

Timing of surgical intervention for developmental dysplasia of the hip: a randomised controlled trial (Hip 'Op)

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Scientific summary

The Hip 'Op RCT

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Scientific summary

Background

Developmental dysplasia of the hip (DDH) is one of the most common congenital disorders. Late-presenting cases are synonymous with the need for surgical intervention. Surgical reduction of the hip may be complicated by the development of avascular necrosis (AVN), which can result in long-term problems such as leg length discrepancy and the need for early hip replacement. AVN is an iatrogenic phenomenon that occurs as a result of an interruption to the femoral head blood supply during treatment. Some surgeons delay surgical treatment until the bony ossific nucleus (ON) has developed because this may provide some mechanical protection to the femoral head blood supply, and may thus reduce the chance of AVN developing. However, others believe that the earlier the reduction is performed, the better the result (providing AVN is avoided). Currently, there is no definitive evidence to support either strategy.

Objectives

To determine, in children aged 12 weeks to 13 months, whether or not delayed surgical treatment of a dislocated hip reduces the incidence of AVN at 5 years of age. The main clinical outcome measures were incidence of AVN and the need for a secondary surgical procedure during 5 years' follow-up. In addition, to (1) qualitatively evaluate parental satisfaction with the strategies and (2) assess NHS and societal costs with the aim of undertaking a health economic analysis.

Methods

Study design

This was a Phase III randomised controlled trial incorporating an internal pilot, and qualitative and health economics analyses. Participants were randomised with a 1 : 1 allocation ratio to undergo early or intentionally delayed surgery for their dislocated hip. The study aimed to recruit 636 children over 4 years; this target recruitment was considered feasible if, within the 18-month internal pilot, 120 children had been recruited. In addition to the internal pilot, a closedown plan had been pre-agreed with the funder, which was activated when the success criteria for the pilot phase of the study were not met.

Settings and participants

Participants were recruited to the Hip 'Op study from 15 paediatric orthopaedic centres in the UK. Children aged 12 weeks to 13 months with DDH, either having been newly diagnosed or had failed splintage, and who required surgery.

Interventions

Participants were randomised to:

- arm A – early treatment
- arm B – (intentionally) delayed treatment.

The actual procedures carried out were decided by the treating clinician, not by the randomisation or the study protocol.

Outcomes

The primary outcome was incidence of AVN at 5 years of age, as classified according to the Kalamchi and MacEwen grading.

Secondary outcomes were the need for secondary surgery on the affected hip, presence of the ON at the time of primary treatment for dysplasia, quality of life for the main carer and child, a health economic evaluation and the qualitative analysis.

Sample size

Allowing for 10% dropout during the 5-year follow-up period, the total number of patients required was 636 (318 per treatment arm). This sample size had 90% power to detect a 10-percentage point difference between treatment arms (10% vs. 20% AVN rate at 5 years) in a 5% two-sided test.

Randomisation and blinding

Randomisation was via the web-based system TENALEA (TENALEA Randomisation System version 3.0; FormsVision BV, Abcoude, the Netherlands). Allocations were assigned in a 1 : 1 ratio and were stratified by failed splintage and age at diagnosis. Randomisation was carried out once eligibility was confirmed and written consent had been provided. Neither parents nor investigators/surgeons were blinded to the treatment allocation.

Analysis methods: statistical and qualitative

Given the small sample size and early cessation of the trial, it was not possible to perform any of the originally planned analyses for the main trial or health economic aspects. The intention for the main trial was to analyse the presence of AVN by logistic regression, with centre as a random effect and the randomisation stratification factors as fixed effects, using the intention-to-treat population. Secondary analyses were intended to explore the need for further surgery defined according to radiographic findings, and grading of AVN between the treatment arms.

The intention for the health economic analyses was to conduct an analysis of the cost and cost-effectiveness of early versus delayed treatment for infants with DDH. Cost and cost-effectiveness for the 'within-trial' period (5 years), and over the expected lifetime of the participant, would have been estimated.

