Exercise or manual physiotherapy compared with a single session of physiotherapy for osteoporotic vertebral fracture: three-arm PROVE RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The PROVE RCT

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Scientific summary

Background

It is estimated that, each year, 25,000 people in the UK have vertebral fractures related to their osteoporosis. Osteoporosis and vertebral fracture can have a considerable impact on an individual's health-related quality of life (HRQoL) because of pain and limitations in activity and social participation. There is increasing evidence that physiotherapy, including manual techniques and exercise interventions, may have an important treatment role in improving outcomes.

Objectives

The primary objective was to undertake a definitive, pragmatic randomised controlled trial (RCT) to assess the effects of a physiotherapy intervention based on exercise or manual therapy that was feasible for delivery within the current commissioning constraints of NHS delivery, compared with a single session of physiotherapy (SSPT) for people with osteoporosis and a clinically diagnosed vertebral fracture [Barker KL, Javaid MK, Newman M, Minns Lowe C, Stallard N, Campbell H, *et al.* Physiotherapy Rehabilitation for Osteoporotic Vertebral Fracture (PROVE): study protocol for a randomised controlled trial. *Trials* 2014;**15**:22].

The secondary objectives of the Physiotherapy Rehabilitation for Osteoporotic VErtebral Fracture (PROVE) trial were to:

- compare the effects of exercise therapy with the effects of manual therapy
- investigate the acceptability of and adherence to the physiotherapy programmes among both participants and therapists
- conduct a parallel health economic analysis to assess the cost-effectiveness of the different treatment strategies from a NHS, Personal Social Services and patient perspective
- conduct an embedded qualitative study to explore the experiences and views of people with osteoporosis and vertebral fracture regarding their treatment, their perceptions regarding the appropriateness and acceptability of the interventions, and the factors influencing their adherence to the intervention programmes.

Methods

A pragmatic, prospective, multicentre, assessor-blinded, adaptive RCT with an embedded qualitative study and economic evaluation. Participants were randomised to one of three arms:

1. exercise therapy, which involved individually prescribed exercise reviewed on a regular basis by a physiotherapist, alongside a home exercise programme (HEP) of strength, balance and walking exercises
2. manual therapy, which was individually prescribed and included spinal and soft-tissue mobilisations and postural taping alongside a home programme of stretches
3. SSPT, which involved a single 1-hour physiotherapy session that included assessment, education and advice in line with Royal Osteoporosis Society (ROS) information.

Participants in the exercise and manual therapy intervention arms were offered up to seven individual physiotherapy sessions over 12 weeks.

Setting

The trial was run in the physiotherapy departments of 21 NHS hospitals across England.

Interventions

Participants in the manual and exercise therapy intervention arms were offered an initial 1-hour assessment and up to six individual physiotherapy sessions over 12 weeks. This broadly reflects the current outpatient physiotherapy commissioning level within the NHS.

For the manual therapy intervention, a package of low-velocity spinal mobilisation performed without discomfort, soft-tissue mobilisations and postural taping was delivered together with a home programme of passive stretches that promoted thoracic extension for 15 minutes per day.

For the exercise therapy intervention, a package of three balance exercises, three progressive strength training exercises and a community walking exercise programme was developed, with specific selection and progression of exercise intensity at a self-perceived moderate to somewhat-hard level of effort (rating of 3 or 4) using the Borg Rating of Perceived Exertion scale.

Participants practised exercises in the treatment sessions and continued the exercises in the HEP. Participants were asked to include short sessions of exercise within daily life, aiming to achieve a total of 60 minutes of exercise per day, three to five times a week, depending on ability.

Strategies to promote adherence to the home programmes were utilised.

Single session of physiotherapy intervention

Currently, relatively few patients are referred for physiotherapy for an osteoporotic vertebral fracture (OVF). The intervention developed as a comparator arm was a single 1-hour assessment and education session with a specialist musculoskeletal physiotherapist. This included general advice about osteoporosis, falls risk reduction advice and lifestyle choices to promote bone health, tailored to an individual's needs and in line with the information available from the ROS.

