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PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL.

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ARTICLE SUMMARY

Article Focus

- null hypothesis that the incidence of fixation failure at one year after index fracture did not differ between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur

Key Messages

- no evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not
- a clinically meaningful difference cannot be definitively excluded

Strengths and Limitations

- pragmatic trial
- includes participants with chronic cognitive impairment

ABSTRACT

Objective To quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip.

Design Single centre, parallel group, participant blinded, randomised controlled trial.

Setting UK Major Trauma Centre.

Participants 200 of 315 eligible patients aged 65 years and over with any type of intracapsular fracture of the proximal femur. Patients were excluded if their fracture precluded internal fixation.

Interventions Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of platelet-rich plasma into the fracture site or not.

Main outcome measures Failure of fixation within 12 months, defined as any revision surgery.

Results Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to test and control groups respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6% (95% CI -10.6 to 21.8%) favouring treatment with platelet-rich therapy (chi^2 test, p 0.569). An adjusted effect estimate from a logistic regression model was similar (odds ratio=0.71, 95% CI 0.36 to 1.40, z-test p=0.325). There were no significant differences in any of the secondary outcomes measures excepting length of stay favouring treatment with platelet-rich therapy (median difference 8 days, Mann Witney U p=0.03). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (hazard ratio 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy).

Conclusions No evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not. However, we cannot definitively exclude a clinically meaningful difference.

Trial registration Current Controlled Trials, ISRCTN49197425, www.controlled-trials.com/ISRCTN49197425

INTRODUCTION

Platelet-rich therapies are autologous blood products with a greater concentration of platelets than physiological whole blood.[1] These preparations have been used since the early 1990s to promote bone and soft tissue healing.[1] Promising preliminary studies have led to the use of platelet-rich therapy in both sports medicine, rheumatology and orthopaedic surgery with the aim of promoting and enhancing soft tissue and bone healing.[2]

Platelet-rich therapies can be produced at the bedside by either centrifugation or filtering of autologous whole blood mixed with an anti-coagulant. Both these processes produce a plasma fraction that has a supra-physiological concentration of platelets. Platelets have long been identified as the main regulators of the inflammatory phase of tissue repair.[3] This same mechanism may also influence the proliferation and differentiation phase of healing tissues.[3] Hence platelet-rich therapy has been used in an attempt to optimise healing by delivering supra-physiological levels of platelet-derived growth factors to the site of injury.[4]

At present, good quality evidence to support the use of platelet-rich therapy in the clinical setting remains sparse. The National Institute of Health and Clinical Excellence (NICE) has advised that its use should be restricted to research settings.[5] One exciting area of research is the use of platelet-rich therapy to enhance healing in osteoporotic fractures.[6]

Intracapsular fractures of the proximal femur are a good example. Failure of internal fixation for these hip fractures is common, with up to 35% of displaced fractures requiring revision surgery.[7-9] Therefore, any adjunct that can accelerate fracture healing and reduce the rate of failure of fixation has the potential to change patient care.

We conducted a randomised controlled trial to quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip. The null hypothesis for this trial was that the incidence of fixation failure at one year after index fracture did not differ between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

METHODS

This study was a single centre, parallel group, participant blinded, randomised standard-of-care controlled trial with a 1:1 allocation to main treatment groups. Full details of the protocol have been published elsewhere.[10] The trial was given ethical approval on 6th July 2009 by Coventry Research Ethics Committee (09/H1210/22).

PARTICIPANTS

All patients aged 65 years and above with an intracapsular hip fracture were eligible, including those with cognitive impairment. Patients were excluded if they were managed non-operatively, presented late following their injury, had serious injuries to either lower limb that interfered with rehabilitation of the hip fracture, or had extant local disease precluding fixation, e.g. local tumour deposit, symptomatic ipsilateral hip osteoarthrosis.

RECRUITMENT AND ALLOCATION OF PARTICIPANTS

Participants were recruited between September 2009 and April 2011 from the acute trauma admissions to University Hospitals Coventry and Warwickshire NHS trust, in Coventry, UK. This is a major trauma centre that serves a population of two million people. Approximately 650 patients per year with a fracture of the proximal femur are treated in the centre.[11] Participants with capacity gave written consent; for those who lacked capacity, written consent was given by a consultee in accordance with the Mental Capacity Act 2005.

Participants were randomly allocated to one of two groups: standard of care fixation or standard of care fixation and platelet-rich therapy injection. Treatment allocation was determined using a computer generated, randomised number sequence administrated by an independent Clinical Trials Unit via a secure online programme. The randomisation code was stratified by displacement of the fracture[12] and split into unequal block sizes. Stratification ensured that the approximately 20% of fractures that were minimally displaced, that are associated with a very substantially improved outcome, were distributed evenly between groups. The code was only broken at the end of the trial once the trial statistician had locked and analysed the dataset.

Allocation to treatment group took place intra-operatively, only after the operating surgeon confirmed a successful reduction of the fracture. Those patients in whom a reduction could not be achieved underwent hip arthroplasty, which reflects standard clinical practice.

INTERVENTIONS

All participants underwent closed reduction of their fracture; where the leg was manipulated until the bones were 'reduced' back into their normal anatomical position. The lower limb was supported on a fracture table. Internal fixation of the fracture was achieved through a standard lateral approach with peri-operative antibiotic cover in accordance with hospital protocol. Post-operative care was the same for both groups of patients with early active mobilisation and immediate full weight-bearing with a standardised physiotherapy rehabilitation regime. All participants received routine prophylaxis against deep vein thrombosis.

Standard of care fixation was with two or three parallel cannulated screws. The number and exact configuration was left to the discretion of the operating surgeon to ensure that the results could be easily generalised. For those participants allocated to platelet-rich therapy, each screw was advanced up to but not beyond the fracture such that no compression was achieved before the platelet-rich plasma was injected. The guidewire of one screw was then removed and 3ml of platelet-rich plasma, harvested in accordance with the manufacturer's recommendations (GenesisCS Component Concentrating System, EmCyte Corporation, FL), was injected through the cannulated screw directly into the fracture site under image intensifier guidance. The guidewire was immediately replaced and the screws advanced across the fracture site. No attempt was made to blind the operating surgeon.

OUTCOME MEASUREMENTS

PRIMARY

The proportion of participants undergoing re-operation for failure of fixation within one year of sustaining the fracture.

SECONDARY

- Radiographic non-union at one year. Non-union was defined as "failure of the fracture to show signs of bony union on the anteroposterior or lateral radiograph one year after surgery".[8]
- Radiographic evidence of avascular necrosis at one year
- The EQ-5D score at 6, 12 and 52 weeks
- Length of index hospital stay
- Mortality
- Adverse events

SAMPLE SIZE

Very few data were available with which to estimate the possible size of a treatment

effect of platelet-rich therapy.[13,14] The minimum clinically important treatment effect of platelet-rich therapy was agreed in discussion with several expert orthopaedic trauma surgeons. Although the figures varied by surgeon, all agreed that an absolute risk reduction (ARR) of between 15% and 25% in fixation failure would be clinically important. The overall rate of fixation failure of all intracapsular fractures of the femur is reported to be 25% and 35%.[7-9] Sample sizes were determined using the PS power and sample size software.[15] Selecting a power of 90%, and the most plausible estimate of fixation failure rate (30%) and an intermediate value for the minimum clinically important ARR of 20% gives a treatment group size of 82. Adding 20% on to the total trial sample size estimate to account for expected patient mortality gives a recruitment target of 200 participants that should provide a good margin for unanticipated recruitment problems and loss to follow-up.

STATISTICAL METHODS

The primary outcome measure, the proportion of patients requiring re-operation for failure of fixation (revision) within one year of sustaining the fracture, was compared between treatment groups (fixation and fixation plus platelet-rich therapy) using a chi^2 test, where data from participants were analysed by treatment allocation. Treatments were considered to differ significantly if p-values were less than 0.05. The primary analysis was an available case analysis where deaths without revision were excluded from the analysis. If mortality differed between the treatment groups, this had the potential to bias the effect estimate, so additional *post hoc* analyses were undertaken with deaths imputed as both revisions and non-revisions to assess the sensitivity of the primary analysis to the decisions regarding handling of the missing data.
Fisher's exact test was used to assess the significance of observed differences for the secondary proportional outcome measures. For continuous outcomes, which were approximately normally distributed, mean differences were tested using a two-tailed t-test; for non-parametric data (length of stay) differences were tested with the Mann-Witney U test. A planned subsidiary analysis used a multiple linear regression model to investigate the relationship between each participant's EQ-5D score at one year post operation and the treatment group, after appropriate adjustment for age, sex and fracture displacement for each participant. The incidences of adverse events were reported for each treatment group stratified by the type of event. Planned subgroup analyses were undertaken only for pre-specified subgroups. Explanatory variables of sex, fracture displacement, dementia and age were entered into a logistic regression model with associated interaction terms with the treatment arm for each.

In addition to the primary analysis comparing risks of revision between groups, the Data Monitoring Committee recommended that a *post hoc* time-to-event analysis was also undertaken to assess temporal differences in revision post operation. In this setting, where failure of the fixation was the event of interest, death was regarded as a competing risk. In the presence of competing risks, the standard cause-specific Cox proportional hazards model is not appropriate as it treats the competing risk (death) as a censored observation. Therefore the approach adopted here was the proportional hazards model proposed by Fine and Gray,[16] based on direct regression modelling of covariates on the cumulative incidence function (CIF). The CIF, the proportion of trial participants at time t who had event j (death or revision), was used to compare treatments and the R software[17] package cmprsk[18] was used to implement the Fine-Gray model using a stepwise fitting algorithm.

RESULTS

PARTICIPANTS

A summary of the flow of participants through the study is at Fig. 1. Of the 388 patients admitted with an intracapsular hip fracture during the recruitment period, 52% underwent trial treatments, which represented 83% of all eligible patients assessed. This was largely due to recruitment only taking place during the working week.

Two hundred and eleven participants were enrolled into the study, of whom 200 were randomly allocated to treatments. Ninety-nine participants were allocated to the control group of whom 76 completed the trial protocol; 101 were allocated to the test group of whom 81 completed the protocol. In the latter group there were three protocol violations leading to three crossovers. Of the 43 participants who died, 3 underwent revision surgery prior to death, so in total 160 participants were available for the primary analysis. The numbers of participants unavailable at each of the four time-points for the EQ-5D score are reported in the trial flow diagram (Fig. 1). Similar proportions of other secondary outcomes were unavailable at different follow-up time-points due to death, co-existing chronic confusional states at the time of recruitment, new onset co-morbidities and participant withdrawals.

