Use of a Muscle Pump Activator Leads to Improved Lower Limb Edema, Lower Limb Blood Flow, and Urine Output Compared With Standard TED Stockings and Compression Devices Following Kidney Transplant: A Randomized Controlled Trial

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ABSTRACT

Objective. The aim of this study was to evaluate the effects of using thromboembolic deterrent (TED) stockings and intermittent pneumatic compression (IPC) vs a muscle pump activator (MPA) device on limb edema and patient satisfaction after transplant.

Methods. In this single-center randomized controlled trial, 118 patients were randomly assigned to wear TED + IPC (n = 64) or the MPA device (n = 54) from postoperative days 1 to 6. We measured patients' weight and lower leg and thigh circumferences daily. Ultrasonography of the allograft and lower limbs was carried out on postoperative days 1 and 5 to assess resistive index in the transplanted kidney and flow in the femoral vein. We monitored urine output and serum creatinine level.

Results. We observed a significant increase in calf and thigh circumference from baseline in the TED + IPC group but not in the MPA group (2.3 [SD, 1] cm vs 0.25 [SD, 0.8] cm, respectively, $P < .002$). Ultrasonography showed higher femoral vein velocities in the MPA group than the TED + IPC group (0.5 [SD, 0.2] cm, $P < .001$). The mean total urine output in 6 days was higher in the MPA group than the TED + IPC group ($P = .05$), which corresponded to large change in TED + IPC weight of 6.2 kg vs 2.1 kg in the MPA group ($P = .04$). Patients were more satisfied with the use of the MPA device than TED + IPC. No major complications were encountered in either group.

Conclusions. This is the first study to show that the use of an MPA device in the immediate postoperative period following kidney transplant leads to decreased lower limb edema and increased total urine output. Patients were more satisfied with the use of the MPA device than TED + IPC.

KIDNEY transplant offers patients improved survival and quality of life compared with dialysis [1,2]; however, transplant patients are often at risk for lower limb edema and deep vein thrombosis (DVT) following surgery [3,4]. In addition, kidney transplant patients experience significant fluid overload in the initial period following the transplant, which leads to lower limb edema, especially in a poorly functioning allograft. This fluid imbalance often leads to patient immobility and discomfort.

All patients undergoing transplant currently wear a combination of intermittent pneumatic compression (IPC) devices and thromboembolic deterrent (TED) stockings

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postoperatively for DVT prophylaxis [5]. Combination of TED + IPC is designed to assist with an impaired musculovenous pump resulting from incompetent lower limb venous valves. 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, such as that which occurs in the postoperative period. Although beneficial in theory, the graduated stockings can be quite painful and hot to wear because of their strong compressive forces at the lower leg, especially in patients with worsening edema [6] In addition, the IPC device that must be worn concomitantly with the TED stockings carries its own set of challenges resulting from improper (1 size fits all) fitting, cumbersome attachments, and need for an external power source [7]. In looking for alternatives, we discovered a muscle pump activator (MPA), which works as a self-powered neuromuscular stimulation device to modulate the common peroneal nerve (Geko Plus, PerfuseMed, United Kingdom). The device measures 2 × 12 inches and is applied to the lower leg circumferentially below the fibular head. It emits a low voltage that stimulates the lower limb musculature, thus improving femoral vein velocity and limb blood flow [8], and has been shown to be beneficial in healing of chronic foot ulcers, primarily because of its effect on microcirculation [9,10]. The potential advantages that the MPA device carries over standard TED + IPC include its portability, ease of application, decreased skin irritation and/or breakdown because of its size, and decreased patient sweating and discomfort.

We set out to test the hypothesis that the use of the MPA device would lead to reduced lower limb edema, improved blood flow to the transplanted graft, and higher patient satisfaction compared with standard TED + IPC stockings alone in the period following kidney transplant.

