Review Article

Does blood flow restriction training enhance clinical outcomes in knee osteoarthritis: A systematic review and meta-analysis

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Knee pain
Resistance training

A B S T R A C T

Objective: To systematically review the efficacy of blood flow restriction training (BFRT) on individuals with knee osteoarthritis (OA).

Design: Systematic review with meta-analysis.

Literature search: Eight electronic databases were searched by one researcher.

Study selection criteria: Randomised clinical trials (RCTs) comparing BFRT to regular resistance training (RT) for knee OA.

Data synthesis: One reviewer selected the eligible RCTs and exported the data. Two reviewers evaluated study quality using the PEDro scale. We performed meta-analysis where appropriate using a random-effects model. We rated the quality of evidence using GRADE.

Results: Five studies were eligible. The key outcomes analysed were pain, self-reported function, objective physical function, strength and muscle size. Across all comparisons, there was low to moderate quality evidence of no difference between BFRT and traditional RT.

Conclusion: The limited available evidence does not suggest that BFRT enhances outcomes for people with knee OA. These findings do not support clinicians using BFRT in people with knee OA. Instead, evidence-based messages regarding exercise and education should remain the mainstay of rehabilitation. Additional studies should clarify whether some people with knee OA who cannot complete an adequate exercise programme due to pain might still benefit from BFRT to facilitate less painful exercise.

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1. Introduction

Knee osteoarthritis (OA) is a painful and debilitating condition, associated with considerable disability and reduced quality of life (Dominick, Ahern, Gold, & Heller, 2004; McAlindon, Cooper, Kirwan, & Dieppe, 1993; Neogi, 2013). Knee OA is associated with a range of biopsychosocial risk factors (DeAngelis & Chen, 2013; Palazzo, Nguyen, Lefevre-Colau, Rannou, & Poiradeau, 2016; Srikanth et al., 2005), and there is no known cure. However, people with knee OA can benefit from appropriate management strategies (Arthritis Foundation, 2019). Current OA treatment guidelines emphasise exercise to manage OA, and prevent OA-related disability, due to its efficacy, safety and potential utility as a self-management strategy (National Institute for Health and Care Excellence, 2014; Walsh, Mitchell, Reeves, & Hurley, 2006). A range of exercise options appear safe and effective, including aerobic exercise (AE) and resistance training (RT) (Arya & Jain, 2013; McAlindon et al., 2014).

One challenge to long-term adoption of exercise for people with knee OA is that exercise can, especially initially, be painful. Not alone is such pain potentially distressing, but it can reduce compliance among people with knee OA due to concerns that exercise is dangerous (Hendry, Williams, Markland, Wilkinson, & Maddison, 2006). Even though the evidence across various musculoskeletal pain conditions suggests exercise need not be completely painfree to be of benefit (Smith et al., 2017), people with knee OA could benefit from exercising with less pain, especially if it allows them to exercise for longer, or at a greater intensity.

One method for facilitating exercise when it is too painful to perform intense exercise is blood flow restriction training (BFRT) (Korakakis et al., 2018b, 2018c). BFRT has been widely used in the bodybuilding arena to facilitate muscular hypertrophy. BFRT...
involves applying pneumatic cuffs proximally on a limb, to reduce arterial inflow and concurrently cause total venous occlusion (Patterson et al., 2019; Scott, Loenneke, Slattery, & Dascombe, 2014). This may reduce the limbs overall oxygen concentration, with this limb-specific hypoxic state being potentially therapeutic due to deoxygenated blood accumulating upon cuff inflation (Iida et al., 2005; Korakakis, Whiteley, & Epameinontidis, 2016; Manini & Clark, 2009; Patterson et al., 2019; Takano et al., 2005). Additional physiological changes have also been observed during BFRT training including fast-twitch muscle fiber recruitment, increased growth hormone levels, and post-exercise hypotension (Fujita et al., 2007; Moore et al., 2004; Nielsen et al., 2012). BFRT can be used to facilitate both AE and RT and is generally performed at a low intensity (LI) (Centner, Wiegel, Gollihofer, & König, 2019; Horiiuchi & Okita, 2012; Patterson et al., 2019; Scott et al., 2014). Training intensity for AE with BFRT is ordinarily at approximately 40% of an individual’s VO2 maximum, for it to be considered low intensity (Abe et al., 2010b; Clarkson, Conway, & Warington, 2017; Conceição et al., 2019; Patterson et al., 2019). When performing RT with BFRT at a LI, current evidence suggests an intensity between 20 and 40% of the 1 repetition maximum (1RM) for greatest results (Counts et al., 2016; Lixandrao et al., 2015; Loenneke et al., 2012; Patterson et al., 2019). Of particular relevance to populations where exercise might be difficult due to pain are data suggesting that performing resistance training at LI (LI-RT) with BFRT produces similar strength adaptations to regular high-intensity resistance training (HI-RT). (Granfeldt, Lindberg Nielsen, Mieritz, Lund, & Aagaard, 2020; Takarada et al., 2000).

Consequently, BFRT has gained considerable popularity in the last decade as a clinical treatment for painful musculoskeletal conditions. A recent review found that BFRT is a reasonably safe intervention for musculoskeletal disorders (Minniti et al., 2019). Recent studies indicate potentially greater pain reductions in other painful knee conditions within a single session (Korakakis et al., 2018a) and over 8 weeks of training (Giles, Webster, McClelland, & Cook, 2017) compared to a standard strengthening intervention. There have also been studies of BFRT among people with knee OA (Bryk et al., 2016; Segal et al., 2015a, 2015b), however the sample sizes of individual studies have been relatively small, and they have not reached all the same conclusions regarding its effectiveness for people with knee OA. While preparing to publish this review, three other systematic reviews (Cuyul-Vásquez et al., 2020; Ferlito, Pecce, Oselame, & De Marchi, 2020; Van Cant, Dawe-Coz, Aoun, & Esculier, 2020) on BFRT for painful knee conditions have been published, one of which focused on knee osteoarthritis (Ferlito et al., 2020). However, some important departures from recommended methodological standards for systematic reviews affect the confidence there can be in these recent reviews, which we highlighted in a recent commentary relating to one of them (Korakakis, O’Sullivan, Whiteley, & Grantham, 2020). Given these ambiguous results, and the large burden associated with knee OA, the aim of this review was to determine the effects of BFRT, relative to regular resistance training, on pain, physical function (self-reported and objective), strength and muscle morphology in individuals with a diagnosis of knee OA or individuals who are identified as being at significant risk of developing knee OA.