The baseline characteristics of the trial participants are described in Table 1. There were no apparently substantial between-group differences for any of the recorded baseline characteristics.

TREATMENTS

Both the test and control treatments were successfully delivered as described previously, under the supervision of 18 Consultant Trauma Surgeons and performed by a total of 21 specialist trainees.

OUTCOMES AND ESTIMATION

Table 2 shows counts and estimated risks of revision surgery by treatment group. There was an ARR of 5.6% (95% CI -10.6 to 21.8%, number needed to treat to prevent one revision, 18) in favour of platelet-rich therapy (χ^2 test, p=0.569). Deaths were also approximately balanced between treatment groups (control n=23 and test n=20). Imputing all the deaths as 'revisions' increased overall estimates of revision risks, but due to the balance across groups had little impact on effect estimates (control risk 52.5%; ARR in favour of platelet-rich therapy 6.0%, 95% CI -8.8 to 20.8%; χ^2 test p=0.480). Similarly, an equivalent analysis re-coding deaths as 'non-revisions' did not modify the conclusions of the primary analysis (control risk

31.3%; ARR in favour of platelet-rich therapy 3.6%, 95% CI -10.0 to 17.2%; chi^2 test p=0.688).

Logistic regression analysis, with sex, fracture displacement, dementia and age added to the model, gave an adjusted odds ratio of 0.71 (95% CI 0.36 to 1.40), which was marginally smaller than the unadjusted odds ratio of 0.79 from Table 2, and provided no evidence for a significant treatment effect (z-test from logistic regression p=0.325). Interaction terms were added to the model to test for pre-specified subgroup effects. Appropriate interaction terms were added individually to the base model to give three separate models. None of the interaction terms significantly improved the model fit, providing no evidence for substantial subgroup effects.

There was no significant difference in unadjusted mean EQ-5D score at one year between the control and treatment groups (mean difference (MD)=0.018, t test p=0.799). After adjusting for age, sex and fracture displacement this was maintained.

A summary of the other secondary outcomes is presented in Table 3. There was no significant difference between treatment groups in any of the measures excepting length of stay. The number and distribution of complications were similar in both treatment groups (Table 4).

Estimated cumulative incidence function (CIF) curves, the probability that the event of interest occurs before a given time, are shown for death and revision as competing events for each treatment group in Figure 2. Estimates of hazard ratios (HR) for the competing risks regression model are reported in Table 5. Estimates indicated an increased risk of revision surgery for participants with a pre-existing diagnosis of osteoporosis and a significantly lower risk for participants with minimally displaced fractures or dementia. There was no evidence for a significant treatment effect (HR 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy). An analogous time-to-event analysis using the more conventional Cox proportional hazards model gave very similar results (HR 0.819, 95% CI 0.489 to 1.372, p=0.449 in favour of platelet-rich therapy).

DISCUSSION

PRINCIPAL FINDINGS

This trial has found no evidence of a difference in the risk of revision surgery between participants receiving platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur. However, we have been unable to definitively exclude a clinically important difference. A sensitivity analysis to explore the effect of decisions regarding the handling of the missing data and the competing risks of death and revision surgery found similar estimates of the effect size.

The majority of secondary outcomes, including radiographic, mortality and patient-reported health related quality-of-life measures, demonstrated effects that were concordant with the primary outcome. The length of inpatient stay was significantly shorter in the group treated with platelet-rich therapy. We are unable to provide a biologically plausible explanation for this difference. There was no evidence of any subgroup interaction effects.

STRENGTHS AND LIMITATIONS OF STUDY

This was a pragmatic trial. Although only conducted at a single centre, a large number of surgeons were involved in the administration of both the interventions. The consequent variety in reduction and fixation strategies probably reflects wider surgical practice in a well recognised cohort of patients. The corollary of this, that the case number for any one surgeon was comparatively low, might have reduced the assay sensitivity of the trial. However, each surgeon was either trained to perform the intervention or supervised suitably. Additionally, since each individual surgeon preformed only a small number of interventions the impact of the 'surgeon effect', related to both experience and technical expertise, was likely to have been small.

The hypothesis of the trial concerned the incidence of fixation failure. Since this is difficult to define a surrogate outcome of revision surgery was chosen. It is possible that other considerations, such as patient comorbidity, may have influenced any decision to undertake revision surgery. However, it is unlikely that such considerations differed between the treatment groups.

Only 80% of the available population was screened for eligibility since the trial staff was often not available outside the working week. This might have produced a sampling bias. However, review of the admission and screening data revealed no substantial differences in the crucial confounders of age, sex, fracture displacement and chronic cognitive impairment between the unscreened and recruited samples.

Some participants were being treated with anti-platelet drugs at the time of recruitment into the trial. These participants were not excluded since the trial was pragmatic and there is no evidence that the mechanism of release of the platelet derived growth factors during platelet-rich therapy administration are dependent on the pathways inhibited by aspirin and other anti-platelet drugs.

COMPARISON WITH OTHER STUDIES

Few data exist from other similar studies with which to compare these findings.[13] Indeed, to our knowledge this is the first trial of this size to be conducted exploring platelet-rich therapy in bone healing.[2]

Our modelling demonstrated that fracture displacement and a pre-existing diagnosis of osteoporosis were significant predictors of revision risk. This is consistent with clinical experience and previous authors' findings.[8] The cohort study reported by Parker et al[8] recruited more participants than this trial and identified risk factors with smaller effect sizes. Interestingly our model found that dementia was a protective factor. It is difficult to develop a biologically plausible explanation for this observation. It may rather reflect the reluctance to embark upon major revision arthroplasty surgery in this group of particularly frail patients.

CONCLUSIONS AND IMPLICATIONS

How does our work contribute to the current debate concerning platelet-rich therapy?

Very little evidence exists to support any routine clinical applications of platelet-rich therapy. NICE have recommended that its use in the treatment of tendonopathy is limited to research settings.[5] To our knowledge this trial is the first to explore the clinical effectiveness of platelet-rich therapy in osteoporotic bone healing.

New NICE guidance for the management of fractures of the proximal femur suggests arthroplasty, with a risk of revision of approximately 5%, as opposed to internal fixation for this group of patients with displaced fractures.[19] We have been unable to definitively exclude an important treatment effect for platelet-rich therapy but in the absence of an approximately 20% reduction in the risk of revision surgery following internal fixation with platelet-rich therapy, the standard of care will remain arthroplasty.

Future work might investigate the effectiveness of platelet-rich therapy in different fracture types such as incomplete fractures or those in bone of normal density.

ADDITIONAL INFORMATION

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Conflict of interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that (1) none has support from companies for the submitted work; (2) none has any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none has any non-financial interests that may be relevant to the submitted work.

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Data: All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Additional data are available via the corresponding author (x.griffin@warwick.ac.uk).

Contributions: All authors participated in the design and management of the study. XLG and NP analysed and interpreted the data. XLG and JA managed the recruitment and follow-up of the patients. XLG and NP planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. The Trial Steering Committee authorised the release of the manuscript XLG is the guarantor.

Table 1: Baseline characteristics for each group		
Characteristic	Group	
	Control (n=99)	Test (n=101)
Age (years)	83 (7.8)	83 (8.2)
Female (%)	73	69
Minimally displaced fractures (%)	22	21
Demented (AMT<8) (%)	31	34
Pre-morbid EQ-5D	0.63 (0.34)	0.69 (0.30)
Previously diagnosed CRF (%)	4.0	4.9
Previously diagnosed diabetes mellitus (%)	6.1	16
Previously diagnosed osteoporosis (%)	18	18
Currently prescribed anti-platelet drug (%)	32	27
Previously or currently prescribed systemic steroid (%)	6.1	6.9
Currently prescribed NSAID (%)	4.0	3.9
Currently smoking (%)	8.1	7.9
Time to theatre (hours)	34 (33)	30 (26)

Key:
Summary statistics: *mean (standard deviation)*
n/a: *not applicable*
n/r: *not recorded*
Data are presented as absolute values (%)

Table 2: Revision at 12 months post index operation				
Group	Unrevised	Revised	Total	Risk (%)
Control	47	31	78	39.74
Test	54	28	82	34.15
Total	101	59	160	36.88

Table 3: Between group differences in secondary outcome measures				
Outcome	Treatment group		Test	Significance
	Control (n=78)	Test (n=82)		
Radiographic non-union at one year (%)	1	2	Fisher Exact	1.00
Radiographic avascular necrosis at one year (%)	1	2	Fisher Exact	1.00
Length of index hospital stay (days)	23 (10-41)	15 (7-27)	Mann Witney	0.03
Mortality (%)	23	20	Fisher Exact	0.61

Key:
Proportions are expressed as percentages; summary statistics as median and IQR

Table 4: Between group differences in complications		
Complication	Absolute number of events	
	Control group (n=99)	Test group (n=101)
Wound infection	3	1
Pulmonary embolus	2	0
Pneumonia	12	9
Urinary tract infection	6	5
Blood transfusion	2	0
Cerebrovascular accident	1	0
Myocardial infarction	1	0
Deep vein thrombosis	2	2
Death	23	20

Key:
Events are not mutually exclusive

Table 5: Estimates of hazard ratios for competing risks model				
Covariate		Hazard Ratio	95% CI	p-value
Displacement	*Minimally displaced*	0.303	0.126 to 0.730	0.008
	Displaced	1	-	-
Steroids	*Yes*	0.165	0.022 to 1.217	0.077
	No	1	-	-
Previously diagnosed osteoporosis	*Yes*	2.207	1.153 to 4.223	0.017
	No	1	-	-
Demented	*Yes*	0.496	0.263 to 0.937	0.031
	No	1	-	-
Treatment	*Test*	0.895	0.533 to 1.504	0.680
	Control	1	-	-

Figure 1: CONSORT flow diagram

Key:

