Blood flow restriction exercise to attenuate postoperative loss of function after total knee replacement: a randomized pilot study

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Abstract

Aging well is directly associated with a healthy lifestyle. The focus of this paper is to relate that attenuation of postoperative loss of muscle function after a total knee arthroplasty (TKA) is an important consideration. Because patients usually do not tolerate standard high-resistance exercise in the preoperative or postoperative period, they often experience a decline in strength and function. Therefore, we tested the feasibility and acceptability of an alternative low-resistance exercise protocol with blood flow restriction (BFR) using a tourniquet in the preoperative period for patients awaiting TKA. We recruited patients undergoing a TKA and randomized six to the BFR exercise for 4 weeks prior to surgery and four to standard of care (no exercise). We measured physical function using the Short Physical Performance Battery (SPPB), the 6-Minute Walk Test (6MWT), leg strength (peak torque), and pain (numerical pain score) 4 to 5 weeks preoperatively and 2 weeks postoperatively. The clinical management, e.g., anesthetic management, did not differ between groups. No complications were observed. Our findings demonstrate the feasibility and acceptability of the BFR intervention. Although preliminary and not powered for comparison, the BFR group demonstrated less decline in SPPB following surgery (−2.2, 95%CI:−4.4,0.1) compared to the no exercise group (−4.8, 95%CI:−7.8,−1.7). No differences were noted for the 6MWT, leg strength, and pain measurements. We conclude that preoperative low-resistance exercise using the BFR is feasible and acceptable, and this test warrants investigation as an intervention to potentially attenuate the postoperative loss of physical function after TKA.

Key Words: Rehabilitation; blood flow restriction exercise; function; short physical performance battery; total knee arthroplasty.

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Total knee arthroplasty (TKA) is a major surgery associated with significant morbidity, including loss of function and strength.[1-3] The surgical procedure is performed under anesthesia and can require hospital admission for 1 to 2 days or more, depending on the clinical course. Some patients require a prolonged stay in an assisted care facility or additional care during the recovery period. Early physical therapy and ambulation are the primary goals in the postoperative course. Additionally, loss of physical function and skeletal muscle atrophy continue after surgery, specifically in older adults, and contribute to poor recovery. A meta-analysis of studies evaluating lower limb strength for up to 3 years after TKA revealed decreased strength in multiple leg muscle groups after TKA compared to controls, despite routine physical therapy/rehabilitation in the first months after surgery.[4,5] Given that suboptimal functional outcomes occur in approximately 20% to 35% of cases,[2,3] there has been considerable interest in developing interventions to improve postoperative outcomes for individuals undergoing TKA. Because knee replacement surgery is an elective scheduled surgery, interventions applied during the preoperative period are feasible. However, available studies focus primarily on exercise interventions several weeks prior to surgery, and they show mixed results.[6,7] Furthermore, intensive