2. Methods

2.1. Protocol and guidelines

The search strategy and reporting of this systematic review adhered to the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) and followed recommendations of the Cochrane Handbook for Systematic Reviews (Higgins & Green, 2011). The protocol of the review was prospectively registered in PROSPERO, submitted online in October 2019 (CRD42020154423).

2.2. Search strategy

The search was completed in January 2020 using the following electronic databases: Allied and Complementary Medicine Database, Biomedical Reference Collection, CINAHL, MEDLINE, PubMed, PsycARTICLES, PsycINFO, SportsDiscus. Grey literature was searched via OpenGrey, as well as the following registries: Clinical Trials.Gov and EU clinical trials register. Additionally, reference lists, citation tracking results, and systematic reviews were manually searched to identify studies that were not found through database searching. Search lines were limited to the ‘Abstract’ and the search terms were limited to synonyms and abbreviations of: ‘blood flow restriction training’ AND ‘knee osteoarthritis’ AND ‘randomized control trial’ OR ‘leg degenerative changes’.

2.3. Study selection

Upon completion of the database search, each study’s title and abstract were collected, imported, and stored in a citation manager. Initially, duplicate studies were removed, followed by the researcher screening titles and abstracts to identify potentially relevant papers. The full-text was then read for any studies that passed initial screening based on viewing the title and abstract, to finalize its eligibility. The search process is shown is based on the PRISMA flow diagram (Fig. 1). (Moher et al., 2009)

Study eligibility was determined using the Population, Intervention, Control, and Outcome (PICO) framework (Scharfd, Adams, Owens, Keitz, & Fontelo, 2007). Studies were eligible if; (i) participants underwent a variation of BFRT; (ii) participants had been diagnosed with knee OA or were deemed at risk of knee OA; (iii) participants did not have other known co-morbidities; (iv) participants were human; (v) the study performed was a randomized control trial (RCT) or similar randomised comparison (e.g. crossover trial); (vi) the study compared using BFRT to either no intervention, or another intervention not involving BFRT; (vii) the study was written in English. Studies must have involved a BFRT programme of at least 4 weeks duration to be eligible.

2.4. Outcomes of interest

Pain intensity, self-reported functional ability or quality of life, objective physical function, lower limb strength and muscle volume were the key outcomes of interest.

2.5. Data extraction

Data was extracted and cross-checked from each eligible study by one researcher (BG). The following data was extracted from each study: (1) participant characteristics: age, sex, body mass index (BMI), and Kellgren-Lawrence OA grade; (2) intervention characteristics: blood flow restriction (BFRT) cuff type and pressures, intervention type and frequency and duration; and (3) data regarding relevant outcome measures. Data were extracted and exported to Microsoft Excel, before being assessed for similarities in participant characteristics, interventions, and outcome measures.

2.6. Quality assessment

Eligible studies identified were critiqued using the Physiotherapy Evidence Database (PEDro) scale by two reviewers, which determines any potential risks for bias within a study and has been
established as a reliable tool for assessing RCTs (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). The scores were confirmed by cross-checking with the scores awarded on https://pedro.org.au/. The PEDro scale consists of 10 questions which identify potential weaknesses within each study (Maher et al., 2003). Questions one and two target participant group allocation and randomization, while questions five, six, and seven explore the types of blinding performed within RCTs (Maher et al., 2003). The remaining questions (four, eight, nine, and ten) assess participant characteristics and methods of reporting results (Maher et al., 2003) and were a crucial focal point when comparing the eligible studies.

2.7. Data analysis, synthesis and summary of findings

Outcome data were transformed to ordinary 0–10 and 0–100-point scales for pain and function where applicable, respectively. As measures of treatment effect, we calculated and presented standardised mean differences (SMDs) and 95% confidence intervals (95%CI). Where possible outcome data were pooled, and heterogeneity was not judged only by the value of I² statistic, as thresholds for the interpretation can be misleading (Schroll, Moustgaard, & Gotzsche, 2011). Since clinical and methodological diversity always occur in quantitative synthesis, statistical heterogeneity is inevitable (Higgins, Thompson, Deeks, & Altman, 2003). Statistical heterogeneity was assessed as follows (Ioannidis & Trikalinos, 2007): (1) overlap (poor or adequate) of CIs presented in forest plots; (2) magnitude and direction of effects; (3) sample sizes and number of studies included (as small number of participants and/or studies included in analysis results in low power of heterogeneity test); and (4) strength of evidence for heterogeneity (p value from χ² test or CI for I²) (Higgins & Green, 2011; Schroll et al., 2011). Based on the characteristics of the included studies we assumed that clinical and methodological heterogeneity was likely to exist and to impact the outcomes; hence we used a random-effects model to pool outcomes. All analyses were conducted using Comprehensive Meta-Analysis software, V3 (Biostat, Englewood, New Jersey, USA).

