Surgical treatments compared with early structured physiotherapy in secondary care for adults with primary frozen shoulder: the UK FROST three-arm RCT

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Scientific summary

The UK FROST three-arm RCT

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Scientific summary

Background

Frozen shoulder occurs when the capsule, or soft tissue envelope, around the ball-and-socket shoulder joint becomes inflamed, scarred and contracted. This makes the shoulder very painful and stiff. Less invasive treatments, such as pain medication, are provided in primary care in the UK. When stiffness becomes more established, treatments include physiotherapy with a steroid injection, manipulation under anaesthesia, and arthroscopic capsular release. With the intention of facilitating quicker recovery, more invasive and costly surgical interventions (manipulation under anaesthesia and arthroscopic capsular release) are being used despite a lack of good evidence that these are effective.

Objectives

The objectives of UK FROST (UK FROzen Shoulder Trial) were to evaluate the clinical effectiveness and cost-effectiveness of early structured physiotherapy compared with manipulation under anaesthesia compared with arthroscopic capsular release for patients referred to secondary care for the treatment of primary frozen shoulder; to carry out a qualitative study to explore the acceptability of the different interventions to trial participants and health-care professionals; and to undertake a systematic review update to explore the trial findings in the context of existing evidence.

Methods

Randomised controlled trial

Design

This was a pragmatic, parallel-group, multicentre, open-label, three-arm, randomised superiority trial. The randomisation sequence was based on a computer-generated randomisation algorithm provided by a remote randomisation service. Individual patients were allocated to manipulation under anaesthesia, arthroscopic capsular release or early structured physiotherapy in the ratio of 2 : 2 : 1, stratified by the presence of diabetes, using random blocks sizes of 10 and 15.

Eligibility criteria

Adults aged $\geq$ 18 years presenting with a clinical diagnosis of frozen shoulder, characterised by restriction of passive external rotation in the affected shoulder to $<$ 50% that of the contralateral shoulder, and radiographs to exclude other pathologies were eligible for inclusion. Exclusion criteria were a bilateral concurrent frozen shoulder; frozen shoulder secondary to trauma that required hospital care; frozen shoulder secondary to other causes; contraindication to any of the trial treatments; not resident in a catchment area of a trial site; or lack of mental capacity to understand the trial.

Setting

The orthopaedic departments of 35 NHS hospitals in the UK across a range of urban and rural areas (April 2015–December 2018).

Interventions

Early structured physiotherapy

Early structured physiotherapy consisted of up to 12 weekly sessions comprising essential 'focused physiotherapy' and optional supplementary physiotherapy. Focused physiotherapy comprised an information leaflet providing education and advice on pain management and function; an intra-articular steroid injection; and hands-on mobilisation techniques, increasingly stretching into the stiff zone of the shoulder as the condition improved. Participants received supervised exercises and instructions on a graduated home exercise programme.

Manipulation under anaesthesia

Manipulation under anaesthesia involved the affected shoulder being manipulated to stretch and tear the tight capsule and to improve the range of movement. An intra-articular corticosteroid injection to the glenohumeral joint was used while the patient was under anaesthesia, unless this was contraindicated. Post-procedural physiotherapy was provided.

Arthroscopic capsular release

Arthroscopic release of the contracted rotator interval and anterior capsule was performed, followed by manipulation under anaesthesia to complete the release of the inferior capsule. Steroid injections were permitted at the surgeon's discretion. Post-procedural physiotherapy was provided.

Outcome measures

The primary outcome was the Oxford Shoulder Score at 12 months post randomisation. The Oxford Shoulder Score is a 12-item patient-reported outcome measure with a score range from 0 (worst) to 48 (best). This was also completed at 3 and 6 months post randomisation. Secondary outcomes, gathered at 3, 6 and 12 months, were the QuickDASH (Quick Disabilities of the Arm, Shoulder and Hand); a Numeric Rating Scale for shoulder pain during the past 24 hours; extent of recovery using a visual analogue scale (0–100); and the EuroQol-5 Dimensions, five-level version. Expected and unexpected complications and adverse events were also recorded.

