Comparison of surgical or non-surgical management for non-acute anterior cruciate ligament injury: the ACL SNNAP RCT

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Scientific summary

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Scientific summary

Background

Anterior cruciate ligament (ACL) injury is a common knee injury that can have a profound effect on knee kinematics (knee movement and forces) with recurrent knee instability as the main problem. This leads to poor quality of life (QoL), decreased activity and increased risk of secondary osteoarthritis of the knee. Management of patients with an ACL injury can include a non-surgical (rehabilitation) or surgical (reconstruction) approach. The rehabilitation involves specialised physiotherapy exercises, while the surgery involves reconstructing the ligament, usually with tissue taken from the injured persons own body (autograft). However, insufficient and conflicting evidence exists to show which of these management strategies is best in order to guide decision-making and treatment.

High-quality trials have been conducted in the management of acutely injured patients with conflicting findings. A Scandinavian study suggested that rehabilitation should always be attempted in the first place for acute cases, whereas a subsequent Dutch study showed that ACL reconstruction (ACLR) gave better results. In the NHS patients often present late for diagnosis and management and the results of these two studies cannot be applied to the longer-standing ACL-injured population often seen in the UK.

A randomised trial was designed to address the uncertainty and fill the gap in the evidence base regarding the clinical and cost effectiveness of these two approaches. The intention was to inform standards of care for ACL injury management in non-acute patients.

Objective(s)

To determine in patients with non-acute ACL injury [commonly referred to as ACL deficiency (ACLD)] whether a strategy of surgical management (reconstruction) without prior rehabilitation was more clinically effective and cost-effective than non-surgical management (rehabilitation with option for later ACLR only if required). The primary end point was a functional knee score at 18-month follow-up from randomisation.

Design

The study was a pragmatic, multicentre, superiority, randomised controlled trial with two-arm parallel groups and 1 : 1 allocation. A two-stage internal pilot study was included to confirm appropriateness of inclusion criteria, assess outcome measures and data capture systems, and ensure adequate recruitment. Rather than a head-to-head comparison of two interventions, the study was designed as a 'management' assessment in which specific events were expected and permitted. This included the subsequent requirement for necessary surgical intervention (ACLR) in patients first allocated to the rehabilitation arm. Both intention-to-treat (ITT) and per-protocol analyses were planned. Due to the nature of the interventions, there was no blinding of the participants nor healthcare practitioners (surgeons and physiotherapists) to receipt of the intervention.

Outcome measures

The primary outcome was the Knee Injury and Osteoarthritis Outcome Score (KOOS4) at 18 months post randomisation. Secondary outcomes included:

- return to activity/level of sport participation: Modified Tegner
- intervention-related complications
- generic QoL: The EuroQol-5 Dimensions, five-level version (EQ-5D-5L)

- knee-specific patient-reported outcomes: All five subscales of the KOOS
- Anterior cruciate ligament quality of life (ACL-QoL) score
- resource-usage data
- expectations of return to activity and confidence in relation to the knee
- patient satisfaction: Simple Likert scale.

The outcomes reflected consensus opinion and the reference standard for evaluating ACL injury/reconstruction and consensus from a specially convened patient and public involvement focus group.

Setting

Twenty-nine secondary care NHS orthopaedic units from across the UK. The study involved 87 surgeons and 205 physiotherapists.

Participants

The inclusion criteria included any patient aged 18 years or above with symptomatic ACLD of the native ligament (instability episodes of frank giving way or feeling unstable) with the ACL injury (either partial or complete tear) confirmed using clinical assessment and magnetic resonance imaging (MRI) scan.

Patients were excluded if they were in the acute phase of primary ACL injury, have had previous knee surgery to the index knee, had meniscal pathology with characteristics that indicate immediate surgery, or any features of late-stage osteoarthritis.

Three hundred and sixteen trial participants with a symptomatic non-acute ACL-injured knee were randomised between February 2017 and April 2020. One hundred and fifty-six participants were randomised to the surgical management arm and 160 to the rehabilitation arm.

Interventions

Patients in the surgical management arm underwent arthroscopic ACLR (using any technique chosen by the surgeon) as soon as possible and without any further formal or prescribed rehabilitation. Patients in the rehabilitation arm (non-surgical) attended rehabilitation sessions at a local physiotherapy department and only were listed for reconstructive surgery on continued instability or symptoms following rehabilitation. Standard postoperative rehabilitation was provided and some assessment of compliance was conducted. Guidance was provided on a minimal rehabilitation protocol for all rehabilitation sites to enable a level of quality control/standardisation without disrupting the pragmatic nature of the study. Compliance and fidelity data were also collected for both surgery and rehabilitation interventions.

Recruitment and consent

Patients with symptomatic knee problems (instability) consistent with an ACL injury were eligible for inclusion. ACL injury (deficiency), either partial or complete tear, was confirmed at a patient's routine outpatient appointment through clinical assessment and MRI scan.