Two reviewers assessed the quality of the current evidence using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (Guyatt et al., 2011). We prepared tables summarizing the findings and assessed the quality of the evidence as "high", "moderate", "low" or "very low" depending on the presence and extent of: risk of bias (mean PEDro Score was <5 out of 10) (Mendonça et al., 2020); inconsistency of effect (based on above criteria for heterogeneity); indirectness (downgrade if clinically heterogeneous); and imprecision (downgrade if upper or lower confidence interval spanned an effect size of 0.5 in either direction). Assessment of publication bias was not possible due to the small number of included trials (Jansen, Viechtbauer, Lenssen, Hendriks, & de Bie, 2011). We a-priori graded an outcome with only one trial as low quality, and if it also had high risk of bias the evidence was graded as very low quality (Atkins et al., 2004).

We undertook subgroup analyses to compare the effect of exercise with or without BFRT on knee OA in trials that used (i) high or low intensity exercise as a comparator and (ii) between studies that included only male or female participants.
2.8. Sensitivity analyses

We aimed to repeat the meta-analyses by excluding studies with poor quality, studies appearing as outliers, and by using weighted values in studies reporting subgroup comparisons and used the same control comparator to assess their influence on the pooled effect. Also, given that the I² statistic provides the proportion of the observed variance that can be attributed to the variance in true effects rather than to sampling error, we also calculated the prediction interval to evaluate the true effect size range in the meta-analyses (Borenstein, Higgins, Hedges, & Rothstein, 2017).

3. Results

3.1. Study selection and participant characteristics

The search strategy identified a total of 3238 studies, including 601 duplicates. After duplicate removal, 87 studies passed initial screening based on viewing the title and abstract, and these full-texts were assessed for inclusion in this review. The flow of trial identification, screening, and eligibility assessment process is presented in Fig. 1. Notable reasons for exclusion from the review were the absence of a true BFRT intervention, a non-RCT design, or the study did not include individuals with (or who were "at risk of") knee OA.

Study characteristics such as, sample size, age, gender, length of follow-up, interventions, outcome measures, main results, and study quality are presented in Table 1. All included studies were published in English and were carried out in 2 countries, USA (3 trials) and Brazil (2 trials).

The eligible studies included 199 participants: 147 females and 52 males, with a mean age of 60.3 (range 54.6–69.1) years. The median number of participants randomised per trial was 42 (IQR 34.5–46.5) and the sample size ranged from 34 to 48. Three studies included participants with previously diagnosed knee OA (n = 117) (Bryk et al., 2016; Ferraz et al., 2018; Harper et al., 2019), and two studies’ participants were defined as “at risk” of knee OA (n = 82) (Segal et al., 2015a, 2015b). In addition, the baseline characteristics between control and BFRT groups did not differ in all five studies, although prior to adjusting for BMI, one study (Nielsen et al., 2012) reported the BFRT group had a significantly lower BMI than the control group. All studies reported only short-term effects of BFRT (4–12 weeks).

Diagnostic criteria for knee OA used by two studies (Bryk et al., 2016; Ferraz et al., 2018) were the clinical and radiographic criteria as established by the American College of Rheumatology (Arthritis Foundation, 2019); one study (Harper et al., 2019) defined the presence of knee OA by (1) radiographic evidence of osteophytes, (2) pain classification > grade 0 on Graded Chronic Pain Scale, and (3) bilateral standing anterior—posterior radiograph demonstrating Kellgren and Lawrence grade 2 of the target knee; while two studies (Segal et al., 2015a, 2015b) included participants that either had radiographic knee OA without symptoms or had at least 1 of the following risk factors for symptomatic knee OA; (1) knee injury resulting in inability to walk without assistance for at least 2 days; (2) knee surgery (other than bilateral knee arthroplasty); (3) knee pain, aching, or stiffness on most of the prior 30 days; (4) or were overweight or obese (BMI >25 kg/m²).

3.2. Intervention characteristics

The duration of interventions ranged from 4 to 12 weeks, with two or three exercise sessions per week. The control groups performed relatively equivalent exercises to the BFRT group, and the training load was based on 1RM. The control group training intensities ranged from low intensity (LI) to high intensity (HI) (30–80% of 1-repetition-maximum (1-RM)), while BFRT group training was always LI (20–30% of 1-RM). Of the five studies, only one (Ferraz et al., 2018) used a 3-arm RCT design with a BFRT intervention group and two control groups: a LI resistance training group and HI resistance group. Exercises performed by BFRT and control groups throughout all five studies primarily focused on knee extensor muscles using a leg-press exercise or knee extension with conventional resistance training machines. However, two studies (Bryk et al., 2016; Harper et al., 2019) included lower-body general strength training along with flexibility exercises and balance training.

All studies provided the name of the exercise intervention, along with information on repetitions and sets. Two studies (Ferraz et al., 2018; Harper et al., 2019) provided a detailed description of loading progression, two studies (Segal et al., 2015a, 2015b) did not adjust the training load during training period, while one study (Bryk et al., 2016) did not provide sufficient details. Three studies (Bryk et al., 2016; Segal et al., 2015a, 2015b) provided rest time between sets, two studies (Harper et al., 2019; Segal et al., 2015b) described time under tension, all studies involved or supervised training and reported who provided the intervention, three studies (Ferraz et al., 2018; Harper et al., 2019; Segal et al., 2015a) gave information about fidelity or adherence, and no study described motivation strategies.

Substantial variability in BFRT cuffs and the precise cuff pressure used during exercise was present among studies and are outlined in Supplementary file 1.

3.3. Adverse events

Two studies (Ferraz et al., 2018; Harper et al., 2019) reported adverse events during training. The majority of these events were related to exercise-induced knee pain, with the BFRT group reporting less than the control group, though the only serious adverse event reported was within the BFRT group (Harper et al., 2019).

3.4. Outcome measures

Substantial variation was evident in the outcome measures used in the included studies. A total of nineteen outcome measures were used.

Knee pain was assessed across all five studies using either the numeric pain rating scale (NPRS) (Bryk et al., 2016), visual analogue scale (VAS) (Harper et al., 2019), WOMAC pain subscale (Ferraz et al., 2018; Harper et al., 2019) or KOOS pain subscale (Segal et al., 2015a, 2015b).