** 31 unavailable at baseline*

*** 35 unavailable at baseline*

Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group

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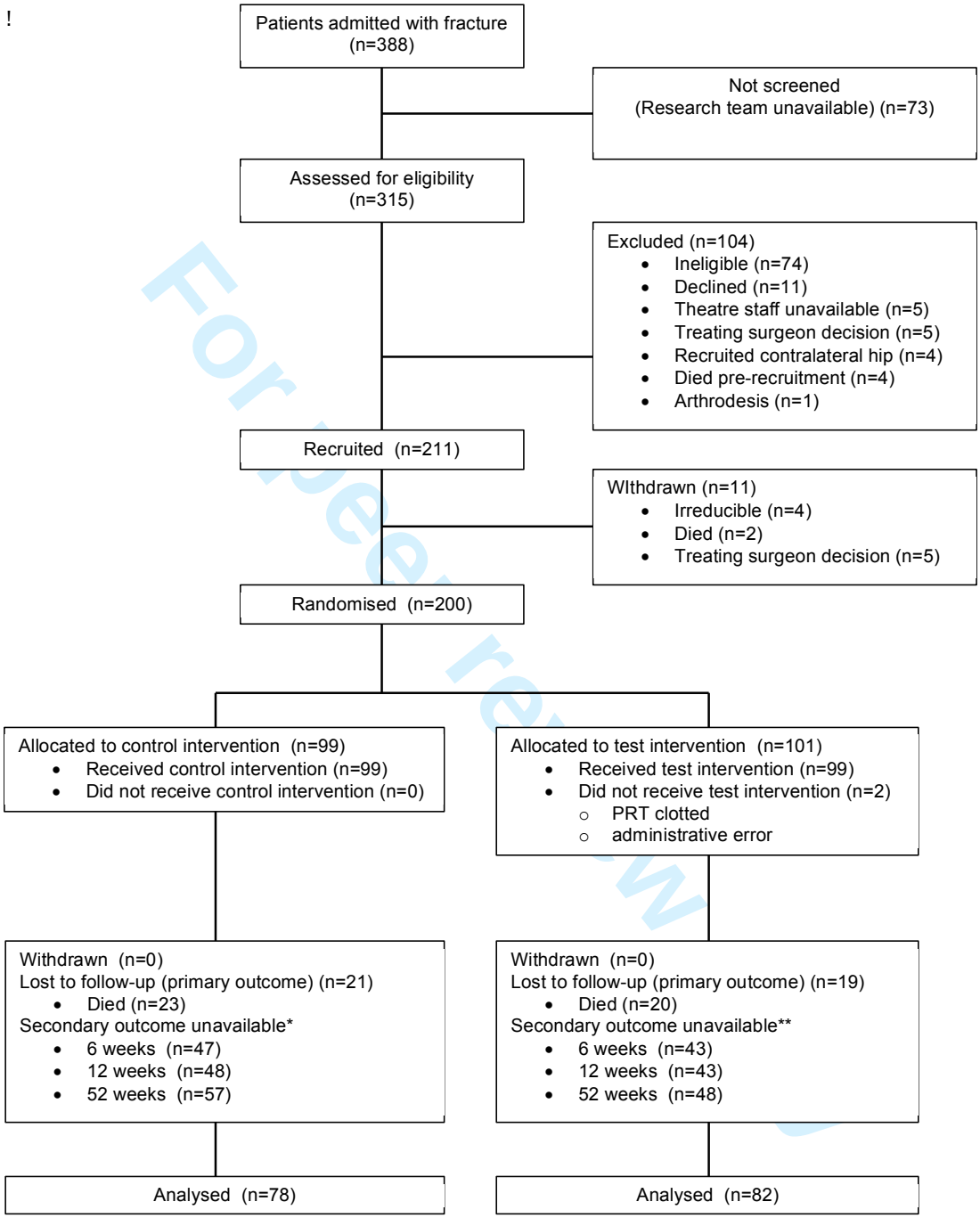
Figure 1: CONSORT flow diagram



Key:

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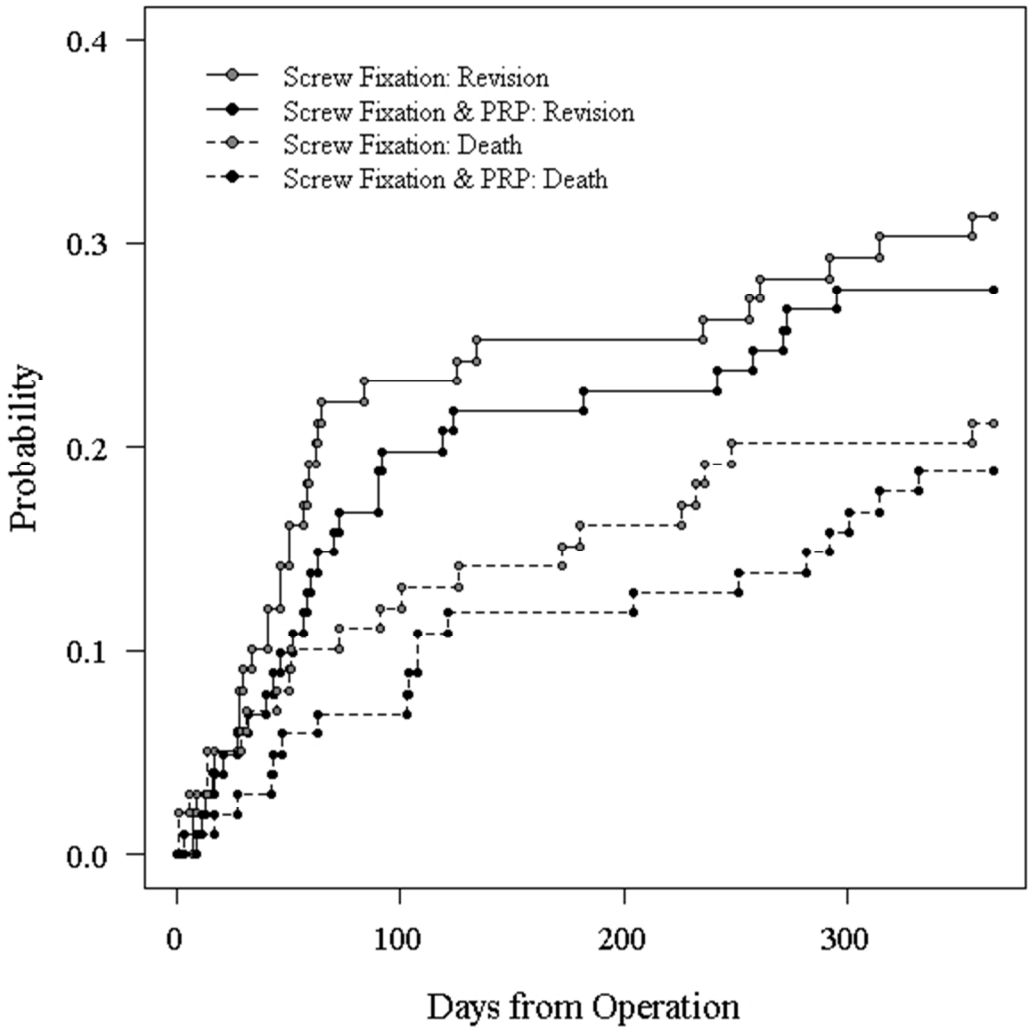
Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group



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BMC Musculoskeletal Disorders

STUDY PROTOCOL Open Access

Warwick Hip Trauma Study: a randomised clinical trial comparing interventions to improve outcomes in internally fixed intracapsular fractures of the proximal femur. Protocol for The WHiT Study

Xavier Luke Griffin*, Nick Parsons, Juul Achten, Matthew L Costa

Abstract

Background: Controversy exists regarding the optimal treatment for patients with displaced intracapsular fractures of the proximal femur. The recognised treatment alternatives are arthroplasty and internal fixation. The principal criticism of internal fixation is the high rate of non-union; up to 30% of patients will have a failure of the fixation leading to revision surgery. We believe that improved fracture healing may lead to a decreased rate of failure of fixation. We therefore propose to investigate strategies to both accelerate fracture healing and improve fixation that may significantly improve outcomes after internal fixation of intracapsular femoral fractures. We aim to test the clinical effectiveness of the osteoinductive agent platelet rich plasma and conduct a pilot study of a novel fixed-angle fixation system.

Design: We have planned a three arm, single centre, standard-of-care controlled, double blinded, pragmatic, randomised clinical trial. The trial will include a standard two-way comparison between platelet-rich plasma and standard-of-care fixation versus standard-of-care fixation alone. In addition there will be a subsidiary pilot arm testing a fixed-angle screw and plate fixation system.

Trial Registration: Current Controlled Trials ISRCTN49197425

Background

Epidemiology

Proximal femoral fractures are one of the greatest challenges facing the medical community. In 1990, a global incidence of 1.31 million was reported and was 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, 1.4% of the total healthcare burden in established market economies [1].

Existing knowledge

Proximal femoral fractures can be subdivided into intra and extracapsular fractures. Approximately half of all proximal femoral fractures are intracapsular. These fractures are at risk of healing complications as the blood supply to the femoral head may be compromised by the fracture. There are two operative strategies in the management of intracapsular fractures of the proximal femur: internal fixation and hip arthroplasty.

Arthroplasty surgery eliminates the risk of fixation failure as the femoral head is replaced. However, it is a major operation with very significant complications of its own including infection, dislocation and periprosthetic fracture. The most common form of arthroplasty in this group of patients is hemiarthroplasty, where the head of the femur is replaced but the acetabulum is left intact, but this procedure is associated with an

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approximately 20% risk of late acetabular wear leading to arthritic changes and the potential need for further surgery [2]. Internal fixation has the key advantage of preserving the patients' own bone and cartilage. It is also a quicker operation requiring a much smaller wound. The principal complication of internal fixation is non-union which is related to the tenuous blood supply to the femoral head. However, the rate of non-union and fixation failure has been reported at up to 33%, [3] leading to re-operation in 90% of these patients. Consequently, the best treatment of these fractures remains controversial. A recent Cochrane review [4] has confirmed that the evidence suggests that there is no clinical benefit of one treatment over the other.

In order for any fracture to heal successfully there must be both a good biological environment and adequate fracture fixation. When a fracture heals there is a balance between the time required to achieve union and the time over which the fixation maintains fracture position. Therefore, the failure of a fracture to heal may be due to an inadequate biological environment (leading to a long healing time) or an inadequate fixation system (leading to a short period of effective fixation). Interventions to improve fracture healing are targeted at one of these two broad areas. In patients with intracapsular fractures of the proximal femur interventions to improve fracture healing may reduce the rate of fixation failure and therefore the requirement for major arthroplasty surgery.

Aim of the trial

The aim of this trial is to investigate the clinical effectiveness of novel surgical interventions to improve clinical outcomes following fracture of the proximal femur. Currently, there are two new techniques available which have shown promising early results for the treatment of acute fractures: firstly, platelet-rich plasma (PRP) which is an autologous source of growth factors derived from a patient's whole blood; secondly, novel fixed-angle screw and plate systems which are available following developments in the field of fragility fracture fixation. Early results of both these interventions are promising but there is no Level I clinical data [5,6].

