Progressive exercise compared with best-practice advice, with or without corticosteroid injection, for rotator cuff disorders: the GRASP factorial RCT

Sally Hopewell,[1*] David J Keene,[2] Peter Heine,[2] Ioana R Marian,[1] Melina Dritsaki,[1] Lucy Cureton,[2] Susan J Dutton,[1] Helen Dakin,[3] Andrew Carr,[2] Willie Hamilton,[4] Zara Hansen,[2] Anju Jaggi,[5] Chris Littlewood,[6] Karen Barker,[2] Alastair Gray[3] and Sarah E Lamb[2,4] on behalf of the GRASP Trial Group

[1]Oxford Clinical Trials Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[3]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[4]College of Medicine and Health, University of Exeter, Exeter, UK
[5]Royal National Orthopaedic Hospital NHS Trust, Stanmore, UK
[6]Manchester Metropolitan University, Manchester, UK

*Corresponding author sally.hopewell@csm.ox.ac.uk

Declared competing interests of authors: Sally Hopewell is a member of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Clinical Evaluation and Trials committee (2018 to present). David J Keene holds a NIHR Postdoctoral Fellowship (PDF-2016-09-056). Ioana R Marian holds a NIHR Pre-Doctoral Fellowship (reference NIHR300479). Helen Dakin is partly funded by a NIHR Senior Research Fellowship through the Biomedical Research Centre (Oxford, UK). Andrew Carr has a patent BioPatch issued and is a member of the UK Research and Innovation/Medical Research Council Developmental Pathway Funding Scheme Panel. He was chief investigator of the NIHR HTA UK Rotator Cuff Surgery (UKUFF) trial and the Can Shoulder Arthroscopy Work (CSAW) trial. He is a consultant to the Novartis Pharmaceuticals UK Ltd Musculoskeletal Board (London, UK). He is chief investigator of a NIHR Innovation for Innovation (i4i) trial of a novel electrospun patch and of a Wellcome Trust (London, UK)-funded trial of a novel electrospun suture in rotator cuff repair surgery. He was director of the NIHR Musculoskeletal British Research Unit (2008–17) and is musculoskeletal theme lead for the NIHR Oxford Biomedical Research Centre (Oxford, UK). He reports personal fees from Novartis Pharmaceuticals UK Ltd Musculoskeletal Advisory Board. Zara Hansen receives personal fees from various health-care trusts and individuals to train health-care professionals in cognitive–behavioural approaches outside the submitted work. Anju Jaggi is currently a council member of the British Shoulder & Elbow Society (London, UK). She is co-applicant of the NIHR HTA PRO CURE (Partial Rotator Cuff Repair) trial. Chris Littlewood is chairperson of the Chartered Society of Physiotherapy Scientific Panel (London, UK). He is chief investigator of the NIHR postdoctoral fellowship-funded SPeEDy (Surgery versus PhysiothErapist-leD exercise for traumatic tears of the rotator cuff) study

(reference PDF-2018-11-ST2-005). He was previously lead researcher for the NIHR Research for Patient Benefit-funded RaCeR (Rehabilitation following Rotator Cuff RepaiR) study (PB-PG-081620009) and chief investigator for the NIHR Doctoral Fellowship-funded SELF study (DRF-2011-04-090). Sarah E Lamb reports grants from the NIHR HTA programme during the conduct of the study and was a member of the following boards: HTA Additional Capacity Funding Board (2012–15); HTA Clinical Trials Board (2010–15); HTA End of Life Care and Add on Studies (2015); HTA Funding Boards Policy Group (formerly Clinical Studies Group) (2010–15); HTA Maternal, Newborn and Child Health Methods Group (2013–15); HTA post-board funding teleconference (2010–15); HTA Primary Care Themed Call board (2013–14); HTA Prioritisation Group (2010–15); and the NIHR Clinical Trials Unit Standing Advisory Committee (2012–16).

Published August 2021
DOI: 10.3310/hta25480

Scientific summary

The GRASP factorial RCT

Health Technology Assessment 2021; Vol. 25: No. 48
DOI: 10.3310/hta25480

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Shoulder pain is very common, with around 70% of cases due to rotator cuff-related shoulder pain. Despite the widespread use of physiotherapy, there is uncertainty regarding which type of exercise therapy is associated with the best outcomes. There is also uncertainty about the long-term benefits and harms of corticosteroid injection therapy, which is often used in addition to physiotherapy.

Objectives

The GRASP (Getting it Right: Addressing Shoulder Pain) trial assessed (1) if an individually tailored progressive home exercise programme prescribed and supervised by a physiotherapist provided greater improvement in shoulder pain and function over 12 months compared with a best-practice advice session with a physiotherapist supported by high-quality self-management materials; and (2) if subacromial corticosteroid injection provided greater improvement in shoulder pain and function over 12 months compared with no injection.