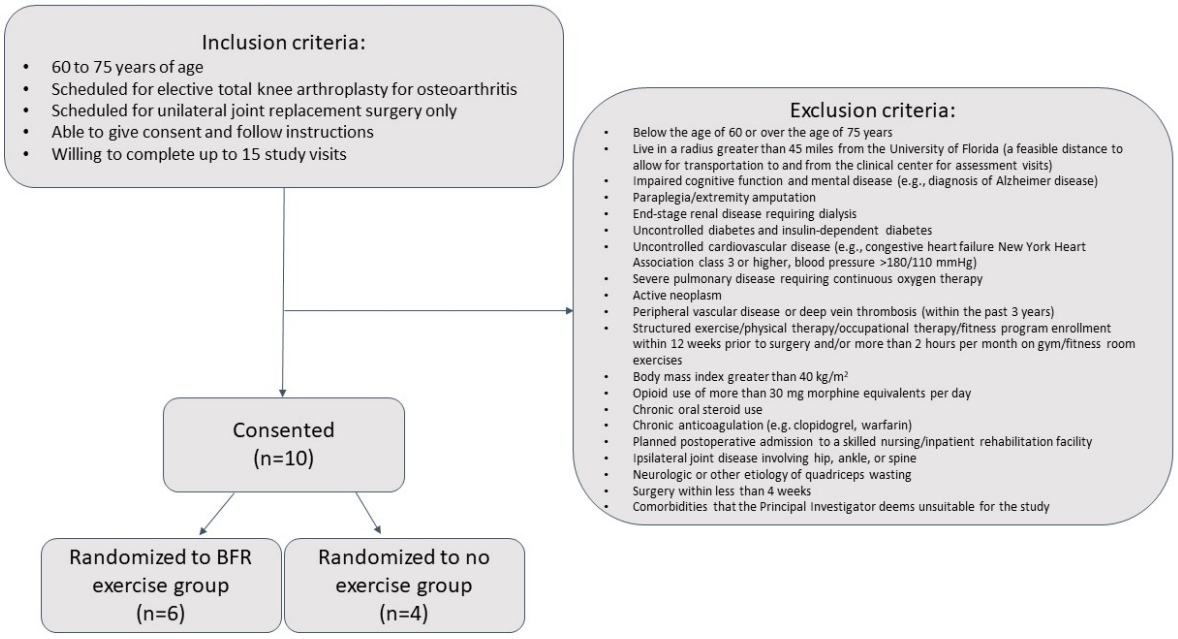

Fig 1. *Inclusion and exclusion criteria of the study.*

exercise protocols over several weeks prior to joint replacement surgery are poorly tolerated and likely ineffective in these patients secondary to pain.[6,7] Based on the number of negative findings, alternative interventions need to be studied to help improve outcomes. Ischemic preconditioning through blood flow restriction (BFR) using a tourniquet during exercise is a promising exercise method. The BFR exercise entails the concurrent application of a tourniquet on a limb during exercise. The BFR exercise has been shown to improve muscle mass in a shorter period of time and at a lower exercise intensity (20% to 30% of 1 Repetition Maximum [1RM] test) compared to standard exercise protocols (70% to 80% of 1RM). The BFR appears to be a promising alternative for patients who cannot undergo a lengthy exercise program secondary to pain and a limited time schedule.[8,9] Effective therapies are urgently needed to prevent mobility loss and disability in the rapidly growing number of older people with knee osteoarthritis (OA) requiring a TKA. BFR can be easily adapted to patient populations at risk of catabolism and loss of physical function, especially older adults, in the ambulatory or hospital setting. Our pilot study sought to measure the feasibility and acceptability of a BFR intervention prior to a TKA procedure. We hypothesized that a BFR exercise intervention completed before the surgery in patients with knee OA requiring a TKA would be feasible to implement and acceptable to participants.[10,11] If our hypothesis is correct, an adequately powered study to test the possible benefits of adding the BFR to standard care would be warranted.

Table 1. *Study protocol overview*

Characteristics	**All groups**	**Exercise group only**	**All groups**
Assessment	Baseline testing	Exercise (8 visits)	Postoperative testing
Time period	4–5 weeks preoperation	4 weeks preoperation	2 weeks postoperation
Consent/randomization	X	N/A	N/A
Pain score	X	N/A	X
SPPB/6MWT	X	N/A	X
Strength	X	N/A	X

Abbreviations: N/A, not applicable; SPPB, short physical performance battery; 6MWT, 6-Minute Walk Test. Note: X indicates performed.

Materials and Methods

The randomized pilot study was approved by our Institutional Review Board and participants provided written informed consent. The general inclusion criteria were 1) adult patients who were 60 to 75 years of age; 2) scheduled for elective TKA for osteoarthritis limited to a unilateral joint replacement surgery only; 3) able to give consent and follow instructions; and 4) willing to complete up to 15 study visits. Exclusion criteria are presented in Figure 1. Patients meeting inclusion criteria were randomized to undergo the BFR exercise (BFR group) 4 weeks prior to TKA or standard of care (no exercise, Control group). Table 1 shows the protocol overview.

Pre-Intervention and Postoperative Measures

We tested the following parameters 4 to 5 weeks preoperatively and 2 weeks postoperatively: the Short Physical Performance Battery (SPPB),[12] the 6-Minute Walk Test (6MWT),[13] leg strength of the operative leg (peak torque knee extension),[14] and pain intensity measure (numerical rating scale). The SPPB includes three objective tests of lower body function: 1) a timed 4-m walk; 2) timed, repetitive chair stands; and 3) a hierarchical test of standing balance.[12] The SPPB summary score is created by adding the three individual test items according to previously established criteria. There is a potential range of 0 to 12, with higher scores indicating better lower body function.[15] A 1-point improvement in the SPPB summary score has been indicated as clinically meaningful and correlated well with increases in overall activity and survival.[15] For the 6MWT, subjects walk back and forth along a 100-ft hallway for 6 minutes after standardized instructions to complete as many laps as possible.[13] The distance covered in 6 minutes was recorded and gait speed was calculated (m/sec). Strength of the quadriceps extensor muscles (peak torque) was tested using a dynamometer (Biodex, Shirley, NY).[14] The subject was seated on the Biodex seat and strapped in around their shoulders/torso and knees to keep them in position. The operative leg was attached to the knee attachment of the dynamometer with a padded strap at the ankle. Subjects were instructed to perform a sufficient number of submaximal repetitions and then three maximal repetitions. The quadriceps femoris peak torques and corresponding knee angles were measured at a speed of 120°/sec. Each subject performed, with verbal encouragement, three maximal voluntary repetitions. The best peak torque was recorded.[14] Pain intensity was measured using the numerical rating scale (0–100), with 0 indicating no pain and 100 indicating worst pain imaginable. The pain intensity rating was obtained at the beginning of each appointment visit.