Self-reported physical function was assessed in four studies (Bryk et al., 2016; Ferraz et al., 2018; Harper et al., 2019; Segal et al., 2015a) by using valid and reliable scales (i.e. Lequesne questionnaire, WOMAC, Late Life Function and Disability Instrument). Interestingly, only one study (Ferraz et al., 2018) evaluated quality of life by using the short-form health survey with 36 questions.

Objective physical function was assessed in four studies (Ferraz et al., 2018; Harper et al., 2019; Segal et al., 2015a, 2015b) using a range of tests (i.e. Timed-Up and Go – TUG, stair climb muscle power, time-stands test, walking speed).

Lower limb strength was evaluated in all five studies using measures such as hand-held dynamometry (Bryk et al., 2016), isokinetic dynamometry (Harper et al., 2019; Segal et al., 2015a, 2015b), and isotonic strength and power (Segal et al., 2015a, 2015b). Leg-press 1-RM was the most commonly assessed outcome (Ferraz et al., 2018; Segal et al., 2015a, 2015b).
Finally, Quadriceps muscle mass was calculated in two studies at different follow-up time points using computed tomography (12 weeks) (Ferraz et al., 2018) and magnetic resonance imaging (4 weeks) (Segal et al., 2015b).

### 3.5. Risk of bias and quality assessment

The methodological quality of the included trials received a rating of ‘high quality’ and ranged from 6 to 7 points on the 0–10 PEDro Scale (Table 2). (O’Keefe, Hayes, McCreesh, Purtil, & O’Sullivan, 2016; Ye et al., 2011) The main methodological concerns were a lack of therapist and patient blinding (5/5), missing data (3/5), unclear allocation concealment (2/5), and absence of intention-to-treat analysis (3/5).

#### 3.6. Effectiveness of BFRT compared to resistance training alone: quantitative meta-analyses

#### 3.6.1. Included and excluded studies

Four studies (Bryk et al., 2016; Ferraz et al., 2018; Segal et al., 2015a, 2015b) were included when pooling data, as one study (Harper et al., 2019) was not powered to detect statistically significant differences in outcomes (only estimated mean differences with 95% CIs were reported).

### Table 1

**Study characteristics.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size, Sex, Mean Age, Mean BMI</th>
<th>Control Intervention</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryk et al., 2016</td>
<td>34 All female 61.4 years 29.9 kg/m²</td>
<td>6-Week Resistance Training Program, 3 Sessions per Week. Program performed at 70% of 1-RM. 12-Week Resistance Training Program, 2 Sessions per Week. Program performed at either LI (30% of 1-RM) or HI (80% of 1-RM), without BFR.</td>
<td>Both groups showed significant improvements in Quadriceps strength, pain, Quadriceps strength. However, no significant differences between groups. BFR group reported reduced anterior knee discomfort compared to the control.</td>
<td>Both groups showed significant improvements in Quadriceps function, pain, Quadriceps strength. However, no significant differences between groups. BFR group reported reduced anterior knee discomfort compared to the control.</td>
<td>PEDro Score: 7/10</td>
</tr>
<tr>
<td>Ferraz et al., 2017</td>
<td>48 All female 60.3 years 30.1 kg/m²</td>
<td>12-Week Resistance Training Program, 2 Sessions per Week. Program performed at 70% of 1-RM. 12-Week Resistance Training Program, 2 Sessions per Week. Program performed at either LI (30% of 1-RM) or HI (80% of 1-RM), without BFR.</td>
<td>Significant improvements in leg press, knee extension, and quadriceps cross-sectional area within the HI-RT and BFRT groups compared to LI-RT. Improved within-group WOMAC pain scores in the BFRT and LI-RT groups only. Improved within-group WOMAC physical function scores in BFRT and HI-RT groups only.</td>
<td>Significant improvements in leg press, knee extension, and quadriceps cross-sectional area within the HI-RT and BFRT groups compared to LI-RT. Improved within-group WOMAC pain scores in the BFRT and LI-RT groups only.</td>
<td>PEDro Score: 7/10</td>
</tr>
<tr>
<td>Harper et al., 2019</td>
<td>35 25 Female / 10 Male 68.2 years 30.8 kg/m²</td>
<td>12-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (60% of 1-RM). 12-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (20% of 1-RM) with BFR.</td>
<td>Study was unable to demonstrate statistically significant between-group differences. However, it was concluded that BFRT ‘may potentially have 6/10 lower efficacy than MIRT’ when measures isokinetic peak torque, leg press and knee extension 1-RM, and the WOMAC pain scale.</td>
<td>Study was unable to demonstrate statistically significant between-group differences. However, it was concluded that BFRT ‘may potentially have 6/10 lower efficacy than MIRT’ when measures isokinetic peak torque, leg press and knee extension 1-RM, and the WOMAC pain scale.</td>
<td>PEDro Score: 6/10</td>
</tr>
<tr>
<td>Segal, Davis, &amp; Mikesky, 2015</td>
<td>42 All Male 56.1 years 30.9 kg/m²</td>
<td>4-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (30% of 1-RM) without BFR. 4-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (30% of 1-RM) with BFR.</td>
<td>Within-group improvements in leg press 1-RM in both groups. Significant improvements in knee extensor strength and KOOS in control group, not BFR group. No statistically significant between-group differences in primary or secondary outcomes.</td>
<td>Within-group improvements in leg press 1-RM in both groups. Significant improvements in knee extensor strength and KOOS in control group, not BFR group. No statistically significant between-group differences in primary or secondary outcomes.</td>
<td>PEDro Score: 7/10</td>
</tr>
<tr>
<td>Segal, Williams, Davis, Wallace, &amp; Mikesky, 2015</td>
<td>40 All Female 55.4 years 30.4 kg/m²</td>
<td>4-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (30% of 1-RM) without BFR. 4-Week Resistance Training Program, 3 Sessions per Week. Program performed at LI (30% of 1-RM) with BFR.</td>
<td>Significant increases in knee extensor strength and isometric leg press 1-RM in the BFRT group. Significant increases in stair climb power in both groups. No worsening or improvement in knee pain in either group.</td>
<td>Significant increases in knee extensor strength and isometric leg press 1-RM in the BFRT group. Significant increases in stair climb power in both groups. No worsening or improvement in knee pain in either group.</td>
<td>PEDro Score: 7/10</td>
</tr>
</tbody>
</table>