Hypothesis

We propose to test the hypotheses that: PRP leads to a reduced incidence of failure of fixation in patients with intracapsular fractures of the proximal femur.

We propose to explore the size of any treatment effect due to a novel fixed-angle screw and plate system in the treatment of patients with intracapsular fractures of the proximal femur.

The need for a trial

A review [4] from The Cochrane Database for Systematic Reviews 2007 states:

> *"Fractures of the thigh bone (femur) near the hip joint (termed intracapsular) may be treated by fixing the fracture (with screws or pins), or alternatively replacing the top of the femur at the hip joint (femoral head) with an artificial hip joint (arthroplasty). This review found that each treatment has its own specific complications. Realigning the bones and fixing the fracture (reduction and internal fixation) is a shorter operation with less blood loss, but is more likely to need a second operation (36% versus 11%). The reason for this is mainly from a failure of the bone to heal in those cases treated with fixation. Internal fixation is associated with less initial operative trauma but has an increased risk of re-operation on the hip."*

A search of the national and international clinical trials databases has revealed that there is only one other trial that is being carried out in the USA [7]. This is a commercial trial assessing the use of bone morphogenetic protein (BMP) only. A commercial trial in Leeds, UK investigating the effect of BMP in proximal femoral fractures has recently been abandoned. Otherwise there is no high quality clinical research in this field.

Good Clinical Practice

The trial will be carried out in accordance with Good Clinical Practice (GCP) and in accordance with the following protocol.

CONSORT recommendations

The trial will be reported in line with the CONSORT statement [8].

Methods

Trial Design

Design summary

This trial will be a three arm single centre, standard-of-care controlled, double blinded, pragmatic, randomised clinical trial.

The study will include a standard two-way comparison between PRP and standard-of-care fixation versus standard-of-care fixation alone. This comparison will be the only hypothesis-testing analysis. In addition there will be a subsidiary pilot arm testing fixed-angle screw and plate fixation. This comparison will be a hypothesis-generating analysis only.

The trial is expected to last a total of two years. It is expected that participant recruitment will take one year and final follow-up will be at one year.

The trial was given ethical approval by the Coventry Research Ethics Committee on 6 May 2009.

Objectives of the trial

The objectives of this trial are to:

1. test the hypothesis that PRP leads to a reduced incidence of failure of fixation.
2. explore the size of any treatment effect of a novel fixed-angle screw and plate fixation system

Measures of efficacy

Primary • The proportion of participants undergoing re-operation for failure of fixation within one year of sustaining the fracture.

Secondary • Radiographic non-union rate at 12 months. Non-union will be defined as "failure of the fracture to show signs of bony union on the anteroposterior or lateral radiograph 1 year after surgery" [9].

- Radiographic evidence of failure of fixation at 6, 12 and 52 weeks
- Radiographic evidence of avascular necrosis at one year
- Magnetic resonance imaging at 6, 12 and 52 weeks. This measure will only be recorded for those participants with capacity.
- The EQ-5D score at 6, 12 and 52 weeks
- Length of index hospital stay

Measures of harm and adverse events

Expected Adverse Events • Wound infection

- Venous thrombo-embolic phenomena
- Death
- Pneumonia
- Urinary tract infection
- Blood transfusion
- Failure of fixation
- Cerebrovascular accident
- Acute coronary syndrome
- Myocardial infarction
- Deep vein thrombosis

Power and sample size

The minimum clinically important treatment effect of PRP was agreed in discussion with several expert orthopaedic trauma surgeons. Although the figures varied by surgeon, all agreed that an absolute reduction of 15% in fixation failure would be clinically important. The overall rate of fixation failure of all intracapsular fractures of the femur is reported to be 20-35% [10]. Table 1 shows the total sample size with two-sided significance set at 0.05 for various scenarios of minimum clinically relevant difference. Sample sizes were determined using the PS power and sample size software [11].

The mortality of patients with intracapsular fractures of the proximal femur is approximately 20% during the first year and this needs to be taken into account in the sample calculation. A recruitment target of 200 participants provides a good margin for unanticipated recruitment problems and loss to follow-up.

In the absence of an agreed method to determine the sample size for a pilot study a group of expert orthopaedic surgeons were consulted. All agreed that a sample of 25 participants in the fixed-angle screw and plate group would be sufficient to provide adequate pilot data.

From a recent audit carried out in our department we know that approximately 450 fractures of the proximal femur are treated operatively per year at University Hospital Coventry and Warwickshire. Approximately 250 of these patients would be eligible for inclusion into this trial. Therefore, even accounting for significant loss to follow-up, the trial sample can be recruited in one year.

Eligibility

Inclusion criteria In order that the results of this randomised clinical trial can be generalised as widely as possible, we propose to include all patients, including those with cognitive impairment, admitted with an intracapsular (displaced or undisplaced) fracture of the proximal femur. This pragmatic approach will mean that any conclusions derived will be widely applicable to clinical practice.

Exclusion criteria • All patients who present late following their injury i.e. more than 48 hours after the index fracture.

- Patients with other serious injuries to either lower limb that would interfere with rehabilitation of the index fracture.
- Patients who are managed non-operatively

Post-randomisation withdrawals and exclusions

Participants may withdraw from the trial treatment and/or the whole trial at any time without prejudice. If a

Table 1 Sample sizes calculated for various scenarios

Rate of failure in control group (%)	Rate of failure in the intervention group (%)					
	10		15		25	
	80% power	90% power	80% power	90% power	80% power	90% power
25	100	133				
30	62	82	121	161		
35	43	57	73	97	329	440

participant withdraws from the trial treatment he will be followed-up wherever possible and data collected until the end of the trial.

The General Practitioners of those participants who are "lost-to-follow-up" will be contacted in order to attempt to complete the follow-up. Failing this then the Hip Fracture Register will be consulted in order to try to establish up-to-date participant contact details. Participants may be withdrawn from the trial at the discretion of the Chief Investigator due to safety concerns.

Consent

An informed consent discussion will be conducted with potential participants after eligibility checks have been performed but prior to randomisation.

Potential participants will be informed about the nature of the trial by the investigator or persons designated by the investigator. This will involve a discussion of purpose and requirements of the trial and the issuing of the participant information sheet.

Patients will be allowed, where possible, at least twenty four hours to consider the information given them prior to being asked to give informed consent to participate in the trial. This period of time will not be allowed to delay any normal standard of care treatment.

Responsibility for recording and dating both verbal and written, signed informed consent will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion. The following information will be discussed during the consent discussion:

- Benefits of internal fixation of intracapsular proximal femoral fractures
- Risks of internal fixation of intracapsular proximal femoral fractures
- Impact of allocation to different treatment arms of the trial
- Requirements of follow-up
- Benefits of taking part in the trial

For those patients who lack the capacity to give informed consent 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 nominated to advise the research team. The following persons will be approached in the order given in the list below:

i. The patient's General Practitioner
ii. Mr Wade FRCS(Tr&Orth), Consultant Orthopaedic Surgeon UHCW.

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

Recruitment

Participant recruitment will begin in August 2009 and be completed by August 2010. Pre-randomisation eligibility checks will be carried out to ensure that participants are not randomised in error, and informed written consent will be obtained prior to randomisation. Confirmation of these checks will be carried out by the investigator, or persons designated by the investigator, prior to randomisation. Inclusion of the patient in the trial will be flagged on their clinical notes by means of a trial sticker.

Treatment allocation

Sequence generation The allocation sequence will be generated randomly. The randomisation will be weighted such that at the end of the trial there will be 25 participants in the fixed-angle screw and plate group and 100 participants in each of the remaining groups. Randomisation will be stratified by displacement of the fracture. Fractures will be defined as undisplaced (Garden grade I or II) or displaced (Garden grade III or IV); Garden's classification of intracapsular fractures is well recognised and universal and it has been validated to distinguish between grades I and II compared with III and IV [12,13]. The surgery will be performed by any of the 16 Consultant Surgeons, two Associate Specialists and 14 Trainees at the University Hospital Coventry and Warwickshire. The large number of surgeons and the wide skill mix should eliminate the 'surgeon effect' such that stratification by surgeon is not required.

Allocation concealment The allocation sequence will be generated using secure, online randomisation via a distant computer generated system administered by The University of York.

Allocation implementation Participants will be enrolled by the trial research associates, co-ordinated by Mr Xavier Griffin. Participants will be assigned to their treatment allocation at the time of surgery by accessing the online randomisation programme. This will allow for treatment allocation to be implemented outside of working hours.

Blinding

Participants will be blinded to the treatment allocation. The operating surgeon will not be blinded to the allocation. All outcomes will be assessed by blinded assessors. The primary outcome measure will be determined by the clinical decision of the responsible consultant orthopaedic surgeon who is independent from the trial. The responsible consultant surgeon will not be the operating surgeon in order to maintain the blind. The EQ-5D is a patient reported measure. Patients will be kept blinded until the completion of the trial when the blind is broken. Radiographic outcomes will be assessed by an independent consultant radiologist who is blinded to the

treatment allocation. There will be no formal analysis of the success of the blinding.

Trial treatments

All participants will have a closed reduction of their fracture. The lower limb will be supported on a fracture table. Internal fixation of the fracture will be achieved through a standard lateral approach with perioperative antibiotic cover in accordance with hospital protocol. Post-operative care will include early active mobilisation managed by a standard physiotherapy rehabilitation regime. All participants will have routine prophylaxis against deep vein thrombosis. Participants will be randomised to one of three groups:

1. Fixed-angle screw and plate fixation
2. Standard of care fixation and placebo injection
3. Standard of care fixation and PRP injection

Group 1: Fixed-angle screw and plate fixation

Fixation will be with the Targon FN Head Preserving System as described in the manufacturer's operative technique manual.

Group 2: Standard of care fixation

Fixation will be with three parallel cannulated screws. The exact configuration will be left to the discretion of the operating surgeon to ensure the results can be easily generalised. Fixation will be achieved using the standard operative technique.

Group 3: Standard of care fixation and PRP injection

Fixation will be with three parallel cannulated screws. The exact configuration will be left to the discretion of the operating surgeon to ensure the results can be easily generalised. Each screw will be advanced up to but not beyond the fracture such that no compression is achieved before the test substance is injected. The guidewire of one screw will then be removed and 5ml of PRP will be injected down the cannulated screw directly into the fracture site under image intensifier guidance. The guidewire will be immediately replaced and the screw/s will then be advanced to compress the fracture site.

Concomitant illnesses and medication

Concomitant illnesses and medication will be recorded at trial entry. Changes to these will be recorded at follow-up visits.