MATERIALS AND METHODS

Study Design

This study was a single-center, open-label, randomized controlled trial. All patients undergoing renal transplant at London Health Sciences Center in 2015 to 2016 were recruited in the study. The trial followed the Consolidated Standards of Reporting Trials 2010 Guidelines (Fig 1). The protocol was approved by the University of Western Ontario Research Ethics Board (Protocol number 103618).

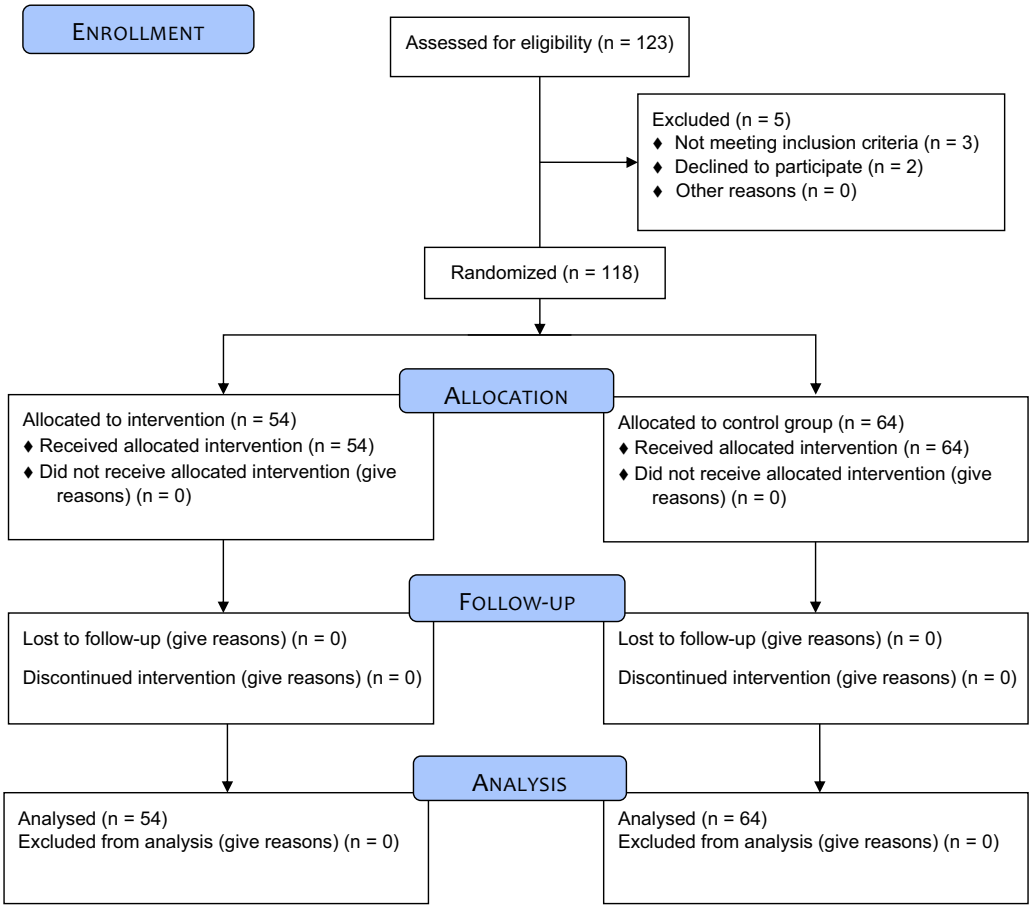

Fig 1. CONSORT 2010 flow diagram.

Sample Size Estimation

Based on data from a previous pilot study at our institution that examined the impact of an MPA on lower limb edema, lower limb blood flow, and urine output compared with standard TED stockings and compression devices following kidney transplant, the sample size calculation was a priori performed with G*Power V.3.1.2. To detect a moderate effect size of 0.6 (mean difference of 3 units, [SD, 5]) with a power of 80% and α set at 0.05, a minimum of 52 participants in each group were required. To account for attrition and the likelihood of increasing pediatric transplant practice at our institution, our accrual target was 60 participants in each of 2 study arms (TED + IPC vs MPA).