**Abbreviations:** BFRT, blood flow restriction; BFRT, blood flow restriction training; BMI, body mass index; CSA, cross sectional analysis; HI, high intensity; HI-RT, high intensity resistance training; KOOS, knee osteoarthritis outcome score; LI, low intensity; LI-RT, low intensity resistance training; MI, moderate intensity; MIRT, moderate intensity resistance training; NPRS, numerical pain rating scale; SF-36, short form 36; TST, timed stand test; TUG, timed up and go test; WOMAC, Western Ontario and McMaster Universities arthritis index; 1-RM, one repetition maximum.
Table 2
PEDro scale scoring of risk of bias.

<table>
<thead>
<tr>
<th>No.</th>
<th>Design characteristics</th>
<th>Bryk et al., 2016</th>
<th>Ferraz et al., 2018</th>
<th>Harper et al., 2019</th>
<th>Segal, Davis, Mikesky, 2015 (male)</th>
<th>Segal, Williams, et al., 2015 (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subjects were randomly allocated to groups.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Allocation was concealed.</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>The groups were similar at baseline regarding the most important prognostic indicators.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>There was blinding of all subjects.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>There was blinding of all therapists who administered the therapy.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>There was blinding of all assessors who measured at least one key outcome.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Measures of at least on key outcome were obtained from more than 85% of the subjects initially allocated.</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>The results of between-group statistical comparisons are reported for at least one key outcome.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>The study provides both point measures and measures of variability for at least one key outcome.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Total Score</td>
<td>6/10</td>
<td>6/10</td>
<td>6/10</td>
<td>7/10</td>
<td>7/10</td>
<td></td>
</tr>
</tbody>
</table>

3.7. Effect of intervention - knee pain

There was a moderate level of evidence suggesting no difference in pain reduction between LI BFRT and resistance training alone at short-term follow-up (Table 3, Fig. 2A). The evidence was downgraded due to clinical heterogeneity.

3.8. Effect of intervention – self-reported functional disability

A low level of evidence suggested no difference in functional disability between LI BFRT and resistance training alone at short-term follow-up (Table 3, Fig. 2B). The evidence was downgraded due to clinical heterogeneity and imprecision.

Table 3
Summary table for the effectiveness of low intensity BFRT compared to resistance training alone.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comparisons</th>
<th>Relative effect (95%CI)</th>
<th>No of patients/ evidence (GRADE)</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average estimate in BFRT group</td>
<td>Average estimate in control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain reduction</td>
<td>BFRT group: not estimable</td>
<td>Control group: not estimable</td>
<td>SMD 0.023 [-0.271, 0.317] Non-statistically significant difference</td>
<td>Moderate (GRADE)</td>
</tr>
<tr>
<td>Short-term follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional disability</td>
<td>BFRT group: pooled weighted mean disability score was 25.4 (range 17.8–32.5)</td>
<td>Control group: pooled weighted mean disability score was 25.6 (range 19.2–35.0)</td>
<td>SMD -0.198 [-0.595, 0.199] Non-statistically significant difference</td>
<td>Low (GRADE)</td>
</tr>
<tr>
<td>(0–100) Short-term follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical mobility &amp; balance</td>
<td>BFRT group: pooled weighted mean time was 6.4 s (range 6.3–6.55)</td>
<td>Control group: pooled weighted mean time was 6.55 s (range 6.3–6.9)</td>
<td>SMD -0.148 [-0.567, 0.271] Non-statistically significant difference</td>
<td>Moderate (GRADE)</td>
</tr>
<tr>
<td>(seconds) Short-term follow-up</td>
<td></td>
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</tr>
</tbody>
</table>

Note: Data from one study (Ferraz et al., 2018) was calculated and extracted from figure. Abbreviations: SMD, standardized mean difference; CI, confidence intervals; BFRT, blood flow restriction training; TUG, timed up and go test.

a Clinical heterogeneity.

b Imprecision (lower confidence interval spanned an effect size of 0.5).
3.10. Effectiveness of BFRT compared to resistance training alone: qualitative analyses

Substantial heterogeneity in reporting did not allow quantitative synthesis of the results for strength and muscle size.

3.11. Effect of intervention — muscle strength

Three of the five studies reported no significant difference in strength gains between BFRT and conventional RT (Bryk et al., 2016; Ferraz et al., 2018; Segal et al., 2015a). The other two studies reported very small differences, in opposite directions, with one study (Segal et al., 2015b) indicating greater strength gains with BFRT while the other study (Harper et al., 2019) suggested inferior strength gains with BFRT. These small contradictions may well simply reflect differences in the intensity of exercise performed in the control arms.

3.12. Effect of intervention — muscle size

Neither of the two studies reported significant between-group differences in muscle size. Only the study with the 12-week follow-up reported significant within-group increases in quadriceps cross sectional area in the HI-RT (+8%, ES = 0.54, P < 0.0001) and the BFRT group (+7%, ES = 0.39, P < 0.0001), but not in the LI-RT group (+2%, ES = 0.12, P = 0.52).