Interventions and assessments

Table 2 details the assessments and interventions that will be carried out during the period that each participant is involved in the trial.

End of the trial

The trial will be closed when all participants have completed the one year follow-up visits. Once the trial is completed participants will be treated as per the standard of care.

Table 2 Trial assessments and interventions

Serial	Intervention/Measurement	Time (weeks)
1	Operation Peri-operative complications	0
2	AP & lateral radiographs MRI (subset of sample) Clinical interview	6
3	AP & lateral radiographs MRI (subset of sample) Clinical interview	12
4	AP & lateral radiographs MRI (subset of sample) Clinical interview	52

Trial Flow diagram

See figure 1.

Data management

Database and data management

Data to be collected from participants can be found at table 3. These data will be entered in the trial database. The trial database will be set up by the computer programmer and all specifications agreed between the computer programmer, statistician and trial co-ordinator. The procedure for data entry will be decided when the database is constructed. If electronic databases are required on computers external to the clinical trials unit, they will be compatible with the systems on site and backed-up accordingly. In the case of any interim analysis the database will be frozen at the analysis time point. Data collected after this point will not be included in the interim report.

The case report forms will be designed by the Trial Co-ordinator in consultation with the Chief Investigator and statistician.

In the event of missing data the relevant clinical databases and case report forms will be accessed to complete the database.

Data access and quality assurance

All data collected will be anonymised after the collection of the baseline demographic data for each participant. Identifiable participant data will be held on a separate database and coded with a trial participant code to tag identifiable data to the outcome data.

All data will be stored in a designated storage facility in the Clinical Sciences Building on the research site at the University of Warwick. Data will be stored on password protected university computers in a restricted access building.

Archiving of trial data

Data will be archived in accordance with The University of Warwick clinical trials unit guidance.

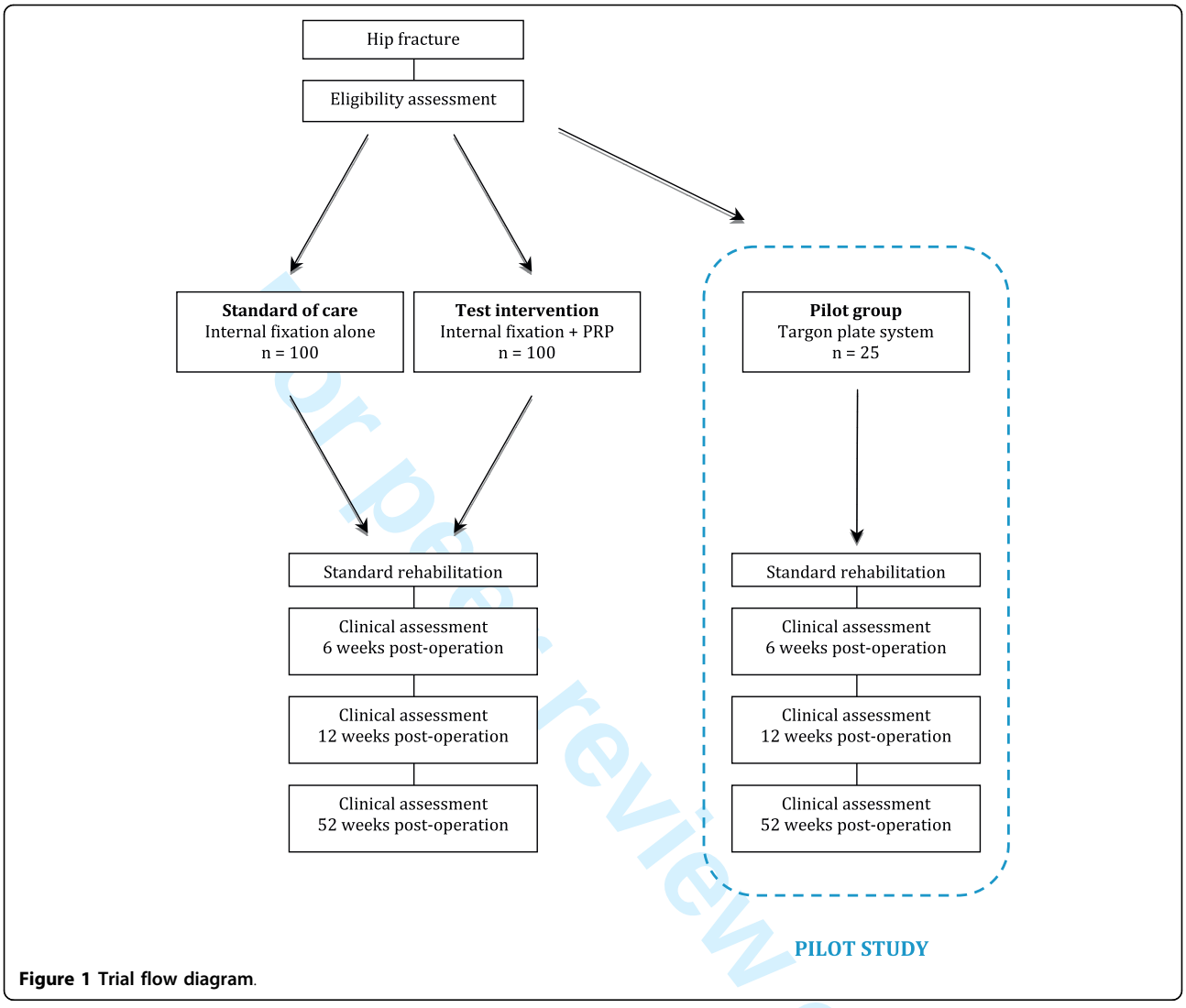

Figure 1 Trial flow diagram.

Table 3 Data to be collected during the trial

Serial	Intervention/Measurement	Time (weeks)
1	Peri-operative complications	0
2	EQ-5D score	6
	Radiographic union and fixation	
	Re-operation	
	Readmission	
3	EQ-5D score	12
	Radiographic union and fixation	
	Re-operation	
	Readmission	
4	EQ-5D score	52
	Radiographic union and fixation	
	Avascular necrosis	
	Re-operation	
	Readmission	

Data monitoring committee

There will be a data monitoring committee convened for this trial.

Statistical analysis plan

Analysis of efficacy

PRP vs standard-of-care (parallel cannulated screws)

The primary outcome measure, the proportion of patients requiring re-operation for failure of fixation within one year of sustaining the fracture, will be analysed using a chi-squared test for differences between internal fixation alone (control) and internal fixation and PRP (PRP) on an intention-to-treat basis. Treatments will be considered to differ significantly if p-values are <0.05 (5% level). Similarly, chi-squared tests will be used to assess the significance of observed differences for the secondary proportional outcome measures. If the numbers in the contingency tables are small (cells

with values below 10) then Fisher's exact test will be used in preference to the chi-squared test. In addition to the main analysis, that will report treatment group effects for the primary outcome measure, a subsidiary analysis will use a multiple linear regression model to investigate the relationship between each patient's EQ-5D Score at 12 months and the treatment arm, age, gender, dementia and fracture displacement for each patient. Estimates, and 95% confidence intervals, from the regression model, and unadjusted results from t-tests will be reported and inferences made on the significance of the treatment effect. All analyses will be based upon an intention-to-treat analysis so missing data due to protocol violations will not be relevant. The primary outcome measure in this study has been chosen in order to limit the possibility of losing data from failed participant follow-up. The primary measure can be sourced from the patient, relative, GP or national hp fracture database.

Fixed-angle plate and screws vs standard-of-care (parallel cannulated screws) No formal inference statistical analysis will be conducted on the data from the pilot arm of the study. The proportional primary event rate, mean estimates and variability of the secondary measures in the two groups will be described. Additionally an estimate of the size of the treatment effect due to the fixed-angle plate will be made to inform further study designs.

Subgroup analyses

Planned subgroup analyses will be undertaken only for fracture displacement (displaced vs undisplaced), dementia and appropriate age groups.

Analysis of adverse events

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

Trial organisation and oversight

Trial steering committee

A trial steering committee will be convened and independently chaired in accordance with the University of Warwick Clinical Trials Unit standard operating procedures. In addition to the independent chair, Mr M Costa, Mr X Griffin, Dr J Achten and Dr N Parsons will form the committee. All issues pertaining to the management of the trial will be co-ordinated by the trial steering committee. The schedule for meetings of the committee will be as follows:

Meeting 1: Trial commencement
Meeting 2: Interim meeting at 50% recruitment
Subsequent meetings: End of trial

Data monitoring committee

A data monitoring committee will be convened once the trial is 50% recruited. The committee will be chaired by Mr S Drew, University Hospital Coventry and Warwickshire NHS Trust.

Trial registration

The trial is registered with the Current Controlled Trials register ISRCTN49197425. The trial has been adopted by the National Institute for Health Research Clinical Research Network Portfolio NIHR CRN Study ID: 7762.

Project timetable and milestones

Trial recruitment commenced August 2009
All participants recruited August 2010
Trial completed August 2011
Trial reported December 2011

Unblinding

The blind will only be broken for clinical management purposes. In exceptional circumstances beyond this agreement will be sought from the Chief Investigator and statistician before the blind is broken.

Interim analysis

There will be no formal interim analysis conducted.

Indemnity/compensation/insurance

All issues of indemnity, compensation and insurance are detailed in the joint sponsorship agreement between the University of Warwick and University Hospital Coventry and Warwickshire NHS Trust.

Essential documents

All essential documentation will be stored as specified under the guidance from the clinical trials unit.

Monitoring and quality assurance policy

The Chief Investigator and data entry technician will conduct sampling of the database quarterly in order to identify any problems in trial procedures.

Dissemination and publication

The results of this trial will be disseminated to the trauma and orthopaedic surgery community via presentations at national and international meetings as well as publication in peer reviewed journals.

Financial support

The trial will be funded by the Furlong Research Charitable Foundation and the Bupa Foundation.

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The authors would like to thank Dr Richard Wellings and Dr Sarah Wayte for their generous help and expertise in developing appropriate MR imaging protocols to assess fracture healing. We would also like to thank Professor Damian Griffin for the support of his department in the preparation of this trial protocol. This work was supported by the Furlong Research Charitable Foundation and the Bupa Foundation (grant number TBF-RR10-001).

Authors' contributions

XG and MC developed the trial concept and design. All authors made significant contributions to the design, drafting and critical revision of the

trial protocol. XG will co-ordinate participant recruitment and follow-up. All authors will be responsible for data interpretation and reporting of the trial. All authors read and approved the final manuscript.