Participants

A total of 118 kidney transplant recipients were randomly assigned to wear either TED + IPC (Covidien and Flowtron Excel, Geko Plus, PErfuse MEd, Firstkind Ltd, Buckinghamshire, UK, n = 64) or a muscle pump activator (Geko Plus, Perfuse Med, n = 54). Informed consent was obtained from every recruited patient. The inclusion criteria for the study included patient's written consent, age older than 18 years, and a body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) between 18 and 34. The exclusion criteria were as follows: patients younger than 18 years, patients with previous history of DVT, patients with contraindications to use of electrical stimulation devices, patients who had previously undergone leg amputation, patients with cardiac defibrillators, patients with a BMI greater than 36, those who were unable to understand the risks and benefits of the study, patients with deep brain stimulators, and lastly those who could not tolerate the MPA device stimulation.

During the transplant surgery, both cohorts of patients were placed on TED + IPC. On postoperative day 1, patients were placed into their assigned groups based on randomization, which took place at the time of admission to hospital. Patients in the MPA arm were fitted, and the devices was set to the appropriate setting (enough to cause a gentle dorsiflexion of the ankle while the patient was lying down). The device was changed each morning by the nurse, according to manufacturer's instructions. If patients fell into the standard TED + IPC arm of the study, they continued to wear the TED + IPC postoperatively. Both groups of patients were followed after surgery for 6 days on a daily basis and at precisely the same time. The decision to remove both devices on postoperative day 6 was to normalize the time with the device prior to discharge and is the current standard of care at our institution

Randomization

Before randomization, surgeons determined each patient's eligibility to enter the trial. The patients were then randomized into the intervention arm (MPA) or control arm (TED + IPC) with an online computer generator sequence. The clinical team was not informed of group allocation.

Primary Endpoints

The primary intent of the study was to assess patient lower limb edema after surgery and patient satisfaction with the MPA device vs TED + IPC stockings following transplant. Both calf and thigh circumference was measured using a measuring tape 15.0 cm below and above the patella's midpoint to assess lower limb edema. The difference in circumference between the first and sixth days reflects amount of lower limb edema. A standardized questionnaire was used, not validated to assess patient satisfaction with the devices on the sixth day post transplant. There were 6 questions that related to leg swelling, device comfort during the period, the intent to use the device in case of future operations, and devices' influence on patient mobility and sleep.

Secondary Endpoints

The secondary endpoints included assessing weight gain, DVT risk, total urine output, kidney function, and kidney blood flow. Weight gain was determined by measuring weight from the admission date to discharge date. The DVT risk was assessed through ultrasonography of the legs on the fifth day following transplant. Total daily urine output was measured and recorded across every patient individually from post-transplant day 1 to day 6. Kidney function was assessed through serum creatinine (μmol/L) assessments on day 6 as well as on day 21 following transplant. Doppler ultrasonography was used to measure velocity at the femoral veins at rest and active device on day 5 post transplant to assess modulation of venous flow by each intervention. Lastly, Doppler ultrasonography was used to measure resistive index of transplanted kidneys at day 1 and 5 after transplant to evaluate whether there was an increase in renal capillary perfusion parameters with either technique to determine their theoretical impact on renal microperfusion.

Statistical Analysis

GraphPad Software was used to conduct a statistic analysis using a *t* test for independent data groups, where $P < .05$ represented the point of statistical significance. The normalcy of distribution of demographics and patient characteristics with outlier detection were assessed by Shapiro-Wilk test. A P value of $< .05$ was considered significant. Data are reported as mean (SD) unless otherwise specified.