4. Subgroup analyses

4.1. Effect of intensity of resistance training

In subgroup analysis we evaluated the effect of low intensity BFRT compared to both high or low intensity resistance training in pain, self-reported functional disability, and objective physical function (mobility and balance) (Table 4, Fig. 3). Three studies used as a comparator a LI-RT group (Ferraz et al., 2018; Segal et al., 2015a, 2015b; Bryk et al., 2016).
Table 4 Subgroup analyses summary table for the effectiveness of low intensity BFRT compared to high or low intensity resistance training alone.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comparisons</th>
<th>Relative effect (95%CI)</th>
<th>No of patients/studies</th>
<th>Quality of evidence (GRADE)</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain reduction</td>
<td>BFRT group: not estimable</td>
<td>SMD 0.136 [-0.234, 0.506]</td>
<td>113/3</td>
<td>@@@ Moderate</td>
<td>Moderate level of evidence suggests no difference in pain reduction between BFRT and LI resistance training</td>
</tr>
<tr>
<td></td>
<td>LI-RT group: not estimable</td>
<td>SMD 0.170 [-0.654, 0.313]</td>
<td>66/2</td>
<td>@@@ Moderate</td>
<td>Moderate level of evidence suggests no difference in pain reduction between BFRT and HI resistance training</td>
</tr>
<tr>
<td>Functional disability</td>
<td>BFRT group: pooled weighted mean disability score was 25.4 (range 17.8–32.5)</td>
<td>SMD -0.237 [-0.721, 0.248]</td>
<td>82/2</td>
<td>@@@ Moderate</td>
<td>Moderate level of evidence suggests no difference in functional disability between BFRT and HI resistance training</td>
</tr>
<tr>
<td></td>
<td>HI-RT group: pooled weighted mean disability score was 28.7 (range 22.1–35.0)</td>
<td>SMD -0.118 [-0.654, 0.313]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical mobility &amp; balance</td>
<td>BFRT group: pooled weighted mean time was 6.4 s (range 6.3–6.65)</td>
<td>SMD 0.056 [-0.427, 0.539]</td>
<td>66/2</td>
<td>@@@ Moderate</td>
<td>Moderate level of evidence suggests no difference in physical mobility and balance (TUG test) between BFRT and HI resistance training</td>
</tr>
<tr>
<td></td>
<td>HI-RT group: pooled weighted mean time was 6.55 s (range 6.3–6.46)</td>
<td>SMD -0.585 [-0.654, 0.313]</td>
<td></td>
<td></td>
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</table>

Note: Data from one study (Ferraz et al., 2018) was calculated and extracted from figure.; Abbreviations: SMD, standardized mean difference, CI, confidence intervals; BFRT, blood flow restriction training; HI-RT, high intensity resistance training, LI-RT, low intensity resistance training, TUG, timed up and go test.

* Impression (upper or lower confidence interval spanned an effect size of 0.5).

2015b), while two studies used as a comparator a HI-RT group (Bryk et al., 2016; Ferraz et al., 2018).

A moderate level of evidence suggests no difference in pain reduction between BFRT and LI (SMD = 0.136, 95% CI: –0.234, 0.506) or HI resistance training (SMD = -0.170, 95% CI: –0.654, 0.313) (Table 4, Fig. 3A and B).

A moderate level of evidence also suggests no difference in functional disability between BFRT and HI resistance training (SMD = –0.237, 95% CI: –0.721, 0.248) (Table 4, Fig. 3C) and a low level of evidence suggests no difference in functional disability between BFRT and LI resistance training (SMD = –0.118, 95% CI: –0.812, 0.575).

Finally, a moderate level of evidence suggests no difference in physical mobility and balance (TUG test in seconds) between LI BFRT and HI resistance training alone (SMD = 0.056, 95% CI: –0.427, 0.539) at short-term follow-up (Table 4, Fig. 3D). Low level of evidence suggests no difference in physical mobility and balance (TUG test in seconds) between LI BFRT and LI resistance training alone (SMD = –0.585, 95% CI: –1.293, 0.123).

4.2. Effect of interventions according to gender

We performed a subgroup analysis by gender to evaluate the effect of interventions in pain. One study included only male participants (Segal et al., 2015a), while three studies recruited female participants (Bryk et al., 2016; Ferraz et al., 2018; Segal et al., 2015b).

A moderate level of evidence (downgraded due to clinical heterogeneity) suggests no difference in pain reduction between BFRT and resistance training alone in women with knee OA (SMD = –0.076, 95% CI: –0.410, 0.258) at 4 weeks (Fig. 3E). A low level of evidence suggests no difference in pain reduction between BFRT and LI-RT alone in men (SMD = 0.363, 95% CI: –0.256, 0.981).

4.3. Sensitivity analyses

We considered no study as being poor quality, or appearing in the analyses as an outlier. Using weighted values in studies reporting subgroup comparisons by using the same control group, did not significantly affect the direction or the size of the pooled effect estimate, while subgroup analyses resolved between-study variability in the CIs of effects.

Finally, the prediction intervals calculated (assuming that the effects were normally distributed) revealed that the true effect size for any single population with knee OA in all outcome measures will usually fall within a greater range than that reported in the present systematic review (Supplementary file 2).

5. Discussion

5.1. Main findings

This systematic review found no difference, albeit based on low to moderate quality evidence, between BFRT and traditional RT for any of the clinical outcomes examined in people with knee osteoarthritis. As such, these findings do not support the current use of BFRT in the rehabilitation of knee OA.