Exercise Protocol for BFR Group

After random assignment to the BFR exercise group and determination of the 1RM, participants engaged 2 days per week with at least 2 days apart in a center-based exercise intervention for 4 weeks, with a maximum number of 12 sessions. Following a brief warm-up, participants performed lower-extremity exercises (leg press, leg extension, leg curl, and calf extension) at an intensity of 30% of 1RM with external compression applied to the proximal thigh of each leg (BFR). Participants performed up to 2 sets per exercise for a total of up to 8 sets per exercise visit. Exercises were performed to volitional fatigue, defined as the inability to complete a pain-free range of motion after strong verbal encouragement. Exercise training was performed using standard isotonic resistance training equipment (Life Fitness, Schiller Park, IL). To assess patient acceptability, patients were asked to rate session exertion using the Borg CR10 (0–10 scale), with higher scores indicating harder, more difficult exertion. Patients also rated the pleasantness of the session on a scale of 0 to 100, with lower scores indicating a more pleasant experience and higher scores indicating a more unpleasant experience. Patients were also asked about their session pain, using a scale of 0 to 100.

Blood Flow Restriction

Thigh compression was applied according to tourniquet guidelines using segmental vascular cuffs (D.E. Hokanson Inc., Bellevue, IL). Cuff pressures were set and maintained by an automated cuff inflator (TD312, Hokanson) designed specifically for rapid and precise control of cuff pressures. Cuff pressures for each individual were determined according to the equation [pressure = 0.5 (systolic blood pressure) + 2 (thigh circumference) + 5], if tolerated by the patient. This approach not only standardized how restriction was

Table 2. *Baseline patient demographics for full sample and stratified by group*

Demographic	Total sample N = 10	BFR Exercise n = 6	No Exercise n = 4
Age, mean year ± SD	67.2 ± 7.1	66.5 ± 9.0	68.3 ± 3.9
Gender, n for women	7/10	4/6	3/4
Ethnicity, n for non-Hispanic	9/10	6/6	3/4
Race, n for white	9/10	6/6	3/4
BMI, mean ± SD	31.2 ± 5.4	29.7 ± 4.7	33.3 ± 6.3

Abbreviations: BFR, blood flow restriction; BMI, body mass index; SD, standard deviation

Table 3. *Adherence and acceptability metrics for patients in BFR exercise group*

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
Number of sessions (out of 12)	11	6	12	12	8	8
Average session Borg CR10 scale (0–10)	8.6	3.7	8.9	9.6	9	8.9
Average session pleasantness (0–100)	86	3	0	6	92	74
Average session pain (0–100)	9.1	4	0	6.5	97.9	82.9

Abbreviation: BFR, blood flow restriction

applied, but it also ensured that cuff pressures were safe across varying limb girths and blood pressures. Before starting the exercise, the participant was acclimated to their specific, tolerated cuff pressure through a series of gradual pressure exposures. Cuffs remained inflated during the performance of each exercise (*i.e.*, in between sets), but they were deflated for 3-minute rest periods between exercises.

Surgical Procedures

Anesthetic and postoperative management was similar among patients; all surgeries were performed under a spinal anesthetic and regional anesthesia including a femoral nerve catheter and sciatic nerve single-injection regional anesthetic.

Statistical Analysis

Measures were summarized as means and standard deviations (SD) for continuous measures and counts for categorical measures. Differences between baseline and follow-up were reported as mean differences with 95% confidence intervals (95%CI), as well as percent change. To compare groups, differences in baseline to follow-up change scores were evaluated using the Mann-Whitney test, with the exact test performed due to small samples. Secondary analyses also examined group differences in individual SPPB tests and used the Mann-Whitney test and Fisher exact test for comparisons. $P<0.05$ was considered statistically significant. All analyses were conducted in JMP Pro 15.0 (SAS Institute, Cary, NC).