Sample size

The minimum clinically important difference on the Oxford Shoulder Score was defined as a 5-point difference (standard effect size 0.42) between surgery and no surgery and a 4-point (standard effect size 0.33) difference between manipulation under anaesthesia and arthroscopic capsular release. A total sample size of 500 patients was required to observe these effect sizes, with 90% power and 5% two-sided significance, adjusting for a moderate estimate ($r = 0.4$) of the correlation between Oxford Shoulder Score over 12 months and allowing for 20% attrition.

Analyses

Analyses were conducted for arthroscopic capsular release compared with early structured physiotherapy, manipulation under anaesthesia compared with early structured physiotherapy and arthroscopic capsular release compared with manipulation under anaesthesia using Stata® version 15 (StataCorp LP, College Station, TX, USA) and two-sided statistical significance at the 0.05 level. The intention-to-treat primary analysis was based on a linear mixed model incorporating the Oxford Shoulder Score at all available time points and using an unstructured covariance pattern to model the relationship of repeated measurements by the same individual. The model was adjusted for Oxford Shoulder Score at baseline and included as further fixed effects treatment arm, time, arm-by-time interaction, age, sex and diabetes, with recruitment site as a random effect. The model provided estimates for each of the three treatment comparisons at individual time points, including the primary end point of 12 months, as well as an overall treatment effect over 12 months. The estimates are reported as mean differences between treatment arms with 95% confidence intervals and associated *p*-values. Continuous secondary outcomes were analysed using the same method as the primary outcome and adjusting for the same covariates.

Prespecified sensitivity analyses explored the effect of non-compliance with early structured physiotherapy using complier average causal effect analysis; the effect of waiting times for interventions using additional data collected just before and 6 months following treatment; the impact of missing data; and the effect of questionnaire return outside the intended follow-up time. The Data Monitoring and Ethics Committee advised that employment status be included as a model covariate in a sensitivity analysis. Prespecified subgroup analyses explored possible treatment effect interactions with diabetes, previous receipt of physiotherapy and patient baseline treatment preference. The Trial Steering Committee advised on including a subgroup analysis for duration of symptoms at the time patient eligibility was confirmed.

Economic evaluation

Costs and health benefits were compared for the three treatment arms over the 12 months and hence discounting was not required. All costs were expressed in Great British pounds at a 2017–18 price base. Health outcomes were assessed in terms of quality-adjusted life-years, based on patients' health-related quality-of-life outcomes obtained from trial participants using the EuroQol-5 Dimensions, five-level version, at baseline and at 3, 6 and 12 months. Differences in mean costs and mean quality-adjusted life-years at 12 months were used to derive the incremental cost-effectiveness ratio for surgery and non-surgical treatment. The base-case analysis was conducted on an intention-to-treat basis, with multiple imputation for missing data, and using a UK NHS and Personal Social Services perspective. A secondary analysis took a broader perspective that included private care and productivity costs (i.e. days lost from work).

Qualitative study

This study explored the trial participants' experience and acceptability of the treatments and taking part in the trial, and surgeons' and physiotherapists' experience of the treatments they delivered in the trial. Face-to-face or telephone interviews were undertaken. Interviews were undertaken by a physiotherapy researcher trained in qualitative research methods who was not involved in the trial. Interviews were semistructured and used open questions, and they were audio-recorded and transcribed. The interviews were analysed using constant comparative methods. Transcripts were coded and categorised into themes using NVivo 11 qualitative data software (QSR International, Warrington, UK) and reviewed by a second researcher. Data from trial participants were mapped against the World Health Organization's *International Classification of Functioning, Disability and Health* framework.

Systematic review update

MEDLINE/PreMEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials), EMBASE, PEDro, Science Citation Index, ClinicalTrials.gov and World Health Organization International Clinical Trials Registry were searched from January 2010 to December 2018, and studies reported prior to 2010 were obtained from our previous Health Technology Assessment review [Maund E, Craig D, Suekarran S, Neilson A, Wright K, Brealey S, *et al*. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. *Health Technology Assessment* 2012;16(11)]. Randomised controlled trials evaluating manipulation under anaesthesia, arthroscopic capsular release, hydrodilatation or physiotherapy plus a steroid injection for treatment of primary frozen shoulder were compared with each other, no treatment or supportive care were eligible. The primary outcome was patient-reported function and disability at 12 months. Study selection was undertaken independently by two researchers. For continuous outcomes, the post-intervention mean (standard deviation, and number of participants) for each arm was extracted, where available. The standardised mean difference was calculated to allow comparison between studies. Data extraction and assessment using the Cochrane Risk of Bias tool was undertaken by one researcher and checked by a second. Narrative and tabular summaries of key study characteristics, results and quality assessment are provided. A pairwise meta-analysis using a random-effects model was undertaken for a single comparison only because of limited data and methodological and statistical heterogeneity.

