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ABSTRACT

Background: The objective was to investigate the feasibility of blood flow restricted exercise (BFRE) as a rehabilitation modality in patients with a unilateral ankle fracture.
Methods: Feasibility study with a prospective cohort design. Inclusion criteria were above 18 years of age and unilateral ankle fractures. Exclusion criteria: history of cardiac or embolic diseases, cancer, diabetes, hypertension and family history of cardio or vascular diseases. The predefined feasibility outcome was based on three criteria regarding patients experience with participating in the BFRE protocol and the absence of any serious adverse events.
Results: Eight patients were included. Median age was 33 years (range: 23–60). All eight patients reported maximum satisfaction on the two questions regarding patient's perception of the overall experience with BFRE training and the feasibility to introduce BFRE as an intervention.
Conclusion: Early use of BFRE in patients with unilateral ankle fractures seems feasible in patients without comorbidity.

1. Introduction

Fractures of the ankle are very common and have an overall incidence of 169.7/100,000/year [1] - representing almost 10% of all bone fractures [2]. The primary aim when treating ankle fractures is to restore normal function of the ankle joint. The acute management of ankle fractures can either be surgical or non-surgical, depending on fracture classification and concomitant injuries to bone and ligaments [3]. Following the initial treatment, the majority of patients have a prolonged period of relative immobilization with partly or no weight bearing to allow for accurate bone union. Such a prolonged period of immobilization often results in skeletal muscle atrophy and loss of range of joint motion [4]. Even a short period of three weeks knee immobilization in cast and no weight bearing cause a 47% decrease in muscle strength in healthy college students [5]. These deficits can negatively impact function and daily activities and the main aim of rehabilitation is to help the patient regain strength and function to the presurgical level.

Resistance training aims to build muscle mass, muscle strength and improve physical function [6]. The basic principle of progressive strength training is to progressively overload the muscle using external weight loads, which is known to increase muscle growth and strength [7]. However, in patients recovering from an ankle fracture, external weights and progressive overload may put too much stress on healing tissues and delay bone union. Therefore, "classic" progressive strength training of the lower extremity with increasing external weight loads might be contra-indicated [7].

A new modality, blood flow restricted exercise (BFRE), has recently been tested in other conditions where patients do not tolerate high external loads [8]. It is characterized by muscle strength training with low external weight loads (20–30% of one-repetition maximum (1RM)) combined with a pneumatic cuff

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inflation that partly reduces arterial blood flow and limits venous return, thus, elevating metabolic stimulus in the working muscles [9–16]. Due to the low external weight needed, BFRE seems useful in the rehabilitation of patients with ankle fractures, and may reduce the negative effects of immobilization.

The objective of the present pilot study was to investigate the feasibility of BFRE when used as a rehabilitation modality in patients with a unilateral ankle fracture.

2. Patients and methods

2.1. Study design

This study used a prospective cohort design to investigate the feasibility of BFRE in patients with unilateral ankle fractures, using pre-defined criteria for feasibility. Patients were included from the Department of Orthopedic Surgery, Aalborg University Hospital, Denmark and assessed for eligibility between September 15. 2020 and December 17. 2020. Outcomes were collected unblinded at baseline, after each BFRE session and after 3 weeks of BFRE.

The Danish Data Protection Agency and the Committee for Science Ethics of Northern Denmark (journal number N-20200052) approved the study, which was performed according to the principles of the Helsinki Declaration. Oral and written information about the study were provided and all patients completed a written informed consent. The reporting of the study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17] and intervention description complies with the Consensus on Exercise Reporting Template (CERT) [18].

2.2. Participants

The inclusion criteria were above 18 years of age, patients with unilateral ankle fractures (AO classification 44). The exclusion criteria were not able to understand written and spoken Danish and patients with previous history of periphery vascular diseases, cancer, deep vein thrombosis or pulmonary embolus, arrhythmia or coronary diseases, diabetic, hypertension 160/95 mmHg and family history of cardio or vascular diseases.

2.3. Intervention

All patients were prescribed an individualized BFRE/exercise program which was supervised by a physiotherapist. The exercise program started about 14 days postoperatively and included 3 weeks of intervention with the BFRE program two times per week. Each exercise session comprises a single unilateral tension band strength training exercise; knee-extension, which was performed at about 30% of 1RM. (Please find detailed CERT in appendix 1).

The blood flow occlusion pressure was established with an air cuff (FitCuffs® V3 Performance Lower) placed on the inguinal fold with a moderate limb occlusion pressure (LOP) at 60% sustained throughout the training session.