Methods

Design

This was a pragmatic multicentre superiority randomised controlled trial using a 2 × 2 factorial design. Participants and physiotherapists were not blinded to group allocation.

Setting

Participants were recruited from 20 NHS primary care-based musculoskeletal and related physiotherapy services.

Participants

Adults aged ≥ 18 years with a new episode of shoulder pain (i.e. in the previous 6 months) attributable to a rotator cuff disorder (e.g. cuff tendonitis, impingement syndrome, tendinopathy or rotator cuff tear), as per British Elbow & Shoulder Society guidelines, not currently receiving physiotherapy or being considered for surgery.

Interventions

Participants ($n = 708$) were randomised (March 2017–May 2019) using a centralised computer-generated 1 : 1 : 1 : 1 allocation ratio to one of four interventions: (1) progressive exercise ($n = 174$) (six or fewer physiotherapy sessions), (2) best-practice advice ($n = 174$) (one physiotherapy session), (3) corticosteroid injection then progressive exercise ($n = 182$) (six or fewer physiotherapy sessions) or (4) corticosteroid injection then best-practice advice ($n = 178$) (one physiotherapy session).

Participants randomised to the progressive exercise intervention received up to six individual face-to-face sessions with a physiotherapist over 16 weeks. Participants were provided with a folder containing an advice booklet, an exercise action planner and diary, and instructions on their exercise programme, which was set up in collaboration with their physiotherapist. A resistance band was issued as required. The progressive exercise programme was highly structured, but could be tailored to the needs and preferences of participants.

Participants randomised to the best-practice advice intervention received a single individual face-to-face session with a physiotherapist. Participants were given an advice booklet. The content of the advice in the booklet was the same as that provided for the progressive exercise group, with the exception of a different exercise programme. Participants were given a simple set of self-guided exercises, at least one level of resistance band and access to an exercise video (available on a website and a digital versatile disc), which could be progressed and regressed, depending on their capability. The exercises were designed using similar concepts to the progressive exercise intervention, such as increased resistance, but these were a simpler range. An exercise diary was provided in addition to an exercise action planner that was simpler than the one provided to those in the progressive exercise group.

Follow-up

Measurements for the primary and secondary outcomes were collected by postal questionnaires at 8 weeks and at 6 and 12 months after randomisation. Telephone follow-up was used to contact those who did not respond or fully complete the returned questionnaire.

Clinical outcomes and analysis

The primary outcome was the mean difference in Shoulder Pain and Disability Index (SPADI) total score over 12 months. The scale is from 0 to 100, with higher values representing worse pain. Secondary outcomes were the pain and function SPADI subdomains, health-related quality of life (assessed using the EuroQol-5 Dimensions, five-level version), sleep disturbance, fear avoidance, pain self-efficacy, return to activity, global impression of treatment, health resource use, out-of-pocket expenses and work disability. Prespecified subgroup analyses included age, sex, smoking status, higher baseline SPADI score ($\geq$ 50) and higher baseline pain self-efficacy score ($\geq$ 8). The planned sample size was 704 participants, assuming 20% loss to follow-up at 12 months, and based on 90% power and 1% two-sided statistical significance to detect a minimally clinically important difference of eight points on the SPADI total scale. The primary analysis was intention to treat. The two main effect comparisons for this 2 × 2 factorial trial were (1) progressive exercise compared with best-practice advice to determine the efficacy of progressive exercise and (2) subacromial corticosteroid injection compared with no injection to determine the efficacy of subacromial corticosteroid injection. The presence of an interaction effect was formally investigated before testing their effects on the primary outcome. The difference in SPADI score between the two intervention groups was estimated overall and at each data collection time point using a repeated measures linear mixed-effects regression model adjusted for baseline and other covariates.

Economic analysis

The cost–utility of interventions was evaluated from an NHS and Personal Social Services perspective, using a within-trial intention-to-treat analysis. Quality-adjusted life-years were estimated from data collected from the EuroQol-5 Dimensions, five-level version, at baseline, 8 weeks and 6 and 12 months. Costs were estimated for each participant over 12 months of follow-up based on patient-reported use of health-care services attributable to their rotator cuff disorder. The cost of delivering each intervention, including physiotherapists' training, materials, delivery of the progressive exercise and advice sessions, and corticosteroid injections, was also estimated.

Results

The mean age of participants was 55.5 (standard deviation 13.1) years, 49.3% of participants were female and the mean duration of symptoms was 4 (interquartile range 3–6) months. Intervention groups were well matched in terms of demographic data and clinical and generic health-related quality-of-life measures. Overall, 92% (324/352) of participants randomised to the best-practice advice intervention and 95% (339/356) of participants allocated to progressive exercise either partially or fully completed the intervention. High levels of protocol adherence were achieved across all intervention groups. Follow-up data were obtained for 87% (618/708), 87% (615/708) and 91% (641/708) of participants at 12 months, 6 months and 8 weeks, respectively.