Results

Randomised controlled trial

Of 914 patients screened, 503 were randomised to one of manipulation under anaesthesia ($n = 201$), arthroscopic capsular release ($n = 203$) and early structured physiotherapy ($n = 99$). Follow-up rates were between 85% and 89%, and no evidence was seen of differential dropout across the treatment arms. The primary analysis comprised all participants with Oxford Shoulder Score outcome data at one or more follow-ups (94%). Average shoulder function improved in all treatment arms, with many participants (24%) regaining function to the top Oxford Shoulder Score at 12 months.

At the primary end point at 12 months, participants randomised to arthroscopic capsular release had, on average, a statistically significantly higher (better) Oxford Shoulder Score than those randomised to manipulation under anaesthesia (2.01 points, 95% confidence interval 0.10 to 3.91 points) or to early structured physiotherapy (3.06 points, 95% confidence interval 0.71 to 5.41 points). There was no statistically significant difference between manipulation under anaesthesia and early structured physiotherapy (1.05 points, 95% confidence interval −1.28 to 3.39 points).

At the short-term follow-up at 3 months, arthroscopic capsular release had lower (worse) Oxford Shoulder Score than the other two interventions (vs. manipulation under anaesthesia −3.36 points, 95% confidence interval −5.27 to −1.45 points; vs. early structured physiotherapy −4.72 points, 95% confidence interval −7.06 to −2.39 points). There was no evidence of statistically significant differences in average Oxford Shoulder Score over the 12 months' follow-up (manipulation under anaesthesia vs. early structured physiotherapy 0.61 points, 95% confidence interval −1.31 to 2.53 points; arthroscopic capsular release vs. early structured physiotherapy −0.23 points, 95% confidence interval −2.15 to 1.70 points; arthroscopic capsular release vs. manipulation under anaesthesia −0.84 points, 95% confidence interval −2.41 to 0.72 points).

Mean differences were short of the minimal clinically important effect size of 4 (arthroscopic capsular release vs. manipulation under anaesthesia) to 5 (arthroscopic capsular release or manipulation under anaesthesia vs. early structured physiotherapy) Oxford Shoulder Score points. However, differences of that magnitude were included in the 95% confidence intervals for the benefit of manipulation under anaesthesia and early structured physiotherapy over arthroscopic capsular release at 3 months, and for the benefit of arthroscopic capsular release over early structured physiotherapy at 12 months. Sensitivity analyses did not substantially alter the results. There were no significant subgroup interactions.

Around 20% of all trial participants did not complete their treatment. The complexity of the multiple alternative pathways for each participant limited the analyses of the effect of compliance. At 12 months, the outcomes for early structured physiotherapy compliers remained lower (worse) than for those who complied in both surgery arms combined (−1.84 Oxford Shoulder Score points, 95% confidence interval −4.41 to 0.74 points; $p = 0.157$).

Among the secondary outcomes, QuickDASH and shoulder pain results followed a similar pattern to the Oxford Shoulder Score, in that, compared with those allocated to manipulation under anaesthesia or early structured physiotherapy, statistically significant poorer outcomes were observed for arthroscopic capsular release participants at 3 months but better outcomes were observed at 12 months. There were no statistically significant differences between the treatment arms in response to the global question on the extent of recovery.

In total, there were only 10 serious adverse events, reported for nine participants. All serious adverse events occurred in the surgical arms (arthroscopic capsular release, $n = 8$; manipulation under anaesthesia, $n = 2$), although one participant in the arthroscopic capsular release arm had a serious adverse event resulting from non-trial physiotherapy. The events mainly related to serious medical complications such as chest infection or stroke. Thirty-three non-serious adverse events were reported

for 31 participants, and these were mainly expected and often were related to persistent or worsening shoulder pain. There was no evidence of a statistical difference in the proportions of non-serious adverse events ($p = 0.186$).