The telephone interviews were audio-recorded, transcribed verbatim, anonymised and analysed thematically using a framework approach. This allowed the interpretation of key issues faced by participants across the sample. Had the trial continued, diachronic case analysis, tracking participants' accounts over time, would have been used to gain a longitudinal perspective.

Follow-up

It was intended that participants would be followed up at 6 weeks, and 3, 6, 9 and 12 months post surgery, then at 2, 3, 4 and 5 years of age in order to carry out an economic evaluation. It was intended that data be collected between visits by site staff from patient medical records; secondary care resource use data immediately before surgery and at every visit except at 4 months post surgery; and radiography be performed at 5 years of age. For the qualitative work, between 3 and 4 months post surgery, all parents/carers of the participants were invited to complete a demographic questionnaire. Those indicating that they would be prepared to take part in an interview were contacted between 4 and 6 months post surgery and invited to take part in a telephone discussion. The intention was to conduct follow-up interviews when the child reached the age of 5 years.

Results

Patient screening

A total of 118 patients were considered for inclusion. Of these, 44 were not eligible, mainly because of an already existing ON. Of the 74 eligible patients, 44 were not randomised. The most common reasons were that the parent/guardian did not want treatment decided by randomisation and the family did not want to take part in research. The number of children screened varied greatly between centres, and there is no clear relationship between this and the length of time each centre was open to recruitment.

Recruitment

Thirty participants were randomised in the 16 months that the trial was open to recruitment. This represents just over 25% of all children screened, and just over 40% of those who were eligible. There was no relationship between the number of sites open and overall monthly recruitment (median two participants per month). Eight of the 15 sites did not recruit any participants.

Assessing barriers to recruitment and actions taken to increase enrolment

In March 2015, the Trial Management Group discussed the emerging recruitment issue. It was noted that there were fewer than expected entries on screening logs and that eligible patients were refusing the trial. Following this, steps were taken over the remainder of 2015 to investigate the issues and stimulate recruitment.

Centres reported that many children were successfully treated in harness or already had an ON, and that many families with eligible children declined to enter the trial mainly for reasons relating to perceived issues if randomised to the delayed treatment arm. When offered training in methods for study introduction, most centres declined and reported that they did not require any training. Arrangements for a training meeting were abandoned because of a lack of response/interest from site teams. Instead, individual site visits were conducted: during these visits, sites reiterated the lack of eligible children and confirmed that they did not feel any training was required.

Withdrawals

Two of the 30 randomised patients were withdrawn from the study. One family, after having agreed to their child taking part in the study, sought a second opinion, following which surgery was conducted in a different centre and not according to allocation. A second child was the subject of a serious breach (unrelated to patient safety). This incident was fully investigated by the sponsor. The child was immediately withdrawn from the study.

Patient follow-up

Of the 14 patients randomised to early treatment, all underwent surgery during the running of the trial and were followed up to at least 3 months post surgery. Of the 15 patients randomised to intentionally delayed treatment, eight were known to have undergone surgery by the trial end.

Baseline data and demographic characteristics

The majority of patients were aged ≤ 10 months when they were recruited to the study, and two-thirds had been treated with a splint before presenting for surgery. More girls than boys were recruited to the study, reflecting the prevalence of DDH. The left hip was more commonly affected. The most commonly used diagnostic imaging technique was ultrasound. The median age at diagnosis was 3 months.

Primary outcome

No primary outcome data were collected by trial closure.

Secondary outcomes

Some secondary outcome data were collected by the time of trial closure, including presence of the ON at the time of the primary treatment for dysplasia and some information on surgery outcome. However, no conclusions can be drawn from these minimal findings.