There is no question that exercise can reduce pain and enhance function in people with knee osteoarthritis, both in the short-term and medium-term (Fransen et al., 2015; Lange, Vanwanseele, & Fiatarone Singh, 2008). A more pertinent question for clinicians, and patients, is whether other therapies or adjuncts might further
### A

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Sample size</th>
<th>Std diff in means and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pain reduction LI-RT at short-term</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferraz 2018 (BFR vs 30%-1RM)</td>
<td>0.000 0.354 0.125 -0.693 0.993 0.000 1.000</td>
<td>16 16</td>
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<tr>
<td>Segal 2015a (BFR vs 30%-1RM)</td>
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<td>19 21</td>
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<td>35.62</td>
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<tr>
<td>Segal 2015b (BFR vs 30%-1RM)</td>
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<td>0.136 0.189 0.036 -0.234 0.506 0.719 0.472</td>
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</table>

Test for overall effect: Z=0.719 (p=0.472)

### B

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<tr>
<td>Pain reduction HI-RT at short-term</td>
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<tr>
<td>Bryk 2018 (BFR vs 70%-1RM)</td>
<td>-0.142 0.343 0.118 -0.615 0.531 -0.414 0.679</td>
<td>17 17</td>
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<td>51.58</td>
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<tr>
<td>Ferraz 2018 (BFR vs 80%-1RM)</td>
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<td>-0.170 0.247 0.061 -0.654 0.313 -0.690 0.490</td>
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</table>

Test for overall effect: Z=0.690 (p=0.480)

### C

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<tr>
<th>Study name</th>
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<th>Sample size</th>
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<td></td>
<td></td>
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<td>Random effects</td>
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</tr>
<tr>
<td>Functional disability HI-RT at short-term</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bryk 2018 (BFR vs 70%-1RM)</td>
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<td>17 17</td>
<td></td>
<td>51.80</td>
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<tr>
<td>Ferraz 2018 (BFR vs 80%-1RM)</td>
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<td></td>
<td>48.20</td>
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<tr>
<td>Total</td>
<td>-0.237 0.247 0.061 -0.721 0.248 -0.957 0.338</td>
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</table>

Test for overall effect: Z=0.957 (p=0.338)

### D

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<td></td>
<td></td>
<td>Random effects</td>
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<td>Physical mobility and balance (TUG test) HI-RT short-term</td>
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<tr>
<td>Bryk 2018 (BFR vs 70%-1RM)</td>
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<td>Total</td>
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</table>

Test for overall effect: Z=0.227 (p=0.820)

### E

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<tr>
<th>Study name</th>
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<tr>
<td>Pain reduction women at short-term</td>
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<tr>
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<td>23.25</td>
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<td>Ferraz 2018 (BFR vs 80%-1RM)</td>
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<td>16 16</td>
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<td>23.13</td>
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<tr>
<td>Segal 2015F (BFR vs 30%-1RM)</td>
<td>0.017 0.317 0.100 -0.604 0.638 0.054 0.957</td>
<td>19 21</td>
<td></td>
<td>28.98</td>
</tr>
<tr>
<td>Total</td>
<td>-0.076 0.170 0.029 -0.410 0.258 -0.448 0.654</td>
<td></td>
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</table>

Heterogeneity: P=0.0% (p=0.654)

Test for overall effect: Z=2.448 (p=0.012)

**Fig. 3.** Subgroup analyses forest plots for the effectiveness of BFR with low intensity resistance training compared to resistance training alone in patients with knee osteoarthritis. Data is depicted according outcome. A) Pain reduction BFRT compared to LI-RT at short-term follow-up, B) Pain reduction BFRT compared to HI-RT at short-term follow-up, C) Functional disability BFRT compared to HI-RT at short-term follow-up, D) Physical mobility and balance BFRT compared to HI-RT at short-term follow-up, and E) Pain reduction BFRT compared to LI-RT only in women at short-term follow-up.

Abbreviations: SMD, standardized mean difference; SE, standard error; CI, confidence intervals; BFRT, blood flow restriction training; RM, repetition maximum; TUG, timed up and go test; HI-RT, high intensity resistance training, LI-RT, low intensity resistance training, F, female.
enhance the known benefits of exercise. Our findings suggest outcomes for people with knee osteoarthritis are not further enhanced by BFRT. This ineffectiveness is consistent with the evidence for many other adjuncts to exercise in painful musculoskeletal conditions (including insoles, taping, manual therapy, electrotherapy) (Collins et al., 2018; Karabulut, Mccarron, Abe, Sato, & Bembrin, 2011; Logan et al., 2017; Zhang, Wang, & Zhang, 2018) where greatest benefits are apparent when they are used without accompanying exercise.

Perhaps reflecting the current interest in BFRT, on completion of this review but before publication, three other systematic reviews (Cuyul-Vásquez et al., 2020; Ferlito et al., 2020; Van Cant et al., 2020) on BFRT for painful knee conditions were published, one of which focussed on knee osteoarthritis (Ferlito et al., 2020). There was considerable overlap between the studies included across these three reviews and our current review, though the precise eligibility criteria varied. We recently published a critique of one of the reviews (Korakakis et al., 2020) which extracted data inaccurately, and pooled a wide range of pain intensity data in a manner which is open to question. Looking across all these reviews, it appears clear that; (i) overall, BFRT does not enhance the key clinical outcomes of pain and disability relative to regular HI-RT; (ii) there may be value in exploring the role of BFRT in situations where HI-RT is not possible e.g. due to excessive pain, though the data for this is not yet strongly established. These findings are also relatively consistent with the most promising results reported for BFRT in other painful musculoskeletal conditions. For example, Giles et al. (2017) (Giles et al., 2017) which was included within two of the systematic reviews (Cuyul-Vásquez et al., 2020; Van Cant et al., 2020) on painful knee conditions, but not in the current review reported that ‘pain with daily activities’ improved significantly more for people with patellofemoral pain using BFRT than those undergoing only traditional RT. However, this additional benefit was only evident immediately post-intervention at eight weeks, and was no longer evident at six months. Secondly, and arguably more importantly, pain with daily activities was not a primary outcome in that RCT, with neither the two primary outcomes (worst pain, and pain-related function) nor any other secondary outcomes demonstrating significant benefits for the BFRT group.