Economic evaluation

The base-case economic analysis showed that, at 12 months, manipulation under anaesthesia was, on average, £276 more costly per participant (95% confidence interval £65.67 to £487.35) than early structured physiotherapy. Manipulation under anaesthesia was slightly more beneficial in terms of utilities (mean 0.0396 more quality-adjusted life-years per participant than early structured physiotherapy, 95% confidence interval −0.0008 to 0.0800 more quality-adjusted life-years). The resulting incremental cost-effectiveness ratio for manipulation under anaesthesia was £6984 per additional quality-adjusted life-year. Arthroscopic capsular release was substantially more costly than early structured physiotherapy [on average costing £1733.78 more per participant (95% confidence interval £1529.48 to £1938.06 more per participant)] for a slight benefit in utilities [mean 0.0103 more quality-adjusted life-years per participant than early structured physiotherapy (95% confidence interval −0.0304 to 0.0510 more quality-adjusted life-years)]; the incremental cost-effectiveness ratio was > £100,000 per additional quality-adjusted life-year. Arthroscopic capsular release was more expensive than manipulation under anaesthesia and resulted in slightly fewer quality-adjusted life-years. Manipulation under anaesthesia was the intervention most likely to be cost-effective at a threshold of £20,000 per quality-adjusted life-year (manipulation under anaesthesia, 86%; early structured physiotherapy, 14%; arthroscopic capsular release, 0%).

Qualitative study

Forty-four interviews (most of which were conducted over the telephone) were undertaken with trial participants, who were evenly distributed across the three interventions, and with eight surgeons and physiotherapists. Trial participants described how frozen shoulder had a major impact on all aspects of their life. They were keen to get their shoulder problems resolved, which motivated them to participate in the trial. They thought that seeking early medical help and having a quicker NHS care pathway were important. In general, trial participants were satisfied with the trial interventions and found them acceptable. They reported improvements in pain, shoulder movements and function. Participants who received arthroscopic capsular release described recovering quicker than they had expected. Surgeons and physiotherapists followed a stage-based treatment approach in their routine practice. Both groups felt that people with diabetes tend to have poorer outcomes. They suggested that hydrodilatation could have been a treatment arm of the trial. Both groups stated that some people who previously had received ineffective physiotherapy had not wanted to take part in the trial.

Systematic review

Nine studies were identified, including UK FROST, which provided by far the largest and most robust evidence. The number of participants in the other studies ranged from 26 to 136, and the studies were mostly single centre. All studies were rated as being at high risk of bias for blinding of participants and clinicians, and outcome assessment. Considerable heterogeneity of the interventions and generally limited evidence for many of the comparisons meant that only two studies could be pooled as part of a meta-analysis (UK FROST and one other trial) comparing long-term shoulder functioning for patients receiving either arthroscopic capsular release or physiotherapy. The pooled effect favoured arthroscopic capsular release; however, the second study provided little additional weighted information.

Conclusions

UK FROST has provided robust clinically relevant evidence that none of the three treatments was clearly superior in patient-reported shoulder pain and functioning at 12 months. Our specifically designed early structured physiotherapy pathway can be accessed quickly in the NHS and has lower costs. However, the likelihood of further treatment being required is higher with early structured

physiotherapy than with the surgical interventions. Manipulation under anaesthesia is the most cost-effective option, with an incremental cost-effectiveness ratio of £6984 per additional quality-adjusted life-year. Patients who receive arthroscopic capsular release are least likely to need further treatment, but arthroscopic capsular release is associated with relatively higher risks and costs.

To address the increasing popularity of hydrodilatation, and the paucity of rigorous evidence of hydrodilatation's effectiveness, a high-quality randomised controlled trial is recommended to compare hydrodilatation with early structured physiotherapy with steroid injection with manipulation under anaesthesia with steroid injection.

Trial registration

This trial is registered as ISRCTN48804508.

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This report

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