Potential patients were identified in routine orthopaedic outpatient and pre-assessment clinics by the local clinical team.

The participating surgeon or member of the clinical team initially approached potential participants who meet the eligibility criteria to inform them of the study. Patients who expressed a potential interest in participating were then referred to a research nurse/physiotherapist for further details about the study and written information. Patients who wished to participate then completed an informed consent form and baseline questionnaire. Written consent was obtained for all patients.

Statistics and analysis

The sample size was calculated using the KOOS4 score and a conservative minimal clinically important change of 8 points with a standard deviation of 19. Given these assumptions, 120 participants per group were required (1 : 1 allocation, 240 in total) to achieve 90% power at two-sided 5% significance level in the absence of any clustering of outcome. To allow for just over 15% missing data, 320 participants were needed.

All principal analyses were based on the ITT principle ('as randomised'), analysing participants in the groups to which they are randomised irrespective of compliance with treatment allocation. Statistical significance was at the two-sided 5% level, with corresponding confidence intervals derived, and the analyses was carried out in Stata® (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Baseline and follow-up data were summarised using descriptive statistics. The analyses were carried out once the 18-month time point has been reached by the last participant.

It was anticipated that the ACL Surgery Necessity in Non-Acute Patients (SNNAP) trial would involve numerous potential treatment pathways due to the complex nature of the interventions and several potential pathway profiles were described and accounted for to inform the per-protocol analyses. Item-level missing data for the primary outcome were dealt with according to the KOOS scoring manual for the primary outcome analysis. However, participant-level missing data were not imputed in the principal analyses.

The principal analysis of the primary outcome measure (KOOS4 score) was compared using a linear regression model including treatment arm, with adjustment for the stratification by site and KOOS4 baseline score. The model included KOOS4 score at baseline as a continuous variable and adjusted for stratification by site using cluster-robust standard errors. Unadjusted analyses included only the treatment variable in the analysis models, with adjusted analyses further adjusting for baseline KOOS4 scores and allowing for intracluster correlation between recruitment sites. Analyses were carried out on the KOOS4 score to assess sensitivity to compliance with the allocated treatment, missing data and to determine if there were any subgroup effects present. Adjusted and unadjusted analyses were carried out on the ITT, conservative per-protocol (PPC) and pragmatic per-protocol (PPP) populations using linear regression. Complier-average causal effect (CACE) analysis assessing compliance to receipt of surgery or not was also carried out using instrumental variable regression. The impact of missing data at the participant level was explored via sensitivity analyses for the primary outcome using the rctmiss package in Stata. A pattern-mixture model was used to extend the adjusted linear regression model used for the primary outcome analysis, in order to show graphically the difference in treatment effect for each treatment arm if different mean values are assumed for the missing data. Subgroup analyses of gender, baseline KOOS4 scores, age and baseline Tegner Activity Scores were carried out using treatment–subgroup interactions and interpreted as exploratory analyses.

A secondary analysis of the primary outcome was also performed on the ITT population using an area under the curve (AUC) approach. The treatment estimates obtained from a mixed model at each time point (baseline, 6, 12 and 18 months) were used to calculate the AUC. The model included repeated measures of the KOOS4 score (level 1), nested within participants (level 2) and adjusted for recruitment site as a random effect (level 3). A treatment by time-point interaction was also included in the model.

For the secondary outcomes, KOOS subscales, ACL-QoL and EQ-5D-5L were analysed using linear regression models with adjustment for randomisation and baseline variables as described in the analysis of the primary outcome. Modified Tegner Activity Scores were analysed using a Mann–Whitney *U*-test, with confidence intervals (CIs) for proportions calculated for patient satisfaction and return to pre-injury activity level.

Numbers of complications were summarised by treatment arm. Surgery after 3 months of rehabilitation was not considered a withdrawal from the rehabilitation arm, as this was part of the management strategy described in the protocol.

Healthcare costs and quality-adjusted life-years (QALYs) for all 316 participants were estimated from the date of recruitment until withdrawal from study or end of follow-up at 18 months. Healthcare resource use data were collected via questionnaires and hospital records and valued using national costs. Responses to EQ-5D-5L questionnaires were converted into utility scores to inform the calculation of QALYs. Healthcare costs and QALYs were discounted at 3.5% per year and missing data were imputed with multiple imputation by chained equations (30 imputed datasets) after assessing missing at random to be a plausible assumption. The incremental cost-effectiveness ratio (ICER) was estimated by dividing the mean cost difference between surgical management and non-surgical management by the mean QALY difference. We captured the uncertainty in the cost-effectiveness results and calculated the probability that surgical management is cost-effective relative to non-surgical management at £20,000–30,000 per QALY gained.

Results

Baseline characteristics for each treatment group were well balanced. Of the patients, 63.8% had sustained their injury over 4 months previously and 22.5% over 1 year previously. The baseline KOOS4 score was 50.1 (standard deviation ± 19.8) for the entire sample.