Competing interests

Gian Medical have agreed to provide the consumables for the production of the platelet-rich plasma used in the treatment of some participants in this trial.

BBraun have agreed to provide the Targon FN Head Preserving System used in the treatment of some participants in this trial.

Neither Gian Medical nor BBraun have any rights to the intellectual property generated from the data produced by this trial.

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CONSORT 2010 checklist - WHiT Study

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5 & 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4 & 5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6 & 7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6 & 7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	80
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8 & 9 Table 2-5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10 & 11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL

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PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL.

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ABSTRACT

Objective To quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip.

Design Single centre, parallel group, participant blinded, randomised controlled trial.

Setting UK Major Trauma Centre.

Participants 200 of 315 eligible patients aged 65 years and over with any type of intracapsular fracture of the proximal femur. Patients were excluded if their fracture precluded internal fixation.

Interventions Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of platelet-rich plasma into the fracture site or not.

Main outcome measures Failure of fixation within 12 months, defined as any revision surgery.

Results Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to test and control groups respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6% (95% CI -10.6 to 21.8%) favouring treatment with platelet-rich therapy (chi^2 test, p 0.569). An adjusted effect estimate from a logistic regression model was similar (odds ratio=0.71, 95% CI 0.36 to 1.40, z-test p=0.325). There were no significant differences in any of the secondary outcomes measures excepting length of stay favouring treatment with platelet-rich therapy (median difference 8 days, Mann Whitney U p=0.03). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (hazard ratio 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy).

Conclusions No evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not. However, we cannot definitively exclude a clinically meaningful difference.

Trial registration Current Controlled Trials, ISRCTN49197425, www.controlled-trials.com/ISRCTN49197425

INTRODUCTION

Platelet-rich therapies are autologous blood products with a greater concentration of platelets than physiological whole blood.[1] These preparations have been used since the early 1990s to promote bone and soft tissue healing.[1] Promising preliminary studies have led to the use of platelet-rich therapy in both sports medicine, rheumatology and orthopaedic surgery with the aim of promoting and enhancing soft tissue and bone healing.[2]

Platelet-rich therapies can be produced at the bedside by either centrifugation or filtering of autologous whole blood mixed with an anti-coagulant. Both these processes produce a plasma fraction that has a supra-physiological concentration of platelets. Platelets have long been identified as the main regulators of the inflammatory phase of tissue repair.[3] This same mechanism may also influence the proliferation and differentiation phase of healing tissues.[3] Hence platelet-rich therapy has been used in an attempt to optimise healing by delivering supra-physiological levels of platelet-derived growth factors to the site of injury.[4]

At present, good quality evidence to support the use of platelet-rich therapy in the clinical setting remains sparse. The National Institute of Health and Clinical Excellence (NICE) has advised that its use should be restricted to research settings.[5] One exciting area of research is the use of platelet-rich therapy to enhance healing in osteoporotic fractures.[6]

Intracapsular fractures of the proximal femur are a good example. Failure of internal fixation for these hip fractures is common, with up to 35% of displaced fractures requiring revision surgery.[7-9] Therefore, any adjunct that can accelerate fracture healing and reduce the rate of failure of fixation has the potential to change patient care.

We conducted a randomised controlled trial to quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip. Specifically, we sought to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

METHODS

This study was a single centre, parallel group, participant blinded, randomised standard-of-care controlled trial with a 1:1 allocation to main treatment groups. Full details of the protocol have been published elsewhere.[10] The trial was given ethical approval on 6th July 2009 by Coventry Research Ethics Committee (09/H1210/22).

PARTICIPANTS

All patients aged 65 years and above with an intracapsular hip fracture were eligible, including those with cognitive impairment. Patients were excluded if they were managed non-operatively, presented late following their injury, had serious injuries to either lower limb that interfered with rehabilitation of the hip fracture, or had extant local disease precluding fixation, e.g. local tumour deposit, symptomatic ipsilateral hip osteoarthrosis.

RECRUITMENT AND ALLOCATION OF PARTICIPANTS

Participants were recruited between September 2009 and April 2011 from the acute trauma admissions to University Hospitals Coventry and Warwickshire NHS trust, in Coventry, UK. This is a major trauma centre that serves a population of two million people. Approximately 650 patients per year with a fracture of the proximal femur are treated in the centre.[11] Participants with capacity gave written consent; for those who lacked capacity, written consent was given by a consultee in accordance with the Mental Capacity Act 2005.

Participants were randomly allocated to one of two groups: standard of care fixation or standard of care fixation and platelet-rich therapy injection. Treatment allocation was determined using a computer generated, randomised number sequence administrated by an independent Clinical Trials Unit via a secure online programme. The randomisation code was stratified by displacement of the fracture[12] and split into unequal block sizes. Stratification ensured that the approximately 20% of fractures that were minimally displaced, that are associated with a very substantially improved outcome, were distributed evenly between groups. The code was only broken at the end of the trial once the trial statistician had locked and analysed the dataset.

Allocation to treatment group took place intra-operatively, only after the operating surgeon confirmed a successful reduction of the fracture. Those patients in whom a reduction could not be achieved underwent hip arthroplasty, which reflects standard clinical practice.

INTERVENTIONS

All participants underwent closed reduction of their fracture; where the leg was manipulated until the bones were 'reduced' back into their normal anatomical position. The lower limb was supported on a fracture table. Internal fixation of the fracture was achieved through a standard lateral approach with peri-operative antibiotic cover in accordance with hospital protocol. Post-operative care was the same for both groups of patients with early active mobilisation and immediate full weight-bearing with a standardised physiotherapy rehabilitation regime. All participants received routine prophylaxis against deep vein thrombosis.

Standard of care fixation was with two or three parallel cannulated screws. The number and exact configuration was left to the discretion of the operating surgeon to ensure that the results could be easily generalised. For those participants allocated to platelet-rich therapy, each screw was advanced up to but not beyond the fracture such that no compression was achieved before the platelet-rich plasma was injected. The guidewire of one screw was then removed and 3ml of platelet-rich plasma, harvested in accordance with the manufacturer's recommendations (GenesisCS Component Concentrating System, EmCyte Corporation, Fort Myers, FL), was injected without an activator through the cannulated screw directly into the fracture site under image intensifier guidance. Details of the bioactivity of this platelet-rich plasma are available elsewhere.[13,14] The guidewire was immediately replaced and the screws advanced across the fracture site. No attempt was made to blind the operating surgeon.

OUTCOME MEASUREMENTS

PRIMARY

The proportion of participants undergoing re-operation for failure of fixation within one year of sustaining the fracture.

SECONDARY

- Radiographic non-union at one year. Non-union was defined as "failure of the fracture to show signs of bony union on the anteroposterior or lateral radiograph one year after surgery".[8]
- Radiographic evidence of avascular necrosis at one year
- The EQ-5D index (York A1 value set)[15] at 6, 12 and 52 weeks
- Length of index hospital stay
- Mortality
- Adverse events

SAMPLE SIZE

Very few data were available with which to estimate the possible size of a treatment effect of platelet-rich therapy.[16,,17] The minimum clinically important treatment effect of platelet-rich therapy was agreed in discussion with several expert orthopaedic trauma surgeons. Although the figures varied by surgeon, all agreed that an absolute risk reduction (ARR) of between 15% and 25% in fixation failure would be clinically important. The overall rate of fixation failure of all intracapsular fractures of the femur is reported to be 25% and 35%.[7-9] Sample sizes were determined using the PS power and sample size software.[18] Selecting a power of 90%, and the most plausible estimate of fixation failure rate (30%) and an intermediate value for the minimum clinically important ARR of 20% gives a treatment group size of 82. Adding 20% on to the total trial sample size estimate to account for expected patient mortality gives a recruitment target of 200 participants that should provide a good margin for unanticipated recruitment problems and loss to follow-up.

STATISTICAL METHODS

The primary outcome measure, the proportion of patients requiring re-operation for failure of fixation (revision) within one year of sustaining the fracture, was compared between treatment groups (fixation and fixation plus platelet-rich therapy) using a chi^2 test, where data from participants were analysed by treatment allocation. Treatments were considered to differ significantly if p-values were less than 0.05. The primary analysis was an available case analysis where deaths without revision were excluded from the analysis. If mortality differed between the treatment groups, this had the potential to bias the effect estimate, so additional *post hoc* analyses were undertaken with deaths imputed as both revisions and non-revisions to assess the sensitivity of the primary analysis to the decisions regarding handling of the missing data.
Fisher's exact test was used to assess the significance of observed differences for the secondary proportional outcome measures. For continuous outcomes, which were approximately normally distributed, mean differences were tested using a two-tailed t-test; for non-parametric data (length of stay) differences were tested with the Mann Whitney U test. A planned subsidiary analysis used a multiple linear regression model to investigate the relationship between each participant's EQ-5D score at one year post operation and the treatment group, after appropriate adjustment for age, sex and fracture displacement for each participant. The incidences of adverse events were reported for each treatment group stratified by the type of event. Planned subgroup analyses were undertaken only for pre-specified subgroups. Explanatory variables of sex, fracture displacement, dementia and age were entered into a

logistic regression model with associated interaction terms with the treatment arm for each.

In addition to the primary analysis comparing risks of revision between groups, the Data Monitoring Committee recommended that a *post hoc* time-to-event analysis was also undertaken to assess temporal differences in revision post operation. In this setting, where failure of the fixation was the event of interest, death was regarded as a competing risk. In the presence of competing risks, the standard cause-specific Cox proportional hazards model is not appropriate as it treats the competing risk (death) as a censored observation. Therefore the approach adopted here was the proportional hazards model proposed by Fine and Gray,[19] based on direct regression modelling of covariates on the cumulative incidence function (CIF). The CIF, the proportion of trial participants at time t who had event j (death or revision), was used to compare treatments and the R software[20] package cmprsk[21] was used to implement the Fine-Gray model using a stepwise fitting algorithm.

RESULTS

PARTICIPANTS

A summary of the flow of participants through the study is at Fig. 1. Of the 388 patients admitted with an intracapsular hip fracture during the recruitment period, 52% underwent trial treatments, which represented 83% of all eligible patients assessed. This was largely due to recruitment only taking place during the working week.