Recruitment

Potential participants were approached by clinicians during their routine clinic attendance. They were contacted to ascertain eligibility. Eligibility criteria included a diagnosis of primary osteoporosis confirmed by radiography or a dual-energy X-ray absorptiometry scan (T-score ≥ -2.5 standard deviations below the young adult mean score at the lowest lumbar level), at least one symptomatic osteoporotic vertebral fracture, being aged ≥ 18 years, being able to walk at least 10 m independently with or without an aid, being able to understand and participate in a physiotherapy programme and, if female, being postmenopausal. Individuals could not enter the trial if they had any condition that might make participating in the physiotherapy or exercise regimes unsafe. People with severe unstable cardiovascular or pulmonary disease, people with significant psychiatric or neurological conditions, people with bone loss secondary to other metabolic bone disorders or disease, those for whom the primary problem was back pain with pain radiating into the lower limbs and individuals who had a vertebroplasty, facet joint injection or any physical therapy (e.g. chiropractic, osteopathy or physiotherapy treatment for back pain in the previous 12 weeks) were ineligible for participation.

Randomisation, blinding and allocation concealment

Randomisation was via the central telephone registration and randomisation service at the Warwick Clinical Trials Unit. Staff registered participants after confirming eligibility, obtaining consent and conducting the baseline assessment, thus ensuring allocation concealment.

Research staff were not involved in delivering the treatment interventions, and baseline and follow-up assessments were carried out by blinded research physiotherapists. All data were entered by a data entry assistant to ensure that the research physiotherapists remained blind to treatment allocation. All trial personnel involved in data entry, management and analysis were blinded until the final analysis was complete. It was not possible to blind the participants or the physiotherapists providing the treatment interventions.

Sample size

The initial sample size calculation was based on a traditional approach to a three-arm trial. The aim was to detect a standardised effect of 0.4 in the QUALEFFO-41 (Quality of Life Questionnaire of the European Foundation for Osteoporosis – 41 items); at 80% power and an alpha of 0.05, this required 180–200 participants in each arm or 540–600 participants in total (a total of 600 participants was used as the upper limit).

An interim analysis was planned when 4-month follow-up data were available for 75 participants per treatment arm for the primary outcome measures. The aim of this interim analysis was to terminate either the exercise therapy or the manual therapy arm if it appeared to be performing poorly relative to the other intervention or to SSPT (planned adaption based on observed outcomes), or to terminate the trial completely if both intervention arms appeared to be performing poorly relative to SSPT under futility rules.

Monitoring and ethics

Trial oversight was provided by a Trial Steering Committee and an independent Data Monitoring Committee. Ethics permission was attained for all participating sites.

Outcomes and analysis

A clinical outcome assessment was carried out at baseline (week 0), 4 months and 12 months, with additional postal questionnaires about quality of life (QoL) administered at 6 and 9 months.

There were two primary outcomes for this trial at 12 months (a measure of QoL and a measure of physical function):

1. the QUALEFFO-41, a disease-specific measure of HRQoL applicable to patients with established vertebral osteoporosis
2. the timed loaded standing (TLS) test to assess back extensor muscle endurance.

The secondary outcomes were thoracic kyphosis measured using a flexicurve ruler, the Short Performance Physical Battery (SPPB) to assess lower-extremity physical function, the functional reach test (FRT) to specifically evaluate standing balance, a 6-minute walk test (6MWT) to measure exercise endurance and the Physical Activity Scale for the Elderly to assess activity in the past week. A health resource use and falls

diary and the EuroQol-5 Dimensions, five-level version, a short, generic measure of HRQoL, was used to assist comparison with other conditions and assess health economics.

The primary analysis used an intention-to-treat (ITT) approach with pairwise comparisons between the SSPT arm and each of the two intervention arms.

The analysis of the co-primary end points of change in the QUALEFFO-41 score and TLS test time from baseline to 12 months was conducted to allow for the adaptive design used and to allow for the multiple comparisons arising from the two pairwise comparisons between SSPT and the two intervention arms. All analyses included prespecified baseline adjustment, including the value of the variable being tested.

Health economic evaluation

The cost-effectiveness analysis reported the incremental costs per quality-adjusted life-year (QALY) gained from the alternative options from an NHS and Personal Social Services perspective. Following National Institute for Health and Care Excellence recommendations, the base-case analysis was conducted from the perspective of the NHS and Personal Social Services. Cost-effectiveness was measured by QALYs, which capture differences in life expectancy and/or QoL.