Forty-one per cent of those allocated to rehabilitation underwent subsequent reconstruction within 18 months with 38% completing rehabilitation and not undergoing surgery. Twenty-one per cent of those allocated to rehabilitation did not start or had insufficient rehabilitation. Seventy-two per cent of those allocated to surgery underwent reconstruction. Eleven per cent of patients allocated to surgery elected not to undergo ACLR (for various reasons) and underwent rehabilitation. Seven per cent of patients were still awaiting surgery and 10% of patients did not undergo surgery or rehabilitation. The median number of formal physiotherapy visits was five with a mixture of one-to-one and group sessions. For surgical reconstruction, the most common procedure was a hamstring graft (in over 80% of those undergoing ACLR). Twenty-six per cent of surgical patients required meniscectomy or meniscal repair.

The adjusted mean KOOS4 scores at 18 months post randomisation had increased to 73.0 in the surgical arm, and to 64.6 in the rehabilitation arm. The adjusted mean difference (ITT analysis) was 7.9 (95% CI 2.5 to 13.2; $p = 0.005$) in favour of surgical management. The PPP and PPC analyses supported the ITT results, with all treatment effects favouring surgical management at a level reaching statistical significance. All unadjusted analyses also produced statistically significant effects in favour of surgical management. A secondary AUC analysis was performed on the ITT population using the KOOS4 scores at baseline, 6, 12 and 18 months and also showed superiority of surgical management.

Subgroup analyses for KOOS4 scores [Gender, KOOS4 score (high/low), Age (over or under 40 years) and Tegner Activity Score (high/low)] showed no effects.

All KOOS4 subscales (Pain, Symptoms, Activities of Daily Living (ADL), Sports and Recreation, and Knee-related Quality of Life (QoL) showed significant differences in favour of surgical management.

At 18 months, 28% ($n = 27$) of participants in the surgical management arm had returned to their pre-injury activity level, compared to 24% ($n = 21$) in the rehabilitation arm. Sixty-five out of the 95 (68%) of participants with available scores in the surgical arm did not reach the activity level they expected to return to post treatment, compared to 63 of the 86 patients with scores (73%) in the rehabilitation arm.

There were no differences between groups in surgical complications ($n = 1$ surgery, $n = 2$ rehabilitation) or clinical events ($n = 11$ surgery, $n = 12$ rehabilitation). Clinical events included episodes of giving way or instability which were especially important for the non-surgical groups.

Significant differences existed in the ACL-QoL questionnaire in favour of the surgical management group (mean 61.7 surgery, mean 57.6 rehabilitation, $p = 0.003$).

Eighty-three per cent of surgery patients were satisfied with their treatment and outcome compared to 68% allocated to initial rehabilitation.

Health economic analysis found that surgical management led to improved health-related QoL compared to non-surgical management but with higher healthcare costs. The ICER for the surgical management programme versus rehabilitation was £19,346 per QALY gain. Using £20,000–30,000 per QALY thresholds, the intervention is cost-effective in the UK setting.

Limitations

There were several limitations to the study, but these did not affect the interpretation. Firstly, not all surgical patients underwent reconstruction, but an ITT analysis still showed a significant difference (and was aligned with per-protocol analyses). Early adjustment of inclusion criteria to facilitate recruitment generated a sample that tended towards a more acute population than ideal but was still considered representative of the intended population.

The hierarchy of treatment could have posed problems in this surgical versus non-surgical study (non-surgical treatment always being the first treatment option). This was mitigated by the design and having a 'management' perspective which predicted and allowed for uptake of surgery in the non-surgical arm.

The healthcare economic analysis had several limitations, including the sizeable amount of missing data on use of healthcare resources and EQ-5D-5L. We accounted for this using multiple imputation.

Conclusions

Surgical reconstruction as a management strategy for more long-standing, non-acute ACL-injured patients presenting in secondary care was shown to be superior to initial non-surgical management with subsequent surgery, if required. This has implications for healthcare and should be discussed in the shared decision-making process with patients. Although a rehabilitation strategy for ACL injury remains a safe and beneficial intervention (and is still warranted in acute patients and useful for those unwilling to undergo surgery), it is advised that more long-standing, non-acute ACL-injured patients undergo surgical reconstruction without necessarily delaying for a prior period of rehabilitation.

This approach is also cost-effective and has the potential to save the NHS millions of pounds in unnecessary physiotherapy treatment and appointments.

Future work

The trial was pragmatic. Studies to explore the influence of treatment fidelity and compliance, especially in the rehabilitation arm, will be useful. Other recommendations for future research include evaluation of innovative surgical reconstruction or even ligament repair. The best form and content of rehabilitation for postoperative ACLR should also be explored. The study did not provide information on why so few patients return to high levels of activity and this could be explored further.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN10110685; ClinicalTrials.gov Identifier: NCT02980367.

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