Two hundred and eleven participants were enrolled into the study, of whom 200 were randomly allocated to treatments. Ninety-nine participants were allocated to the control group of whom 76 completed the trial protocol; 101 were allocated to the test group of whom 81 completed the protocol. In the latter group there were three protocol violations leading to three crossovers. Of the 43 participants who died, 3 underwent revision surgery prior to death, so in total 160 participants were available for the primary analysis. The numbers of participants unavailable at each of the four time-points for the EQ-5D score are reported in the trial flow diagram (Fig. 1). Similar proportions of other secondary outcomes were unavailable at different follow-up time-points due to death, co-existing chronic confusional states at the time of recruitment, new onset co-morbidities and participant withdrawals.

The baseline characteristics of the trial participants are described in Table 1. There were no apparently substantial between-group differences for any of the recorded baseline characteristics.

TREATMENTS

Both the test and control treatments were successfully delivered as described previously, under the supervision of 18 Consultant Trauma Surgeons and performed by a total of 21 specialist trainees.

OUTCOMES AND ESTIMATION

Table 2 shows counts and estimated risks of revision surgery by treatment group. There was an ARR of 5.6% (95% CI -10.6 to 21.8%) in favour of platelet-rich therapy (χ^2 test, p=0.569).

Deaths were also approximately balanced between treatment groups (control n=23 and test n=20). Imputing all the deaths as 'revisions' increased overall estimates of revision risks, but due to the balance across groups had little impact on effect estimates (control risk 52.5%; ARR in favour of platelet-rich therapy 6.0%, 95% CI -8.8 to 20.8%; χ^2 test p=0.480). Similarly, an equivalent analysis re-coding deaths as 'non-revisions' did not modify the conclusions of the primary analysis (control risk

31.3%; ARR in favour of platelet-rich therapy 3.6%, 95% CI -10.0 to 17.2%; chi^2 test p=0.688).

Logistic regression analysis, with a binary response variable (1=revised and 0=unrevised), was used to assess the effect of treatment group allocation on revision after adjustment for sex, fracture displacement, dementia and age. This model gave an adjusted estimated odds ratio of 0.71 (95% CI 0.36 to 1.40), which was marginally smaller than the unadjusted odds ratio of 0.79 from Table 2, and provided no evidence for a significant treatment effect (z-test from logistic regression p=0.325). Interaction terms were added to the model to test for pre-specified subgroup effects; that is additional terms were included in the model that tested to see if the treatment effect was changed (moderated) by fracture displacement, dementia or age group. Appropriate interaction terms were added individually to the base model to give three separate analyses; none of the interaction terms significantly improved the model fit, providing no evidence for substantial subgroup effects.

There was no significant difference in unadjusted mean EQ-5D score at one year between the control and treatment groups (mean control group EQ-5D=0.588, mean difference (MD)=0.018 in favour of the control group, t-test p=0.799). After adjusting for age, sex and fracture displacement this was maintained. A summary of the other secondary outcomes is presented in Table 3. There was no significant difference between treatment groups in any of the measures excepting length of stay. The number and distribution of complications were similar in both treatment groups (Table 4).

Estimated cumulative incidence function (CIF) curves, the probability that the event of interest occurs before a given time, are shown for death and revision as competing events for each treatment group in Figure 2. Estimates of hazard ratios (HR) for the competing risks regression model are reported in Table 5. Estimates indicated an increased risk of revision surgery for participants with a pre-existing diagnosis of osteoporosis and a significantly lower risk for participants with minimally displaced fractures or dementia. There was no evidence for a significant treatment effect (HR 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy). An analogous time-to-event analysis using the more conventional Cox proportional hazards model gave very similar results (HR 0.819, 95% CI 0.489 to 1.372, p=0.449 in favour of platelet-rich therapy).

DISCUSSION

PRINCIPAL FINDINGS

This trial has found no evidence of a difference in the risk of revision surgery between participants receiving platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur. However, we have been unable to definitively exclude a clinically important difference. A sensitivity analysis to explore the effect of decisions regarding the handling of the missing data and the competing risks of death and revision surgery found similar estimates of the effect size.

The majority of secondary outcomes, including radiographic, mortality and patient-reported health related quality-of-life measures, demonstrated effects that were concordant with the primary outcome. The length of inpatient stay was significantly shorter in the group treated with platelet-rich therapy. We are unable to provide a biologically plausible explanation for this difference. There was no evidence of any subgroup interaction effects.

STRENGTHS AND LIMITATIONS OF STUDY

This was a pragmatic trial. Although only conducted at a single centre, a large number of surgeons were involved in the administration of both the interventions. The consequent variety in reduction and fixation strategies probably reflects wider surgical practice in a well recognised cohort of patients. The corollary of this, that the case number for any one surgeon was comparatively low, might have reduced the assay sensitivity of the trial. However, each surgeon was either trained to perform the intervention or supervised suitably. Additionally, since each individual surgeon preformed only a small number of interventions the impact of the 'surgeon effect', related to both experience and technical expertise, was likely to have been small.

The hypothesis of the trial concerned the incidence of fixation failure. Since this is difficult to define a surrogate outcome of revision surgery was chosen. It is possible that other considerations, such as patient comorbidity, may have influenced any decision to undertake revision surgery. However, it is unlikely that such considerations differed between the treatment groups.

Only 80% of the available population was screened for eligibility since the trial staff was often not available outside the working week. This might have produced a sampling bias. However, review of the admission and screening data revealed no substantial differences in the crucial confounders of age, sex, fracture displacement and chronic cognitive impairment between the unscreened and recruited samples.

Some participants were being treated with anti-platelet drugs at the time of recruitment into the trial. These participants were not excluded since the trial was pragmatic and there is no evidence that the mechanism of release of the platelet derived growth factors during platelet-rich therapy administration are dependent on the pathways inhibited by aspirin and other anti-platelet drugs.

COMPARISON WITH OTHER STUDIES

Few data exist from other similar studies with which to compare these findings.[16] Indeed, to our knowledge this is the first trial of this size to be conducted exploring platelet-rich therapy in bone healing.[2]

Our modelling demonstrated that fracture displacement and a pre-existing diagnosis of osteoporosis were significant predictors of revision risk. This is consistent with clinical experience and previous authors' findings.[8] The cohort study reported by Parker et al[8] recruited more participants than this trial and identified risk factors with smaller effect sizes. Interestingly our model found that dementia was a protective factor. It is difficult to develop a biologically plausible explanation for this observation. It may rather reflect the reluctance to embark upon major revision arthroplasty surgery in this group of particularly frail patients.

CONCLUSIONS AND IMPLICATIONS

How does our work contribute to the current debate concerning platelet-rich therapy?

Very little evidence exists to support any routine clinical applications of platelet-rich therapy. NICE have recommended that its use in the treatment of tendonopathy is limited to research settings.[5] To our knowledge this trial is the first to explore the clinical effectiveness of platelet-rich therapy in osteoporotic bone healing.

New NICE guidance for the management of fractures of the proximal femur suggests arthroplasty, with a risk of revision of approximately 5%, as opposed to internal fixation for this group of patients with displaced fractures.[22] We have been unable to definitively exclude an important treatment effect for platelet-rich therapy but in the absence of an approximately 20% reduction in the risk of revision surgery following internal fixation with platelet-rich therapy, the standard of care will remain arthroplasty.

Future work might investigate the effectiveness of platelet-rich therapy in different fracture types such as incomplete fractures or those in bone of normal density.

ADDITIONAL INFORMATION

We thank Becky Kearney, Katie McGuinness, Helen Richmond, Kate Dennison, Zoe Buckingham, Troy Douglin, Filo Eales, Gail McCloskey and Catherine Richmond for their assistance in recruitment and data collection during the trial; Philip Roberts, Ceri Jones, Peter Kimani and Steve Drew for their clinical, trials, and regulatory expertise in the trial steering committee and data monitoring committee for this trial; and all the patients for their time and effort in participating in this trial.

Conflict of interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that (1) none has support from companies for the submitted work; (2) none has any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none has any non-financial interests that may be relevant to the submitted work.

Trial registration: Current Controlled Trials, ISRCTN49197425. The trial registration is dated on this database as 23 April 2010. However, the registration process was begun prospectively. An initial application was made to Current Controlled Trials on 8 Jan 2009. However, at this time the study was also being adopted onto the UKCRN Portfolio. Coincidentally a change in registration policy occurred such that adopted studies would be registered with Current Controlled Trials through UKCRN. This process led to a delay such that registration was not completed until April 2010.

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Data: All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Additional data are available via the corresponding author (x.griffin@warwick.ac.uk).

Contributions: All authors participated in the design and management of the study. XLG and NP analysed and interpreted the data. XLG and JA managed the recruitment and follow-up of the patients. XLG and NP planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. The Trial Steering Committee authorised the release of the manuscript XLG is the guarantor.

ARTICLE SUMMARY

Article Focus

- to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

Key Messages

- no evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not
- a clinically meaningful difference cannot be definitively excluded

Strengths and Limitations

- pragmatic trial
- includes participants with chronic cognitive impairment

Table 1: Baseline characteristics for each group		
Characteristic	Group	
	Control (n=99)	Test (n=101)
Age (years)	83 (7.8)	83 (8.2)
Female (%)	73	69
Minimally displaced fractures (%)	22	21
Demented (AMT<8) (%)	31	34
Pre-morbid EQ-5D	0.63 (0.34)	0.69 (0.30)
Previously diagnosed CRF (%)	4.0	4.9
Previously diagnosed diabetes mellitus (%)	6.1	16
Previously diagnosed osteoporosis (%)	18	18
Currently prescribed anti-platelet drug (%)	32	27
Previously or currently prescribed systemic steroid (%)	6.1	6.9
Currently prescribed NSAID (%)	4.0	3.9
Currently smoking (%)	8.1	7.9
Time to theatre (hours)	34 (33)	30 (26)

Key:
Summary statistics: mean (standard deviation)
Data are presented as absolute values (%)

AMT: Abbreviated mental test score
CRF: Chronic renal failure
EQ-5D EuroQoL 5 Dimensions Index
NSAID: Non-steroidal anti-inflammatory drug
n/a: not applicable
n/r: not recorded

Table 2: Revision at 12 months post index operation				
Group	Unrevised	Revised	Total	Risk (%)
Control	47	31	78	39.74
Test	54	28	82	34.15
Total	101	59	160	36.88

Table 3: Between group differences in secondary outcome measures				
Outcome	Treatment group		Test	Significance
	Control (n=78)	Test (n=82)		
Radiographic non-union at one year (%)	1	2	Fisher Exact	1.00
Radiographic avascular necrosis at one year (%)	1	2	Fisher Exact	1.00
Length of index hospital stay (days)	23 (10-41)	15 (7-27)	Mann Whitney	0.03
Mortality (%)	23	20	Fisher Exact	0.61