RESULTS

A total of 123 patients underwent kidney transplant during the period of the study from 2015 to 2016. However, 5 of the patients were excluded for failing the inclusion policy, and, hence, only 118 were included into the study. Of the excluded patients, 1 patient had a neurologic disorder, 2 had previous histories of venous thromboembolism, and 2 patients were not explicitly willing to participate in the study. There was no statically significant difference in the age, sex, BMI, initial weight, height, form of renal replacement therapies prior to transplant, and source of kidney donors from living and deceased donors (neurologic determination of death and donation after cardiac death [DCD]) (Table 1). Induction treatment was used and consisted of antithymocyte globulin (5.0–8.0 mg/kg total) for the majority of the patients and basiliximab (20.0 mg intravenously days 0 and 4) was given to low-immunologic-risk kidney transplant recipients. There was no difference between the induction regimens between groups. Preoperative antimicrobial prophylaxis was standardized and consisted of cefazolin in the recipients. In addition, all patients received maintenance immunosuppressive regimen consisting of prednisone, tacrolimus, and mycophenolic acid. Levels were monitored closely in both groups and adjusted according to accepted practices. Sulfamethoxazole + trimethoprim (Septra DS) was given as prophylaxis for both urinary tract

Table 1. Comparison of Patient Demographic Characteristics Between TED + IPC and MPA Groups

	Type of Recipients		
	TED + IPC	MPA	*P* Value
Patients, No.	64	54	–
Age, (range), y	50 (26–68)	52 (41–64)	.97
Male:female	37:27	33:21	.72
BMI, mean (SD), kg/m^2	26.2 (4.1)	25.4 (4.8)	.24
Weight, mean (SD), kg	82.3 (6)	84.5 (4)	.20
Height, mean (SD), cm	160.0 (5.02)	158.9 (2.92)	.43
Type of dialysis, No.			
HD	42	36	.91
PD	14	12	.96
Preemptive	8	6	.82
Type of donor, No.			
LD	19	16	.99
NDD	32	28	.84
DCD	13	10	.81

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DCD, donation after cardiac death; HD, hemodialysis; IPC, intermittent pneumatic compression; LD, living donor; MPA, muscle pump activator; NDD, neurologic determination of death; PD, peritoneal dialysis; TED, thromboembolic deterrent stockings.

infections and pneumocystis pneumonia 3 times per week indefinitely. Our standard fluid replacement protocol was used for both cohorts and included the following: 0.45% normal saline (NS) 30.0 mL/h + previous hour urine output and 0.9% NS according to central venous pressure (CVP) protocol, if CV*P* < 5 rate is 250.0 mL/30 min and recheck CVP, 5 to 9 CVP rate is 100.0 mL/h, > 9 CVP 30.0 mL/h. Routinely, we do not use postoperative diuretics in either group. With respect to postoperative complications, there were equal amounts of delayed graft function found in both groups. In the TED + IPC group, 4 patients developed superficial wound infection, and 2 developed it in the MPA group ($P = .53$) following kidney transplant. All superficial wound infections were managed conservatively with penicillin-based antibiotics for 10 days.

Primary Endpoint Results

Lower limb edema. Transplant led to an overall increase in the circumference of the lower legs of both groups of patients because of significantly increased fluid administration. However, this increase was significantly greater in the TED + IPC stockings group with an average increase of 2.3 (SD, 1.1) cm, whereas the MPA group had an increase of 0.25 (SD, 0.8) cm ($P = .002$). Additionally, the thigh circumference increased by 2.5 (SD, 0.9) cm in the TED + IPC stockings group but only by 0.5 (SD, 0.2) cm in the MPA group ($P = .001$, Table 2).