The load was individualized and each patient exercised with a resistance of an elastic band (TheraBand® dark blue) corresponding to a relative load of about 30% 1 RM. While the patient sat on a chair, a 150 cm double elastic band was used as external resistance (Fig. 1). The knee-extension exercise was performed in 4 sets with 30, 15, 15, 15 repetitions in each set, with a tempo of 1 s concentric and 1 s eccentric contraction phase. A 30-sec rest interval was allowed between sets throughout the training protocol. When a given resistance in the elastic exercise band became too low (i.e., more than 30,15,15,15 repetitions per set could be performed), the patient was instructed to adjust the resistance in the elastic exercise band (moving the chair 30 cm. further away from the door to achieve a new resistance).

Fig. 1. Tension band strength training exercise.

2.4. Descriptives and outcomes

Baseline characteristics including age, gender, height, weight, BMI and AO classification were obtained at the time of inclusion/baseline. Feasibility data from individual patients were collected after each BFRE session.

2.4.1. Feasibility outcome questions and criteria

1. Based on your current knowledge and experience, how likely is it that you will choose BFRE training if you experience an ankle fracture tomorrow?

This question intends to evaluate the patients overall combined experience with participating in the BFRE training following an ankle fracture and the patients' reflections regarding discomfort and insecurity during the training combined with patients perceived and expected outcome.

2. How likely are you, based on your current knowledge and experience, to recommend BFRE training to friends and family?

This question intends to evaluate the patients' perception of to what degree BFRE training can be introduced in the general population of ankle fractures.

A feasible outcome was predefined based on at least 75% of patients reporting 4 point or above on a 5-point Likert scale on both questions regarding patients experience with participating in the BFRE protocol. Feasibility outcome was evaluated after the last BFRE session. The scale for answers were as follow: much likely, likely, neither/nor, not likely, not at all likely.

Furthermore, feasibility will be claimed based on the absence of any serious adverse events (SAE). SAE was predefined as events resulting in life-threatening conditions, death, permanent

Table 1
Baseline characteristics.

Baseline characteristics of the 8 patients	
Age at follow-up, median (range)	33 (23–60)
Gender, n	
Male	3
Female	5
Fracture classification, n	
AO-44A	3
AO-44B	3
AO-44C	2
Treatment, n	
Conservative	3
Operative	5
LOP	197 (160–220)

N = number, LOP = Limb occlusion pressure.

disability, or damage. Information regarding SAE were obtained at each BFRE session.

2.4.2. Secondary outcome measurements

Acceptance of pain/discomfort during treatment was evaluated on a 5-point Likert scale by a single question after each BFRE session (very much, much, niter/nor, not, not at all):

How acceptable was it for you to have pain/discomfort during the BFRE session?

Patients evaluated perception of security of BFRE on a 5-point Likert scale after each BFRE session by a single question (very much, much, niter/nor, not, not at all):

To what degree did you experience security in today's BFRE session?

2.4.3. Muscle function outcomes

Maximum isometric knee-extension strength was tested bilateral with the patient sitting on an examination table with 60 degrees knee flexion by a strap-mounted dynamometer attached to the wall (Mecmesin AFG2500, Mecmesin Ltd, West Sussex, UK) [19]. Maximum isometric knee-extension strength was obtained at baseline and after the last BFRE session.

Adverse events/harms: An AE was defined as any undesirable experience during follow-up. If an AE result in hospitalization, prolonged inpatient hospital care, result in re-surgery, or if an AE is life-threatening, result in death, permanent disability or damage, they will be categorized as serious adverse events (SAEs). AE and SAE were obtained at each BFRE session.

2.5. Statistics

Approaches to sample size justification for pilot and feasibility trials vary. We aimed for a target sample size of 8 participants due to the descriptive design and as no efficacy testing was planned [20]. Data was assumed missing at random and no imputations were made.

3. Results

During the study period 21 patients were admitted at Aalborg University Hospital with a unilateral ankle fracture and all were assessed for eligibility. Eight patients were included in the study.

Eleven patients were excluded due to the exclusion criteria and two patients did not want to participate.

The median age was 33 years with a range of 23–60. Baseline characteristics are presented in Table 1.

3.1. Outcomes related to intervention feasibility

Based on the predefined three criteria of feasibility of BFRE as early intervention the unilateral ankle fractures the degree of feasibility was high.