Discussion

Main findings

Study conduct

With a few notable exceptions, most centres cited the lack of suitable patients as the reason for poor recruitment. Initial estimates of patient numbers seen at each centre may have included patients who would, in the study setting, be excluded because they already had an ON. Numbers provided at feasibility were much higher than actual numbers screened. Some sites suggested that this was as a result of an improvement in early detection and with patients being referred at a younger age to specialist centres who have a higher success rate using splints, thereby leaving fewer children needing surgery. Some centres were screening and recruiting as expected, whereas others were not and there was no clear reason why; many centres appeared unenthusiastic or uncommunicative when efforts were made to improve recruitment. Consequently, we conclude that some investigators had difficulties with surgical equipoise and, thus, did not screen or recruit many, or indeed any, patients. The findings from the Hip 'Op study suggest that it has suffered from the same difficulties as many other surgical trials – lack of robust and honest feasibility, lack of real commitment on the part of some local investigators and their teams and, primarily, lack of surgical equipoise, which was of paramount importance to a study such as Hip 'Op.

It could be suggested that our initial assumption, that half of all eligible patients would enter the trial, was overly optimistic. We considered it possible – children with DDH in the UK are seen in a comparatively small number of specialist centres, so only a limited number of clinicians had to be engaged in recruitment. In actuality, we managed to recruit 40% of eligible screened patients. The more significant issue would appear to be that fewer patients were screened than was assumed when the study was planned. This might result from a lack of enthusiasm in recruiting centres or from a change in management leading to more DDH being detected and treated before 3 months of age.

Study results

As a result of the early closure of the trial, no primary outcome data were collected, and no meaningful analysis or conclusions could be made from the very small number of secondary outcome data that were collected. In terms of safety, it is worth noting that no significant adverse events occurred: this was as expected because all procedures within the trial were as per standard practice.

Qualitative aspects

The qualitative data generated rich data around three key themes: (1) access to, and experiences of, primary and secondary care (including challenges of raising concerns); (2) the impact, and burden, of surgery on family life (including financial impact and implications for parental physical/mental well-being); and (3) participants' experiences of being in the trial. These findings have relevance for both clinicians and researchers in developmental dysplasia.

Methodologically, this pilot work, if extended further, could contribute to the growth and application of qualitative work within clinical literature, particularly paediatric orthopaedics, in which DDH is an important area of interest and qualitative research is underutilised.

Strengths and limitations

The main strengths of Hip 'Op were (1) the pragmatic design, (2) the study management, (3) the 18-month pilot (it established a clear cut-off point that prevented wasting resources on a failing trial) and (4) inclusion of the qualitative aspect. The major limitation is that the study closed without recruiting a sufficient number of patients to answer the trial question.

Lessons for the future

If we were setting up Hip 'Op again, ideally we would conduct face-to-face interviews with the team at each prospective site to investigate potential pitfalls, loopholes and concerns at the outset. Second, prior to opening, we would agree with the sites a standardised way in which to present the trial in an unbiased manner to minimise numbers who decline to take part. We would undertake more intensive work with patient support organisations to bring the study to the attention of parents before their first orthopaedic outpatient attendance. We would also investigate whether or not it was feasible to conduct the study in centres internationally rather than in the UK only. We would also investigate expected eligible patient numbers at each site more closely.

Future research

The question posed by Hip 'Op is still valid and remains unanswered; however, it is clear that it cannot currently be answered in the UK with a randomised trial. Similar research is under way internationally, and it is likely that data from Hip 'Op could contribute to a meta-analysis from this effort. The qualitative part of the study could have far-reaching impacts on clinical decision-making and practice, and family support. This study has identified areas where information could be improved for families of children who are diagnosed with DDH and require surgery, and further funding is being sought to explore the experiences of a greater diversity of families and to examine the long-term impacts. In addition, the possibility of at least partially addressing this question using routinely collected data is being explored.

Conclusion

Hip 'Op has highlighted how important accurate feasibility information up front, as well as commitment from all participating investigators, is when conducting surgical research, and how lack of these important elements can lead to a spectacular inability to recruit. The Hip 'Op trial was novel because of the inclusion of the qualitative research aspects. The study has underlined how important these results are, not only in terms of patient participation in clinical research, but in in terms of highlighting the need for appropriate advice and robust support for parents regarding the 'real-life' aspects of managing an infant with DDH.

Trial registration

This trial is registered as ISRCTN76958754.

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