Medical City: (2007-2008)
    - Resident in urology, King Abdulaziz Medical City, Riyadh, Saudi Arabia: (2008-2013)
    - Urologist Assistant Consultant, King Abdulaziz Medical City, Riyadh, Saudi Arabia: (2013-2015).
    - Master of Science in Surgery (2015-now).

- Kidney Transplant Fellow (2015-now).

- Fields of interest:
  1- Male sexual medicine and reconstruction.
  2- Renal Transplantation, uro-oncology
- Research:
  I am very interested in research and because of that I am studying Master of Science in Surgery.
  1- Urology Division, King Abdulaziz Medical City

- Is Routine Testicular Biopsy Necessary for Azoospermic Patients? (2014) in progress.

  2- Urology Division, LHSC, University of Western Ontario.
- The effect of Geko device on post kidney and pancreatic transplant leg edema.
- Impact of pancreas transplant failure in quality of life in simultaneous kidney pancreas transplantation.
- Survival outcomes from DCD renal transplant are comparable to DBD renal transplant from kidneys procured from donors more than 50 years of age. A UNOS/OPTN analysis.

- Courses and conferences:

1-intraoperative and delayed urologic consultation for bladder and ureteric injuries
2- 20th Saudi urology conference
3- fundamental critical care support course
4- ACLS (advanced cardiac life support)
5-BCLS (basic cardiac life support)
6- 22nd Saudi urology conference
7- 2nd gulf andrology conference
8- Evidence based medicine course

- Teaching experience:

In last year of my residency I was the chief resident so I was involved in teaching the junior residents and supervise them.

- Exams:

  Medical Council of Canada Evaluating Examination(MCCEE)

- Languages:
  - Arabic

- English
- Level 1 French Language

Recommendations:

1- Dr. Sultan Alkhateeb

Head, Division of Urology
Consultant Urology and Urological Oncology Assistant Professor of Surgery
King AbdulAziz Medical City
King Saud Bin AbdulAziz University for Health Sciences Riyadh, Kingdom of Saudi Arabia

2- Dr. Ahmad Alshamari

Pediatric Urology Consultant
Department of surgery
King Abdulaziz Medical City
National Guard Health Affairs
Riyadh, Kingdom of Saudi Arabia

3- Dr. Yahia Ghazwani

Consultant, division of urology
Program Director, Urology Residency Training Program Department of surgery
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