Results

Ten patients were included in this study (n = 6, BFR exercise group; n = 4, no exercise group). Table 2 reports baseline patient demographics for the full sample and stratified by intervention group.

The average age of patients was 67.2 and the average body mass index (BMI) was 31.2; group differences in BMI were not statistically significant (P = 0.25) from the Mann-Whitney test. The majority of the sample were women, non-Hispanic, and white. Table 3 reports adherence and acceptability metrics for patients in the BFR exercise group. Out of 12 sessions possible, patients completed 6 to 12 sessions, with 5 out of 6 patients completing at least 8 sessions. One patient had a reported session absence due to a physician's advice. Within each session, a maximum of 8 sets of exercises were performed. There was only one instance across all sessions in which a patient did not complete 8 sets. The reason for this was the patient reporting pain. There were no complications associated with the BFR exercise. Reported session pain, perceived exertion, and pleasantness were averaged within patients across sessions (Table 3). Average session pain varied widely from none to very high (range 0–97.9). Session pleasantness similarly varied from completely pleasant to nearly completely unpleasant (range 0–92). Reported perceived exertion was overall high across patients. Only one patient had an average session exertion rating less than 8. Postoperatively, both groups showed a decrease in all functional measurements. Preliminary findings demonstrated evidence of group differences in change for SPPB (Table 4). While both BFR exercise (18% decrease, −2.2, 95%CI: −4.4,0.1) and no exercise (44% decrease, −4.8, 95%CI: −7.8,−1.7) groups showed decreases in the SPPB at follow-up, the SPPB change was lower in the BFR exercise group and did not differ significantly from zero, *i.e.*, the confidence interval included zero. Both the BFR exercise and no exercise groups showed similar decreases in peak torque (50% vs. 33% decrease) and walking speed (37% vs. 35% decrease), as well as similar increases in pain (45% vs. 32% increase; Table 4). In secondary analyses, both the BFR exercise (median change: 0.85 secs, 25^{th}, 75^{th} percentiles: 0.29, 2.28) and no exercise group (median change: 1.46 secs, 25th, 75th percentiles: 0.33, 19.9) showed slight increases in the 4-m walk time (P = 0.59). Interestingly, at follow-up, no patients in the no exercise group (0/4, 0%) were able to complete chair stands; thus, all received the lowest score for SPPB on that measure. However, 5/6 (83%) of patients in the BFR exercise group were able to complete the chair stand task at follow-up. This difference in the proportion of patients completing the chair stand task was statistically significant (P = 0.047). Finally, at follow-up, 5/6 (83%) in the BFR exercise group and 3/4 (75%) in the no exercise group had maximum balance score (P = 1.0).

Table 4. *Outcome measure comparison between groups*

	BFR Exercise			**No Exercise**		
	Baseline mean (SD)	**Follow-up mean (SD)**	**Change mean (95%CI)**	**Baseline mean (SD)**	**Follow-up mean (SD)**	**Change mean (95%CI)**
SPPB	11.8 (0.4)	9.7 (2.0)	−2.2 (−4.4, 0.1)	10.8 (0.5)	6.0 (0.7)	−4.8 (−7.8, −1.7)
Peak torque (°)	60.2 (28.9)	23.3 (10.0)	−25.4 (−55.8, 4.9)	66.9 (62.6)	21.2 (4.9)	−11.8 (−90.6, 67.0)
Gait speed (m/s)	1.20 (0.15)	0.74 (0.16)	−0.45 (−0.70, 0.20)	0.96 (0.26)	0.63 (0.17)	−0.37 (−0.89, 0.16)
Pain score (0–100 scale)	28.2 (21.7)	41.0 (23.5)	12.8 (−2.9, 28.6)	39.0 (27.0)	51.3 (19.6)	12.3 (−39.0, 63.5)

Abbreviation: BFR, blood flow restriction; SD, standard deviation; 95%CI, 95% confidence interval.
Note: p-value from Mann-Whitney test