Patient satisfaction. Overall, compared with the TED + IPC device, transplant patients reported that wearing the MPA device was more comfortable, led to reduced lower leg edema, did not impact their sleep patterns, and enabled them to be more mobile (Table 3). The first question asked of the recipient was, "Does wearing the device impact your level of comfort?" When level of discomfort was evaluated

Table 2. Comparison of Postoperative Outcomes Between TED + IPC and MPA Groups

	Type of Recipients		
	TED + IPC	MPA	*P* Value
Kidney transplant, No.	64	54	
Length of stay, mean (SD), d	7.7 (1.18)	7.4 (1.25)	.81
Complications, No.			
Superficial wound infection	4	2	.53
Subclinical DVT	1	0	
Total urine output, mean (SD), L	8.8 (8)	18.4 (10)	.05
LD	17 (6)	28 (8.3)	
NDD	5 (2)	12 (3.8)	
DCD	3 (2.3)	6 (2.7)	
Changes in calf circumference, mean (SD), cm	2.3 (1.1)	0.25 (0.8)	.002
Changes in thigh circumference, mean (SD), cm	2.5 (0.9)	0.5 (0.2)	.001
Weight changes, mean (SD), kg	6.2 (2.3)	2.1 (1.7)	.04
Femoral vein velocity, mean (SD), cm/s	21 (6)	29 (7)	.04
Creatinine day 6, mean (SD), μmol/L	240 (45)	210 (50.2)	.55
LD	88 (20)	95 (12)	
NDD	145 (37.4)	150 (30)	
DCD	270 (29)	240 (36.1)	
Creatinine day 21, mean (SD), μmol/L	130 (22)	110 (28.9)	.50
LD	85 (17)	80 (20.7)	
NDD	130 (20.5)	123 (14.3)	
DCD	204 (40.1)	199 (7.6)	
Ultrasonography kidney RI			
Day 1	0.83	0.75	.80
Day 5	0.70	0.74	.89

Abbreviations: DCD, donation after cardiac death; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LD, living donor; MPA, muscle pump activator; NDD, neurologic determination of death; RI, resistive index; TED, thromboembolic deterrent stockings.

Table 3. Comparison of Patient Satisfaction Outcomes Between TED + IPC and MPA Groups on Post-transplant Day 6

	Type of Recipients		
	TED + IPC	MPA	*P* Value
Device comfort, %			
Decreased	57	13	<.001
No effect	29	23	.36
Increased	14	64	<.001
Lower limb swelling, %			
Decreased	30	48	.04
No effect	18	30	.17
Increased	52	22	.001
Total Sleep, %			
Decreased	31	16	.04
No effect	49	50	.87
Increased	20	38	.04
Mobility, %			
Decreased	28	10	.009
No effect	29	17	.98
Increased	43	73	.002
Future use, %	57	83	.002

Abbreviations: IPC, intermittent pneumatic compression; MPA, muscle pump activator; TED, thromboembolic deterrent stockings.

in TED + IPC group, 57% reported a decreased level of discomfort, 29% reported no effect on comfort, and 14% reported that they were comfortable. Conversely, only 13% ($P < .001$) of patients in the MPA group reported increased discomfort, whereas 64% of the patients reported that they were comfortable ($P < .001$). In response to second question, "How do you perceive the extent of your leg swelling?", 52% of TED + IPC patients felt there was noticeable leg swelling following transplant compared with only 22% in the MPA cohort ($P = .001$). Interestingly, the perception that post-transplant lower limb edema was reduced on day 6 was greater in the MPA patients (48%) than the TED + IPC (30%) group ($P = .039$). In response to the third question, "Did wearing the device affect your sleep patterns?", 31% of TED + IPC participants indicated a negative impact, 49% reported no change, and 20% reported an easier time going to sleep. In contrast, in the MPA group, 12% reported negative impact ($P = .04$), 50% reported no effect ($P = .87$), and 38% said it was easier to get to sleep ($P = .04$). In response to the fourth question, "Does wearing this device impact your mobility after surgery?", 28%, 29%, and 43% of patients in the TED + IPC group reported difficulty, no effect, and improvement in mobility, respectively. On the other hand, in the MPA group, 10%, 17%, and 73% of patients reported difficulty ($P = .009$), no impact ($P = .98$), and improvement in mobility ($P = .002$), respectively. The final question was, "Would you want to use the same device if you had another surgery?" with 57% of TED + IPC participants acknowledging that they would use it again, whereas 83% ($P = .002$) of the MPA cohort indicated that they would ask for it for their next surgery.

