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TRAUMA

The Warwick Hip Trauma Evaluation One – an abridged protocol for the WHiTE One Study

AN EMBEDDED RANDOMISED TRIAL COMPARING THE X-BOLT WITH SLIDING HIP SCREW FIXATION IN EXTRACAPSULAR HIP FRACTURES

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Fractures of the proximal femur are one of the greatest challenges facing the medical community, constituting a heavy socioeconomic burden worldwide. Controversy exists regarding the optimal treatment for patients with unstable trochanteric proximal femoral fractures. The recognised treatment alternatives are extramedullary fixation usually with a sliding hip screw and intramedullary fixation with a cephalomedullary nail. Current evidence suggests that best results and lowest complication rates occur using a sliding hip screw. Complications in these difficult fractures are relatively common regardless of type of treatment. We believe that a novel device, the X-Bolt dynamic plating system, may offer superior fixation over a sliding hip screw with lower reoperation risk and better function. We therefore propose to investigate the clinical effectiveness of the X-bolt dynamic plating system compared with standard sliding hip screw fixation within the framework of a the larger WHiTE (Warwick Hip Trauma Evaluation) Comprehensive Cohort Study.

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Introduction

Fracture of the proximal femur is one of the greatest challenges facing the medical community. In 1990, a global incidence of 1.31 million was reported, associated with 740 000 deaths.[1] Proximal femoral fractures constitute a heavy socioeconomic burden worldwide. The cost of this clinical problem is estimated at 1.75 million disability adjusted life years lost, and 1.4% of the total healthcare burden in established market economies.[1]

Fixation using the sliding hip screw (SHS) is well established in the treatment of extracapsular fractures. In the majority of relatively stable fractures it is very effective at allowing controlled collapse of the fracture, leading to mechanical stability and subsequent union.[2] However, unstable fractures of the proximal femur often present with too much comminution and deficient bone to share load with the fixation device. Rather than controlled collapse along the line of the screw, the fracture may collapse into varus with cut-out of the screw from the head, necessitating more complex revision surgery.[3]

The X-Bolt dynamic plating system (X-Bolt Orthopaedics, Dublin, Ireland) builds on the successful design features of the SHS by using a plate attached to the lateral femur and a single telescoping screw in the femoral head, but differs in the nature of the fixation in the head. Expanding flanges are deployed to engage and compress the surrounding cancellous bone, thereby improving fixation.[4] Unstable trochanteric fractures rely more on the quality of fixation in the femoral head to prevent cut-out and the poor bone quality encountered in the patients sustaining these fractures often contributes to failure.

The aim of this trial is to investigate the clinical effectiveness of the X-bolt dynamic plating system compared with the sliding hip screw in the treatment of unstable trochanteric fractures of the proximal femur.

Patients and Methods

Study design. This will be a single-centre, multi-surgeon, parallel, two-arm, standard-of-care randomised controlled clinical trial. It will be embedded within the WHiTE Comprehensive Cohort Study.[5] The study will include a two-way superiority comparison between X-Bolt dynamic plating system and SHS.

Ethical approval. This study has been reviewed by the National Research Ethics Service Committee West Midlands – Coventry and Warwickshire (12/WM/0352). The study was given ethical approval on

6 November 2012. The research will be carried out in compliance with the Helsinki Declaration.

Study registration. This study has been registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN85181068) and the NIHR Comprehensive Research Network Portfolio (ID14104).

Study participants. All patients aged ≥ 60 years with an AO/OTA type A2 and A3 fracture[6] of the proximal femur, including those with cognitive impairment, are eligible for inclusion in this study. Patients will be excluded if they are deemed by the Consultant Trauma Surgeon to be medically unfit for an operation and are treated non-operatively.

Recruitment. Patients will be recruited from trauma meetings at University Hospitals Coventry and Warwickshire NHS Trust. Pre-enrolment eligibility checks will be carried out to ensure that participants are not enrolled in error, and informed written consent will be obtained once participants regain capacity. Inclusion of the participant in the study will be recorded in the clinical notes by the research associate.

Those participants, or consultees, who do not wish to participate in the study following the informed consent discussion, will be withdrawn from the study. Baseline data and any information about serious adverse events obtained from this group of patients up until the point of withdrawal will be included in the final analysis.

Similarly, data of patients who die before consent can be gained, will be included in the final analysis. For those patients who lack capacity, and die before agreement can be obtained from the patients' relatives/next-of-kin, it is our intention not to contact relatives of patients to inform them of the patients' initial inclusion in the study, in order to avoid distressing the relatives unnecessarily. For those patients withdrawing from the trial after written consent has been obtained, data obtained up until the point of withdrawal will be included in the final analysis.