Results

Overall, there was no statistically significant benefit from either of the treatment interventions over the single session of physiotherapy on either of the primary outcome measures when assessed at 12 months.

At the planned interim analysis, the difference in 4-month change in QUALEFFO-41 between each of the intervention arms and SSPT met the prespecified criteria for continuation of the trial with all three arms. However, this finding did not carry through to the full trial results at 12 months.

In addition to improvements in QUALEFFO-41 scores for exercise therapy relative to SSPT at 4 months, there were significant improvements due to exercise therapy in the SPPB score, the FRT and the 6MWT at clinically important levels. The effect of exercise therapy on the QUALEFFO-41 pain and social function subscales at 4 months also approached statistical significance. At 4 months in the manual therapy arm, there were significant improvements in TLS test duration and FRT, relative to SSPT. For the pre-planned subgroup analyses, there was a highly significant treatment*age group interaction for TLS test change at 4 months only, with significant treatment differences between SSPT and both the manual therapy arm and the exercise therapy arm for participants in the ≤ 70 years age group; there was no effect in the > 70 years age group.

The results of the complier-average causal effect analysis, with compliance defined as attending either at least four or all of the maximum of seven sessions, showed that the effects of the interventions are larger in magnitude for full compliers (attending all seven sessions) than for partial compliers (attending at least four sessions). For both full and partial compliers, a significant treatment effect of manual therapy was observed on the TLS test at 4 months in the ITT analysis. The effect of exercise therapy on TLS test change at 4 months also approached statistical significance for partial and complete compliers. However, at 12 months there were no significant treatment effects for full or partial compliers. Increases in TLS test duration were at a level that could be considered clinically significant.

Improvements in thoracic kyphosis in both the manual and exercise therapy groups increased in size over the 12-month period compared with SSPT, in which effects declined from 4 to 12 months.

Although not statistically significant, the reduction in thoracic kyphosis from baseline in the exercise and manual therapy arms was of a magnitude that has been recognised as clinically significant in other trials.

Exercise therapy resulted in higher QALY gains but higher costs than SSPT, whereas manual therapy was more costly and resulted in lower QALY gains than SSPT. However, neither exercise nor manual therapy were cost-effective relative to SSPT using the £20,000-per-QALY threshold. Overall, exercise therapy was more effective but more costly than SSPT, whereas manual therapy was less effective and more costly than SSPT.

Qualitative study

This qualitative study was carried out to explore the experiences and views of people with osteoporosis regarding their participation in the PROVE trial and their treatment interventions, their perceptions regarding the appropriateness of the interventions and the factors influencing adherence to the intervention programmes. Sampling was purposive, with the assumption that five participants from each arm would provide a rich insight into the experience of the intervention, including a mix by sex, treatment site and number of fractures at baseline. Eighteen participants were recruited.

Of the 18 people interviewed, 17 were highly positive about their participation in the PROVE trial, which was perceived as important, beneficial, organised and well run.

Participants were keen to receive manual therapy and all participants interviewed who had received manual therapy were vocally positive about its effects. Participants perceived manual therapy to be safe, enjoyable and effective. Participants in the qualitative study who had been allocated to the exercise arm, with one exception, accepted this intervention as an appropriate and effective treatment approach. Participants allocated to the SSPT arm did not perceive this intervention as an equal approach to manual or exercise therapy and some participants felt that they had received no physiotherapy treatment. There was a mismatch between the perception of benefit voiced by the participants in the qualitative data and the main RCT quantitative findings.

Conclusions

This was the largest trial to be conducted on physiotherapy and OVF by a significant margin. All previous studies were characterised by low numbers and short follow-up times.

Both the manual and exercise therapy interventions were perceived as beneficial by the participants and were well tolerated. However, they did not confer more benefit than a single 1-hour session of physiotherapy at 12 months, nor was there evidence that they were cost-effective.

Future research questions

Signals of early intervention effectiveness and greater effect when participants were more compliant were observed. Future research should concentrate on enhancing the intervention effect by using treatment protocols that exceed current commissioning practices and allow for a greater number of sessions over a longer period of time, assessed for both clinical effectiveness and cost-effectiveness.

Trial registration

This trial is registered as ISRCTN49117867.

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