Secondary Endpoint Results

Femoral vein velocity. When we evaluated femoral vein velocity using Doppler ultrasonography on day 5 following transplant, we observed a 21.0 (SD, 6) cm/s femoral vein flow velocity in the TED + IPC patients, whereas we observed a significantly higher velocity in the MPA group (29.0 [SD, 7] cm/s ($P = .04$, Table 2).

Total urine output. Urine volume was collected and recorded daily for a total of 6 days from the patients. The mean urine output was 8.8 (SD, 8) L in the TED + IPC group, whereas it was higher in the MPA cohort at 18.4 (SD, 10) L ($P = .05$, Table 2). Although not statistically significant, the increased urine output observed in the MPA cohort translated across all forms of donor organs.

Measurement of intrarenal resistive index. We evaluated intrarenal resistive indices in the 2 groups to determine whether there would be a difference in renal microcapillary perfusion. We found that there was no observable difference in the measurements on postoperative day 1 ($P = .80$) or on day 5 ($P = .89$) in the resistive index of the renal arcuate artery between the TED + IPC arm and MPA arm (Table 2).

Weight change, serum creatinine, and subclinical DVT. We evaluated weight changes after transplant, subclinical DVT presence, and kidney function on postoperative days 6 and 21. There was greater weight gain in the TED + IPC arm (6.2 [SD, 2.3] kg) from baseline than MPA patients (2.1 [SD, 1.7] kg) ($P = .04$). There was no difference in serum creatinine (μmol/L) or in the estimated glomerular filtration rate on either day 6 ($P = .55$) or day 21 ($P = .5$) between the 2 cohorts. There was 1 case of subclinical DVT in the TED + IPC group (Table 2).

DISCUSSION

The results of the current study are the first to show a direct comparison between standard TED + IPC treatment vs the MPA device, a novel neuromuscular stimulator, in the transplant setting. We show, for the first time, that the use of the MPA device in the immediate postoperative setting following a kidney transplant results in a significant reduction in leg and thigh circumference that was evident as early as 1 to 2 days after surgery, which correlated with greater urine output and less overall weight gain in the MPA group. Importantly, there was higher patient satisfaction with the MPA device than the TED + IPC device in this early period following kidney transplant. Patients reported improved comfort, perception of decreased edema, improved postoperative sleep hygiene, and enhanced early mobility. In the current climate where patient satisfaction with their hospital stay and outcomes is paramount to ensuring continued support from institutions, a simple modification to standard postoperative therapies such as an MPA device may be an inexpensive method of achieving multiple clinical and social goals.

The MPA must offer objective and clinically significant improvements to be accepted as a therapeutic device

postoperatively for lower limb edema and DVT prophylaxis. Both the TED + IPC and MPA devices work by stimulating muscles that promote the blood flow and consequently reduce the chances of edema and thrombosis, which are rampant in transplant surgery patients. However, the results of our study demonstrate that active contraction with the MPA device compared with passive contraction with TED + IPC appears to promote better circulation as indicated by femoral velocity, lower limb edema, and urine output. This becomes exceptionally important when fluid balance is paramount in the early period following transplant. The increased urine output may have a significant impact on the rates of dialysis in these patients following transplant, thus contributing negatively not only to overall health care costs but also to patient psychology and well-being. The results of the impact of these devices on DVT prophylaxis are inconclusive as the current study was not powered to detect such a rare event. In fact, the only case of DVT was found in a patient in the IPC + TED group, but this was subclinical and would not have been discovered if not for the ultrasonographies that were being done as part of this study. A larger, multicenter trial would be needed to further evaluate if the use of the MPA device had an impact on DVT in the surgical population.