Timeline. The study commenced recruitment on 25 February 2013. Recruitment is planned to last for one year in the first instance.

Consent. The large majority of patients with fracture of the proximal femur are a clinical priority for urgent operative care. They will undergo surgery on the next available trauma operating list. All patients with a fracture of the proximal femur are in pain and have received opiate analgesia. It is therefore understandable that patients find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next-of-kin, carers and friends are anxious at this time and may also have difficulty in weighing the large amounts of information that they are given about the injury and plan for treatment.

In this emergency situation the focus is on obtaining consent for surgery (where possible) and informing the patient and any next of kin about immediate clinical care. It is not possible for the patient/consultee to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to participate.

Conducting research in this 'emergency setting' is regulated by the Mental Capacity Act 2005 (MCA).[7] As patients are likely to lack capacity as described above, and because of the urgent nature of the treatment limiting access to and appropriate discussion with personal consultees, we propose to act in accordance with section 32, subsection 9b of the MCA following a process approved by the relevant research ethics committee. Those patients who have surgery on the next available trauma operating theatre enter the study under presumed consent; we will not obtain consent prior to surgery but will endeavour to inform an appropriate consultee. Where a Personal Consultee is available, they will be provided with the study information. The Personal Consultee will be given the opportunity to ask questions and discuss the study after which their oral agreement will be recorded.

Due to the urgent nature of the treatment limiting access to and appropriate discussion with Personal Consultees, we will act in accordance with section 32 subsection 9b of the MCA. Where a Personal Consultee is not available, a Nominated Consultee will be identified to advise the research team. The Nominated Consultee will be the patient's treating Trauma and Orthopaedic Surgeon. If that surgeon is a member of the research team, another independent surgeon will be identified.

At the first appropriate time when the patient has regained capacity (this will usually be on the first day after surgery) the research associate will provide the participant with all of the study information. The participant will be given the opportunity to ask questions and discuss the study with their family and carers. They will then be asked to provide written consent for continuation in the study.

Rarely, some patients may be able to consent before their operation, namely those whose surgery has been delayed for clinical reasons. These patients will be approached by the research team before their operation for consent to participate in the study. Some patients, whose surgery has been delayed, may still not have capacity, e.g. those who are acutely confused. If the clinical team in charge of that patient's care do not think that the patient is able to provide clinical consent for their operation, then the research team will approach a consultee for agreement that the patient participate in the study. The patient themselves will be approached for consent as soon as the clinical team deem that they have regained capacity following their operation.

For participants who do not regain capacity or lack capacity, reasonable efforts will be made to identify a Personal Consultee as described in the Mental Capacity Act 2005. If no Personal Consultee can be identified then a Nominated Consultee will be identified to advise the research team.

At all times the Chief Investigator will act in accordance with the patients' best interests.

Best efforts will be made to involve participants who, temporarily or permanently, lack capacity in the decision to be involved in the study. The clinical team will make a judgement about the amount and complexity of the information that the participant is able to understand and retain on an individual basis. Appropriate information will be communicated to the participant and updated as their understanding changes.

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants. A revised consent form will be completed if necessary.

Responsibility for recording and dating both oral and written informed consent or agreement will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion.

Post-recruitment withdrawals and exclusions. Participants may withdraw from the study at any time without prejudice. The General Practitioners of those participants who are 'lost to follow-up' will be contacted in order to attempt to complete the follow-up. Participants may be withdrawn from the study at the discretion of the Chief Investigator due to safety concerns.

Treatment allocation

Sequence generation. The allocation sequence will be generated randomly to achieve a 1:1 ratio using blocks of variable sizes, stratified by cognitive status.

Allocation concealment. The allocation will be determined using secure, online randomisation via a distant computer generated system administered by The University of York (York, United Kingdom).

Allocation implementation. Participants will be enrolled by the trial research associates. Participants will be assigned to their treatment allocation prior to the time of surgery by accessing the online randomisation programme. This will allow for treatment allocation to be implemented outside of working hours.

The surgery will be performed by any of the 16 Consultant Surgeons, two Associate Specialists and 14 Trainees at the University Hospitals Coventry and Warwickshire NHS Trust. The large number of surgeons and the wide skill mix should eliminate the 'surgeon effect' such that stratification by surgeon is not required.

Blinding. Participants will be blinded to the treatment allocation. The operating surgeon will not be blinded to the allocation. All clinical outcomes will be assessed by blinded assessors. Patients will be kept blinded until the completion of the trial when the blinding is broken. There will be no formal analysis of the success of the blinding.