Our findings are also consistent with Ladlow et al. (2018) (Ladlow et al., 2018) who reported no significant benefit of BFRT over conventional RT among people with lower limb musculoskeletal pain. We are aware of no other RCTs demonstrating a sustained (e.g. at least 4 weeks) clinical benefit on pain or disability for BFRT, over and above the benefit of exercise, among people with painful musculoskeletal conditions.

5.2. Clinical implications

The most promising aspect of BFRT for painful conditions is that it might allow more intense exercise with less pain, and/or reduce within-session increases in pain associated with exercise. While there is preliminary evidence to support this (Giles et al., 2017; Korakakis et al., 2018b, 2018c), any such differences in pain are not always statistically significant. While within-session pain reports were not a key outcome for our review, it is worth noting that less people discontinued their exercise due to pain in the BFRT group in one of the five studies (Ferraz et al., 2018). Furthermore, greater within-session soreness associated with the exercises was reported in another two studies (Bryk et al., 2016; Harper et al., 2018). We do not suggest such pain experiences are irrelevant, as ideally patients would not experience any more pain that necessary during rehabilitation. However, any potential benefits related to this within-session pain relief did not result in better clinical outcomes.

A critical consideration here is whether it is necessary and beneficial, as opposed to desirable, for patients to have less pain during exercise. A recent systematic review (Smith et al., 2017) found no evidence that painfree exercise results in better outcomes long-term than exercise involving pain among people with painful musculoskeletal conditions. This is also consistent with contemporary evidence regarding pain mechanisms, in that pain being experienced does not always mean harm is being done (‘hurt is not harm’) (Butler & Moseley, 2003). In that regard, it would seem sensible to encourage exercise and simply monitor the pain response to exercise over time (Domenech, Sanchis-Alfonso, López, & Espejo, 2013; Silbernagel, Thomée, Eriksson, & Karlsson, 2007) to determine if the exercise needs to be modified to ensure patient comfort, and maximise compliance. Rather than being part of a regular protocol, it is perhaps only in the event that pain is deemed excessive by the patient during exercises, that there might be a role for adjunct therapies to ease within-session pain. BFRT is one such adjunct, and the choice of clinicians and patients might depend on the importance placed on being able to achieve a high intensity stimulus without as much effort being required by the patient, versus the complexity and cost of adding BFRT to a simple exercise programme.

There was no evidence of significant harm associated with BFRT in the eligible studies. While reports of serious adverse events (e.g. embolism) are rare, they do occur (Minniti et al., 2019; Nakajima et al., 2006), and are possibly more likely in populations presenting with OA due to their age. In this regard, there are perhaps parallels with cervical manipulation for neck pain, where the overall risk is low, but potentially very serious if it occurs. For these rare examples of when conservative rehabilitation can cause serious danger, the importance of proving efficacy becomes even greater. Further research into how such rare adverse events can be minimised would be valuable.

We appreciate a real challenge for clinicians is meeting patient expectations, and indeed funding pressures, in an evidence-based manner. It can be easier to offer a novel therapy, and charge a fee commensurate to such novelty, than to persist with the evidence-based message that chronic health conditions such as knee OA require long-term behavioural change such as investing in changing activity patterns, exercising, altering diet and managing mental health. In this regard, we found it interesting that three of the five included studies actually portrayed their findings in a positive manner in their conclusions, typically with statements such as BFRT being ‘similarly effective’ to RT. If a clinician is to add another therapy to the management plan for a person with knee OA, considering the potentially extra costs, risks and burdens, it should surely improve existing outcomes, not merely match them.

5.3. Strengths and limitations

This review was registered prospectively, analysed a wide range of outcomes and has been reported in accordance with recommendations. We acknowledge the quality of evidence is only low to moderate, including only five studies with relatively small samples. Importantly, only three of the five studies included people with established knee osteoarthritis. None of the trials were adequately blinded, though this is common for exercise trials. There was considerable variation between the BFRT protocols used in the studies, in terms of the frequency (2-3 sessions per week) and duration of the training programme (four to 12 weeks), the precise training pressure used, whether the pressure was expressed relative to the pressure needed for arterial occlusion, the duration of a single BFRT session and BFRT cuffs used (See Supplementary file 1). While such variation leaves open the possibility that more consistent application of a specific BFRT protocol could be more effective, none of the various protocols showed clear benefits in the eligible
studies. In three studies (Bryk et al., 2016; Ferraz et al., 2018; Harper et al., 2019) the control group exercised at a higher intensity than the BFRT group. While this disadvantages the BFRT group to some extent, this is the very premise upon which BFRT for painful conditions is based i.e. that it can mimic higher-intensity training with less pain and/or greater adherence (Abe et al., 2005a; Horiuchi & Okita, 2012; Takarada et al., 2000). It is possible RCTs in languages other than English were missed.

6. Conclusion

Across all comparisons, this systematic review found low to moderate quality evidence of no difference between BFRT and traditional RT for any clinical outcome. While the conclusions of this review need to be tempered by the small number of studies, and the varying outcome measures and protocols employed, the findings do not support the use of BFRT as the default choice in rehabilitation programmes for knee OA. In the event that some people with knee OA cannot complete an adequate exercise programme due to pain, BFRT may be an option to facilitate less painful exercise.

7. Key points

- BFRT has been advocated as a potential mechanism to improve clinical outcomes in painful musculoskeletal conditions by allowing more challenging exercise to be performed with less pain.
- In this systematic review, there was low to moderate quality evidence of no difference between BFRT and traditional RT for any clinical outcome.
- BFRT does not enhance clinical outcomes for people with knee OA, though there may be occasions when BFRT could be considered such as if people with knee OA cannot complete an adequate exercise programme due to excessive pain.

Ethical statement

Systematic review of previously published data-no ethical approval sought.

Grant support

None.

Financial disclosure and

Nothing to declare.

Institutional review board approval

Not required.

Registration details

Prospero (CRD42020154423).

Declaration of competing interest

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Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1101/j.pstp.2021.01.014.

References