All eight patients reported maximum on the two questions regarding patient's perception of the overall experience with BFRE training and then possibility to introduce BFRE training as an intervention on unilateral ankle fracture patients. No serious adverse event (SAE) was observed during the study period.

3.2. Other outcomes

The individual patient's acceptance of pain/discomfort during each BFRE training together with patient's confident status are reported in Table 2. Results indicate very high degree of patients acceptance of pain and discomfort and patients confident status with BFRE training.

The development in maximum isometric knee-extension strength for individual patients are shown in Fig. 2. Results indicate that sitting test of maximum isometric knee-extension strength are feasible both at baseline and after 6–8 weeks following the fracture. Results show that muscle strength increase for both the injured and non-injured leg during the BFRE treatment. However, the difference after 6–8 weeks was median 18% decrease in muscle strength for the injured leg compared with the non-injured leg.

3.3. Adverse events

Seven of the eight patients reported delayed onset muscle soreness (DOMS). One patient reported pain from the cuff after one session. One patient reported temporary peripheral paresthesia to the front of the knee and the anterior portion of the crura after a single session. All AE disappeared within 24 h.

4. Discussion

This study indicates that early use of BFRE in patients with ankle fractures is feasible and have the potential to be used in future studies to evaluate the effect of BFRE on the development in rehabilitation following ankle fractures. Patients' overall satisfaction with the BFRE intervention were very high, and no serious adverse events were reported. Pilot study data in new treatment modalities is essential prior to large scale RCT trials evaluating efficacy, to guard against in inability to recruit, feasibility of intervention, sample size calculation and SAE [21,22]. Data from the present study indicate that a large-scale, confirmatory trial is feasible.

4.1. The potential of enhanced and accelerated rehabilitation following ankle fractures

Ankle fractures are very common in the emergency departments world-wide [1]. During the past decades, the number of ankle fractures has increased steadily, which is thought to be caused by an increase in the number of people participating in sports and a shift in demographics towards an elderly population [2,23,24]. Following ankle fractures, patients commonly report a period of sick leave, pain, restrictions in range of joint motion, muscle weakness and difficulties with weight-bearing tasks such as sport, walking and climbing stairs [25–28]. Furthermore, long-term outcomes following ankle fractures are reported with increased risk of ankle pain and posttraumatic osteoarthrosis [29]. Although optimal treatment, including surgery and rehabilitation are offered, the socioeconomic cost associated with

Table 2
Individual patient's acceptance of pain/discomfort during each BFRE training and patient's confident status.

Intervention		1	2	3	4	5	6
How acceptable was the level of pain/discomfort during the BFRE session?	Very much	7	7	7	7	7	7
	Much	1	1	1	1	1	1
	Neiter/nor						
	Not						
	Not at all						
To what degree did you experience security in today's BFRE session?	Very much	8	8	8	8	8	7
	Much						1
	Neiter/nor						
	Not						
	Not at all						

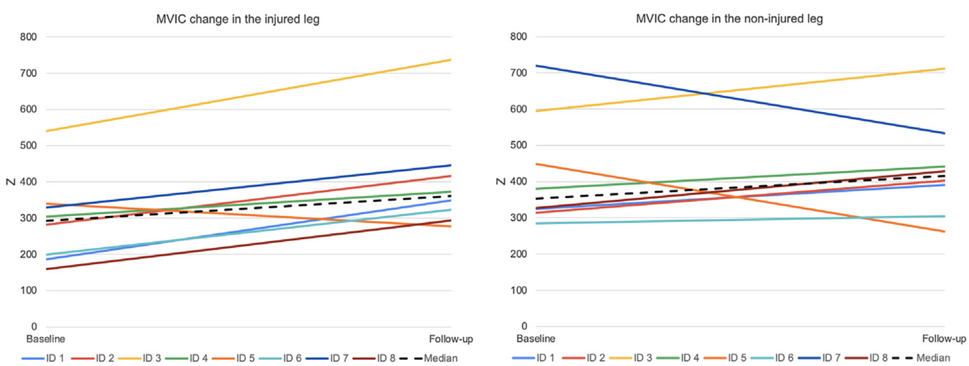

Fig. 2. Development in maximum isometric knee-extension strength. Legend: N = newton.

treatment of ankle fractures are considerable with an estimated cost between $8688 and $20,414 (2016 USD) per patient [30]. As a consequence, time effective, evidence based and safe rapid rehabilitation returning patients to previous function are of high interest for both patients and society. To achieve successful outcome following an ankle fracture restoration of muscle mass and muscle strength may be critical. BFRE training may represent the potential to facilitate a rapid rehabilitation following an ankle fracture.