Although it was a secondary endpoint, the total urine output was higher in patients wearing the MPA device. Physiologically this makes sense as we observed increased femoral vein velocities and reduced leg edema in this cohort. In the transplant population, urine output in the early transplant period becomes very important as it not only is a sign of early graft recovery but also influences the team's decision to dialyze the patient in the face of fluid overload. In the current study, we observed that the increased urine output was consistent across all donor types. In fact, a key observation was that in DCD kidney recipients wearing the MPA device, urine output in the first 6 days following transplant trended to be double that observed of patients wearing TED + IPC. Although this is only a clinical observation rather than based on statistical significance, it deserves further evaluation in a larger study. If it could be proven that the use of the MPA device in the peritransplant period could reduce delayed graft function rates and minimize the number of dialysis sessions in DCD kidney recipients, it would offer a previously unexplored therapeutic option for these patients.

Apart from objective measures, patient comfort and satisfaction are also critical in expediting the recovery process. In fact, an increasing number of health care facilities are being ranked according to patient experiences following surgery. To date, a comparison of existing strategies, such as TED + IPC, had not been evaluated directly against an MPA device with respect to patient satisfaction following transplant. Often the biggest complaint for patients using TED + IPC is that it makes them perspire and itch and often keeps them awake at night. Our study is the first to demonstrate that the use of the MPA device instead of the standard TED + IPC led to significantly improved patient satisfaction scores with respect to sleep satisfaction and comfort of wear. In addition, patients on surgical wards have been known to remove their TED + IPC devices so that they are able to go for a walk in the postoperative period and then never put it back on because of its cumbersome nature, thus losing its intended benefit. In the current study, we found that the use of the MPA device led to increased mobility as patients felt that they were not encumbered by the device. In the TED + IPC group, patients found that they had reduced mobility. In the current study we did not aim to evaluate whether alteration of patient mobility in the immediate post-transplant period leads to improved return of bowel motion, postoperative physical reconditioning, and time to discharge. Despite this, the early signals from the MPA cohort suggest that the use of this device, at least in kidney transplant patients, may have a positive impact on mobility-related outcomes and deserves further evaluation. It could be argued that to get a better representation of the 2 devices, patients should have been switched back and forth in a crossover design; however, this was not possible in the short period we evaluated. On the other hand, the randomized nature of this study enabled us to evaluate these patients regardless of any preconceived notions they may have had. Many patients had previous surgery and had experience with the TED + IPC, so the MPA group had previous recollections to base the comparison. In addition, all patients started with the TED + IPC and were randomized over on postoperative day 1 so they would have had some experience with the standard stockings prior to MPA use. Furthermore, 85% of patients in the MPA group mentioned they would use this device again postoperatively compared with only 57% in the TED + IPC group. This positive feedback alone warrants a larger, more robust trial in multiple institutions [11–13].

This study shows benefit of using the MPA device over the TED + IPC in post–kidney transplant patients. The benefits include improved systemic circulation and patient satisfaction with the device. Since edema affects a large percentage of post-transplant patients, any device that reduces edema is a major factor in the recovery process of the patients. One of the major strengths of this study was randomization of participants and prospective collection of data to reduce selection bias. The main limitation of this study was the limited number of patients involved as this may have contributed to the insignificant results noted with DVT prophylaxis and serum creatinine between the 2 groups.

CONCLUSION

We demonstrated, for the first time, use of the MPA device in the immediate postoperative period leads to an improvement in lower limb edema, postoperative weight gain, urine output, and patient satisfaction with their overall experience following kidney transplant compared with standard TED + IPC device use. The findings of this study suggest that further, larger studies are warranted to better delineate whether the use of the MPA device in this cohort

of patients could improve graft outcomes types of deceased donor transplants, such as DCD, which may benefit directly from our findings.

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