Discussion

The purpose of this pilot study was to evaluate the feasibility and acceptability of the BFR exercise in the preoperative period to reduce functional decline in the postoperative period for patients undergoing a TKA. We found that the BFR was feasible and acceptable in the 4-week preoperative period. As we anticipated, we found a clinically significant reduction in decline in physical function and strength of the lower extremity in patients undergoing our intervention. Although preliminary, a reduction in decline in physical function measured by the SPPB specific to the BFR group compared to the control group is in line with the overarching hypothesis. Studies comparing patients who have undergone a TKA to healthy age-matched control subjects have demonstrated that patients who have undergone a TKA remained weaker in quadricep strength throughout study periods beyond 3 years.[4] No stringent recommendations exist for how to address this clinical problem. Moreover, patients frequently do not tolerate conventional exercise programs due to preoperative knee pain preceding the surgery or postoperative pain after the TKA.[4] When compared to conventional exercise interventions, the BFR exercise has been shown to improve muscle mass in a shorter time and at a lower exercise intensity in subjects without knee OA.[16] Our findings indicate that the BFR is feasible and acceptable presurgically. Future investigations to determine whether the BFR will improve the development and retention of muscle mass following TKA are warranted. Additional considerations specific to gender, the potential utility of the SPPB, and molecular mechanisms as identified in muscle biopsies are addressed below. Gender may be a factor to consider with a BFR exercise intervention.[17] A randomized study by Segal et al. (2018)[18] compared BFR to low-resistance training in female patients with risk factors for knee OA. The team enrolled 45 patients and 40 patients completed the protocol of 4 weeks of exercise 3 times per week.[18] Of the five patients who did not complete the protocol, only one patient discontinued the study secondary to intolerability (three discontinued due to a lack of time and one patient was lost to follow-up). Isokinetic knee extensor strength scaled to BMI and isotonic 1RM leg press significantly improved in the BFR exercise group compared to the exercise group without BFR. A similar effect was not indicated in male patients with moderate knee OA, although the intervention was well tolerated.

In line with the overall hypothesis, a pattern of less decline on the SPPB was indicated in the BFR group compared to the control group. The SPPB has been studied across a wide range of populations; however, it is not typically included in the evaluation of physical performance following TKA. As a postoperative functional outcome measurement, the SPPB has mainly been investigated and used in patients undergoing cardiac or pulmonary surgery.[19,20] The SPPB has also been studied in pain medicine addressing the effects of pain interventions on lower extremity function. Przkora et al. demonstrated improvements in the SPPB scores in ambulatory patients undergoing lumbar epidural steroid injections for degenerative spine disease.[21] Given our

preliminary findings, future studies including the SPPB as an outcome measure warrant further investigation. Muscle biopsies have identified promising pathways providing insight into the molecular mechanisms activated by the BFR exercise. The activity of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway is increased in older patients undergoing the BFR exercise.[22] The mTORC1 pathway is involved in the accretion of muscle protein. Additionally, mTORC1 activation during the BFR exercise can be inhibited by the administration of rapamycin, indicating a direct mechanistic link between the mTORC1 pathway and BFR exercise.[23,24] Studies in healthy young adults have shown that the BFR exercise downregulates pathways involved in proteolytic activities such as MuRF1 and Atrogin1, whereas anabolic genes (MyoD and Myogenin) are not affected by BFR exercise or exercise alone.[23,24] Moreover, we have shown that the BFR has beneficial effects on angiogenic gene expression in healthy adults.[25] These molecular pathways identify possible interesting targets to enhance the effect of the BFR exercise in combination with nutritional or performance-enhancing agents to characterize synergistic effects such as amino acids, e.g., leucine or mTORC1 upstream activators such as growth factors (e.g., insulin-growth factor or attenuators such as resveratrol).[22] Thus, there are numerous mechanistic considerations to inform and perhaps enhance targeted BFR interventions.

Limitations of this pilot randomized study include that it was not powered to test differences in pre- and post-performance measurements or comparisons between groups. As such, the optimal dose for BFR sessions preceding surgical intervention is unknown. Additionally, based on the literature of the TKA recovery curve, a longer postoperative follow-up to evaluate the effectiveness of the presurgical BFR exercise is needed. Furthermore, the BFR interventions may be bolstered by a combination of BFR exercise with an additional strategy such as growth factors or nutritional supplements.

In conclusion, our pilot study indicated that the BFR exercise presurgically in patients with knee OA undergoing a TKA is feasible and acceptable. The potential utility of the BFR to preserve muscle and function is encouraging and warrants further investigation.

List of acronyms

1RM – 1 repetition maximum
6MWT – 6-minute walk test
BFR – blood flow restriction
BMI – body mass index
CI – confidence interval
OA – osteoarthritis
SD – standard deviation
SPPB – short physical performance battery
TKA – total knee arthroplasty

Authors contributions

All authors made substantial contributions to the conception, design, and analysis and interpretation of data for this work. All authors contributed substantially to the drafting and critical revision of the manuscript, provided final approval of the version submitted, and agree to be held accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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