The overall mean baseline SPADI score was 54.1 (standard deviation 18.5), with higher baseline levels of shoulder pain (mean SPADI pain subscale score 63.9; standard deviation 17.1) than impaired function (mean SPADI function subscale score 44.3; standard deviation 22.1). There was an overall improvement in SPADI score in each of the four groups from baseline over time, representing a 32.2-point improvement (standard deviation 23.9 points) on the SPADI scale [with a SPADI score of 21.9 (standard deviation 23.4) at 12 months]. There was no evidence of an interaction effect and so results were analysed for the two main effect comparisons.

Clinical results

Over 12 months, there was no evidence of a difference in the SPADI scores between the progressive exercise intervention and best-practice advice intervention (adjusted mean difference between groups over 12 months −0.66, 99% confidence interval −4.52 to 3.20); nor was there evidence of a difference when analysed at the 8-week and 6- and 12-month time points (adjusted mean difference at 12 months −3.10, 99% confidence interval −7.85 to 1.64). There was also no difference between groups for secondary outcome measures, with the exception of progressive exercise, which resulted in an improvement in patient-reported global impression of treatment over the 12 months (adjusted mean difference over 12 months 0.38, 95% confidence interval 0.10 to 0.66) and at the 6- and 12-month time points.

Over 12 months, there was also no evidence of a difference in SPADI scores between the injection and the no injection groups (adjusted mean difference over 12 months −1.11, 99% confidence interval −4.47 to 2.26). There was a small difference in SPADI scores at 8 weeks (adjusted mean difference at 8 weeks −5.64, 99% confidence interval −9.93 to −1.35) in favour of the injection group, but not at the 6- and 12-month time points (adjusted mean difference at 12 months 1.93, 99% confidence interval −2.41 to 6.27). There was no difference between groups for secondary outcome measures, with the exception of the injection group at 8 weeks, which resulted in a small improvement in shoulder pain, shoulder function, sleep disturbance, return to desired activities and global impression of treatment.

Prespecified subgroup analysis showed that the effect of injection was stronger at 8 weeks in people with a higher baseline SPADI score (adjusted mean difference at 8 weeks −9.67, 99% confidence interval −15.37 to −3.97) than in those who received injections but had a lower baseline SPADI score (adjusted mean difference at 8 weeks −0.36, 99% confidence interval −8.87 to 6.16). No differences were observed for other prespecified subgroup analyses. No serious adverse events were associated with treatment interventions.

Economics results

The base-case cost-effectiveness analysis showed that, over the 12-month period, participants in the best-practice advice treatment group gained, on average, 0.74 quality-adjusted life-years (95% confidence interval 0.710 to 0.763) and an NHS cost of £195. Adding progressive exercise to best-practice advice resulted in a gain of an additional 0.019 quality-adjusted life-years ($p = 0.220$), compared with best-practice advice alone, at an additional cost of £52 ($p = 0.247$). Adding corticosteroid injection to best-practice advice resulted in a gain of 0.021 quality-adjusted life-years ($p = 0.184$), compared with best-practice advice alone, and increased the cost by £10 per participant ($p = 0.747$). At a £20,000 per quality-adjusted life-year ceiling ratio, best-practice advice plus injection was found to have a 54.93% probability of being best value for money of the four treatments evaluated in the trial. Best-practice advice plus injection cost £475.59 per quality-adjusted life-year gained compared with best-practice advice alone, and strongly dominated progressive exercise alone and progressive exercise plus injection, being less costly and accruing more quality-adjusted life-years. Sensitivity analyses assuming additive effects, taking a societal perspective and varying the cost of training physiotherapists, confirmed the base-case conclusion that best-practice advice plus injection is expected to be best value for money at a ceiling ratio of £20,000 per quality-adjusted life-year, although there was substantial uncertainty around this conclusion in all analyses.

Conclusion

Implications for health care

The GRASP trial shows that the progressive exercise intervention was not superior to a best-practice advice session with a physiotherapist. Subacromial corticosteroid injection improved shoulder pain and function at 8 weeks, but provided modest short-term benefit only, with the greatest benefit being in those with higher levels of pain and functional impairment. Best-practice advice in combination with corticosteroid injection has a 54.93% probability of being the most cost-effective intervention for the NHS.

Recommendations for research

There is a case to extend follow-up to assess long-term outcomes, as some participants still reported ongoing pain and impaired shoulder function at 12 months. There is a need to better understand the natural history of rotator cuff disorders, including whether symptoms resolve over an extended period or persist in the longer term. Longer-term follow-up would also address concerns regarding later surgery and corticosteroid injection, and potential long-term harm due to its possible effects on tendon structure.

Trial registration

This trial is registered as ISRCTN16539266 and EudraCT 2016-002991-28.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 48. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/26/06. The contractual start date was in October 2016. The draft report began editorial review in November 2020 and was accepted for publication in April 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).