Study treatments. Pre-operative assessment, anaesthetic technique and post-operative rehabilitation will be identical to all other participants recruited into the larger WHiTE Comprehensive Cohort Study.[5]

Surgical intervention

All participants will have an attempted closed reduction of their fracture. If satisfactory reduction cannot be achieved, the surgeon will proceed to open reduction. The lower limb will be supported on a fracture table. Internal fixation with either device will be performed following the manufacturers' guidelines with peri-operative antibiotic cover in accordance with hospital protocol. Participants who can tolerate penicillins will receive 1 g flucloxacillin and 3 mg/kg to 5 mg/kg gentamicin at induction as an intravenous (IV) infusion over 15 to 30 minutes. Penicillin-sensitive participants will receive teicoplanin 600 mg, or 800 mg if weight exceeds 80 kg, as an IV bolus and 3 mg/kg to 5 mg/kg gentamicin as an IV infusion over 15 to 30 minutes. Those who have a positive screen for methicillin-resistant *Staphylococcus aureus* (MRSA) will be given the same prophylaxis as those who are penicillin-sensitive.

Participants will be randomly allocated to one of two groups: 1) sliding hip screw; or 2) X-Bolt dynamic plating system.

Group 1: Sliding hip screw. Fixation will involve a SHS with a plate as long as the surgeon feels necessary to achieve adequate fixation in the femoral shaft. The use of supplementary fixation such as wires, cables, lag screws and trochanteric stabilisation plate attachments is permitted at the surgeon's discretion.

Group 2: X-Bolt dynamic plating system. Fixation will involve an X-Bolt dynamic plating system following the manufacturer's guidelines. A four- or six-hole plate will be used as the surgeon feels necessary to achieve adequate fixation in the femoral shaft. Supplementary fixation with wires, cables and lag screws is permitted at the surgeon's discretion.

Follow-up

Schedule. Participant outcomes will be assessed at baseline (pre-injury status recorded upon admission to hospital) and at four, 16 and 52 weeks.

Measures of clinical effectiveness. The primary outcome will be the EuroQol 5-Dimension (EQ-5D)[8] measure of general health. Secondary outcomes will include the Oxford hip score,[9] ICEpop CAPability measure for Older people (ICECAP(O)),[10] mortality risk, revision risk and cause, and length of index hospital stay.

For those participants with cognitive impairment the patient-reported outcomes will be limited to the EQ-5D, which will be reported by an appropriate proxy.

Power and sample size

In the absence of an agreed method to determine sample sizes for pilot studies we will recruit a convenience sample of 100 participants; 50 in each of the two study groups.

Using a crude approximation for sample size estimates[11] and a standard deviation of 0.3 for EQ-5D one year post-injury as observed for the WHiTE study,[12] this gives 80% power to detect an effect size of 0.17 at the 5% level. This is a medium standardised effect size[13] of approximately 0.6. Based upon the report from the National Hip Fracture Database (NHFD) we know that approximately 650 fractures of the proximal femur are treated operatively per year at University Hospitals Coventry and Warwickshire NHS Trust.[14] Based on our experience, approximately 120 of these patients per year would be eligible for inclusion into this trial. Therefore the trial sample can be recruited within one year.

Statistical analysis

The primary outcome measure (EQ-5D at one year post-injury) will be analysed using a two-sided *t*-test for differences between SHS (control) and X-Bolt dynamic plating system (test) on an intention-to-treat basis. It seems likely that some data may not be available due to death of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for incomplete data will be ascertained and reported. The nature and pattern of missing data will be carefully considered – including in particular whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed. The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation

A subsidiary analysis will use a multiple linear regression model to investigate the relationship between each participants' EQ-5D score at one year and the treatment arm, age, gender and cognitive impairment for each participant. Estimates from the regression model with 95% confidence intervals will be reported, along with unadjusted results from *t*-tests, and inferences made on the significance of the treatment effect.

Exploratory, hypothesis-generating analyses of all secondary measures will also be reported. Continuous data will be summarised with point estimates of mean and standard deviations; treatment effects will be estimated using mean differences and reported with 95% confidence intervals using a two-sided *t*-test for differences between SHS (control) and X-Bolt dynamic plating system (test) on an intention-to-treat basis. Categorical data will be summarised as proportions; treatment effects will be estimated using risk ratios and reported with 95% confidence intervals using a chi-squared test for differences between SHS (control) and X-Bolt dynamic plating system (test) on an intention-to-treat basis.

The number and temporal pattern of adverse events will be investigated to assess if these differ between treatment groups.

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- X. L. Griffin: Inception, Design, Writing of the protocol, Guarantor
- J. McArthur: Preparation of protocol
- J. Achten: Preparation of protocol
- N. Parsons: Writing the paper
- M. L. Costa: Inception

ICMJE Conflict of Interest:

- None declared