4.2. Feasibility of BFRE in patients with ankle fractures

From the first introduction of BFRE to increase muscle strength and hypertrophy in healthy athletes [31,32] the indications have expanded to medical rehabilitation of different musculoskeletal diagnosis [33]. This study shows that early use of BFRE in patients with ankle fractures is feasible and associated with a high degree of patient satisfaction. Results from the present study are supported by Cancio et al. [34] reporting that BFRE are well-tolerated for patients with distal radius fractures. However, the current literature included limited information regarding the feasibility of BFRE in patients with fractures of weight bearing bones in the lower extremities [35].

4.3. Intervention

The use of tension band for exercise may limit the accuracy of the load for exercise. This may influence the predefined goal of 30% of 1RM in the present study and thereby the effect of the intervention. However, other studies have used elastic exercise band exercise together with BFRE for the lower extremities in older adults with excellent results [36]. The advantages for elastic tension band versus knee extension machine primary includes the ability for home exercise which may increase the ability for the use BFRE as an early intervention following ankle fractures. However, the present study did not include feasibility of home base BFRE.

4.4. Safety of BFRE in patients with ankle fractures

In general BFRE is considered safe for healthy active adults [11]. The safety of BFRE as intervention for patients with musculoskeletal diseases has been discussed in several papers. [16,33]. However, few studies associate BFRE with increased risk of serious cardiovascular adverse events, especially in patients with cardiovascular diseases [37,38]. Furthermore, rhabdomyolysis, numbness, bruising, subcutaneous haemorrhage, delayed onset muscle soreness, and pain are reported as potential side effects to BFRE [37,38]. This study did not observe any serious adverse events. One patient reported temporary peripheral paresthesia to the front of the knee and the anterior portion of the crura after a single session which disappeared within 24 h and almost all patients reported DOMS. To the authors knowledge, no studies have been reported on the safety of BFRE in patients with fractures of the lower extremities and therefore, little is known regarding safety. From the literature it is well know that surgery increases the risk of venous thromboembolism [39]. In the present study all patients with a previous history of cardiovascular diseases were excluded and the feasibility of BFRE may be interpreted with this in conclusion. Due to the lower number of participants even unexpected common SAE are not likely to have been captured in the present study population. As a consequence, data regarding safety should be interpreted with caution and are an important question in future research.

4.5. Limitations

Mains limitations to this study is the selected group of patients included represented by almost young and healthy patients and a short follow-up period. Our group of patients do not represent the full spectrum of patient with ankle fractures which include a bimodal distribution with younger men and older women [1].

Another limitation is the use of use of tension band for exercise which may limit the accuracy of the load for exercise. Furthermore, the sample size are limited due to the pilot and feasibility study design, and no conclusion regarding potential effect of the intervention can be made.

5. Conclusion

Early use of BFRE in patients with unilateral ankle fractures seems feasible in patients without severe comorbidities. Patients' overall satisfaction with the BFRE intervention was very high. No serious adverse events were reported, although the study was not powered for these outcomes. BFRE training may represent the potential to facilitate an enhanced and accelerated rehabilitation following unilateral ankle fractures. Data from the present study will help inform a large-scale, confirmatory trial.

Conflict of interest

Peter Larsen, Oscar Just Platzer, Lærke Lollesgaard, Samuel Krogh Pedersen, Peter Kruse Nielsen, Michael S. Rathleff, Stefan Teglhus Jensen and Rasmus Elsoe have no conflicts of interest to report.

Professor Thomas Bandholm report the following conflicts of interest:

Financial interests: I have received speaker's honoraria for talks or expert testimony on the efficacy of exercise therapy to enhance recovery after surgery at meetings or symposia held by biomedical companies (Zimmer Biomet and Novartis).

I have received fees for writing textbook chapters (Munksgaard) and for organising post-graduate education, such as post-graduate courses in clinical exercise physiology (Danish Physical Therapy Organization) or PhD courses on clinical research methodology (University of Copenhagen). Non-financial interests: I am an editorial board member with Br J Sports Med and PLOS ONE. I am a steering group member for "Clinical guidance catalogues" commissioned by the Danish Society of Sports Physical Therapy. I am a board member for the PhD-program: Basic and Clinical Research in Musculoskeletal Sciences (MUSKOS), University of Copenhagen. I am an exercise physiologist and physical therapist and may have a cognitive exercise bias.

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