Key:
Proportions are expressed as percentages; summary statistics as median and IQR

Table 4: Between group differences in complications		
Complication	Absolute number of events	
	Control group (n=99)	Test group (n=101)
Wound infection	3	1
Pulmonary embolus	2	0
Pneumonia	12	9
Urinary tract infection	6	5
Blood transfusion	2	0
Cerebrovascular accident	1	0
Myocardial infarction	1	0
Deep vein thrombosis	2	2
Death	23	20

Key:
Events are not mutually exclusive

Table 5: Estimates of hazard ratios for competing risks model				
Covariate		Hazard Ratio	95% CI	p-value
Displacement	*Minimally displaced*	0.303	0.126 to 0.730	0.008
	Displaced	1	-	-
Steroids	*Yes*	0.165	0.022 to 1.217	0.077
	No	1	-	-
Previously diagnosed osteoporosis	*Yes*	2.207	1.153 to 4.223	0.017
	No	1	-	-
Demented	*Yes*	0.496	0.263 to 0.937	0.031
	No	1	-	-
Treatment	*Test*	0.895	0.533 to 1.504	0.680
	Control	1	-	-

Figure 1: CONSORT flow diagram

Notes:

a 2 participants underwent revision prior to death

b 1 participant underwent revision prior to death

c 31 unavailable at baseline

d 35 unavailable at baseline

Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group

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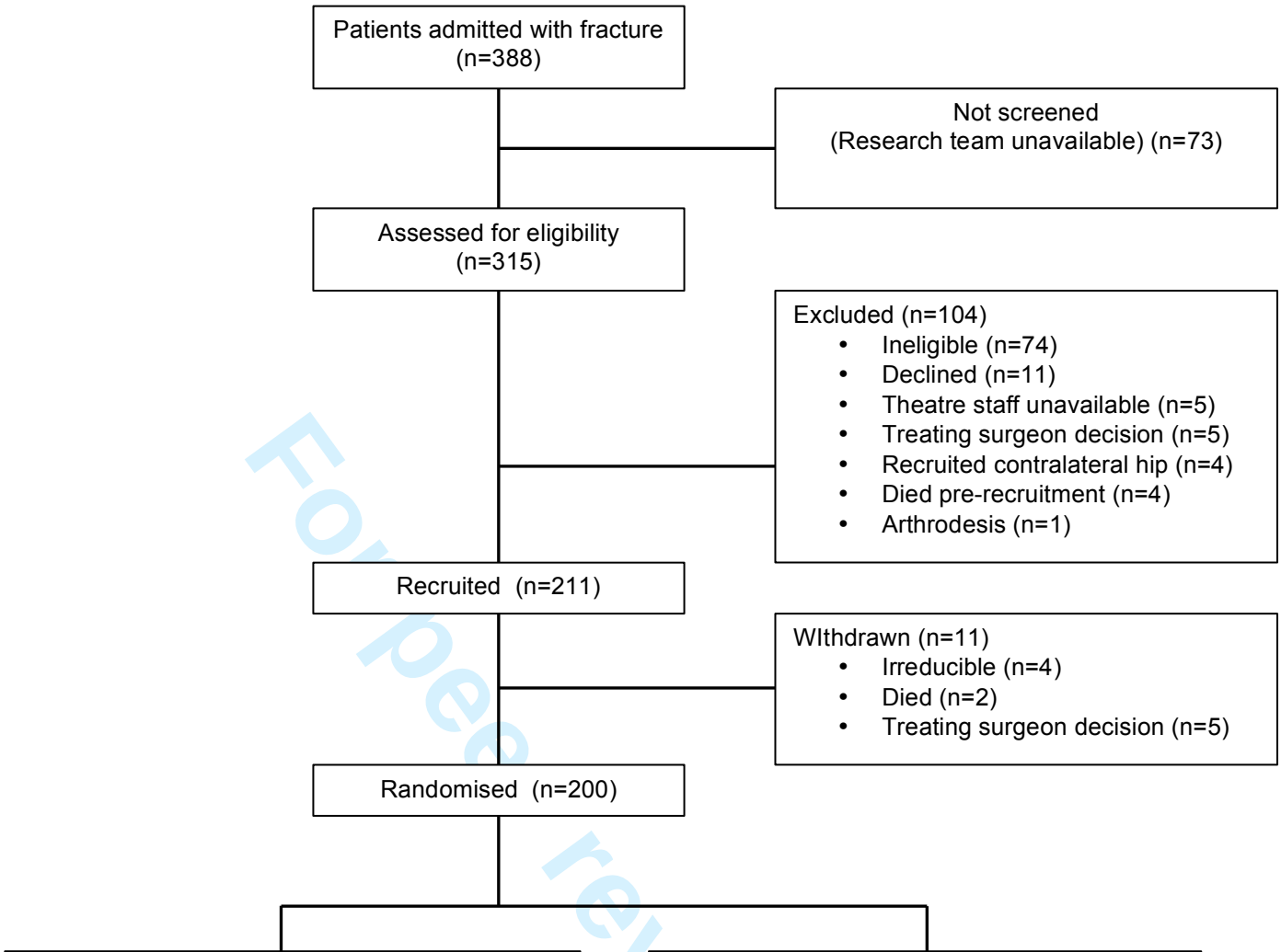
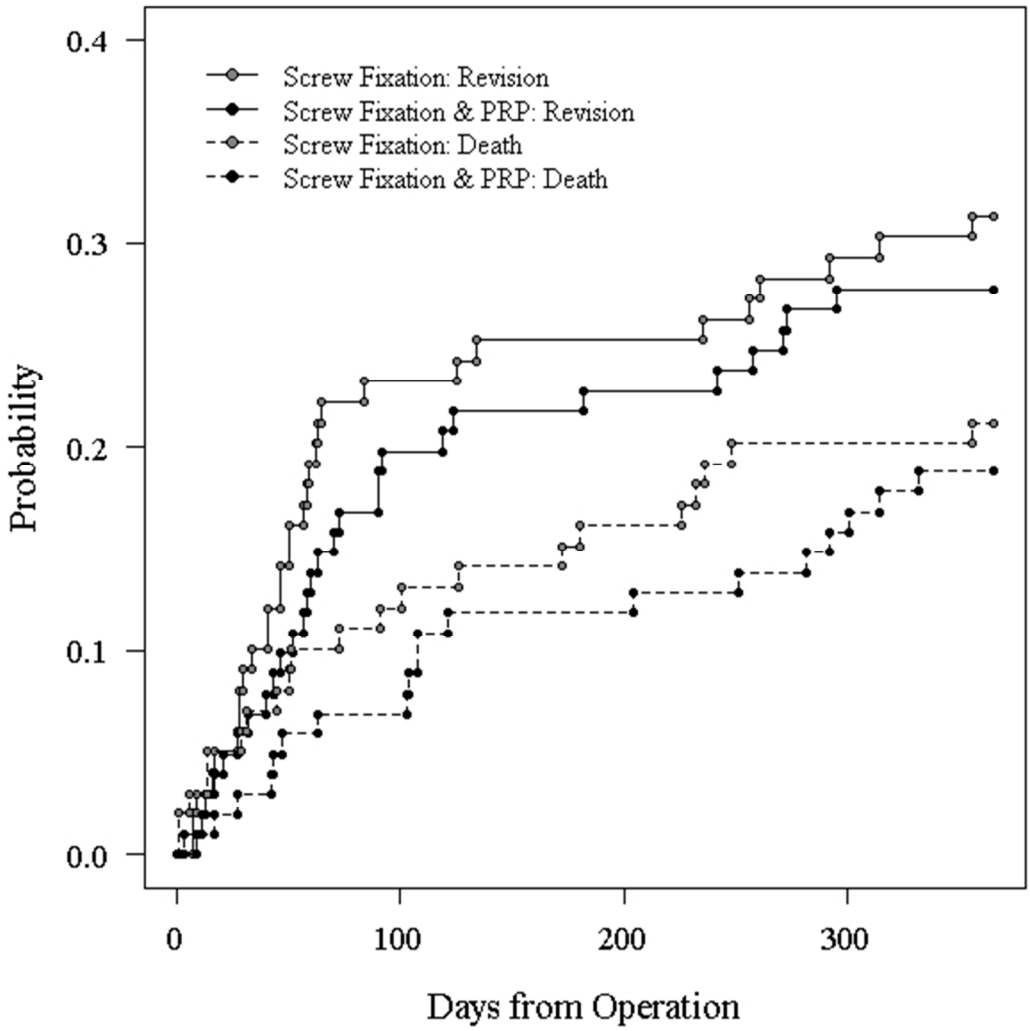


Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group



CONSORT 2010 checklist - WHiT Study

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5 & 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4 & 5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6 & 7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6 & 7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	80
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8 & 9 Table 2-5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10 & 11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL

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PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL.

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ABSTRACT

Objective To quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip.

Design Single centre, parallel group, participant blinded, randomised controlled trial.

Setting UK Major Trauma Centre.

Participants 200 of 315 eligible patients aged 65 years and over with any type of intracapsular fracture of the proximal femur. Patients were excluded if their fracture precluded internal fixation.

Interventions Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of platelet-rich plasma into the fracture site or not.

Main outcome measures Failure of fixation within 12 months, defined as any revision surgery.

Results Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to test and control groups respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6% (95% CI -10.6 to 21.8%) favouring treatment with platelet-rich therapy (chi^2 test, p 0.569). An adjusted effect estimate from a logistic regression model was similar (odds ratio=0.71, 95% CI 0.36 to 1.40, z-test p=0.325). There were no significant differences in any of the secondary outcomes measures excepting length of stay favouring treatment with platelet-rich therapy (median difference 8 days, Mann Whitney U p=0.03). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (hazard ratio 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy).

Conclusions No evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not. However, we cannot definitively exclude a clinically meaningful difference.

Trial registration Current Controlled Trials, ISRCTN49197425, www.controlled-trials.com/ISRCTN49197425

INTRODUCTION

Platelet-rich therapies are autologous blood products with a greater concentration of platelets than physiological whole blood.[1] These preparations have been used since the early 1990s to promote bone and soft tissue healing.[1] Promising preliminary studies have led to the use of platelet-rich therapy in both sports medicine, rheumatology and orthopaedic surgery with the aim of promoting and enhancing soft tissue and bone healing.[2]

Platelet-rich therapies can be produced at the bedside by either centrifugation or filtering of autologous whole blood mixed with an anti-coagulant. Both these processes produce a plasma fraction that has a supra-physiological concentration of platelets. Platelets have long been identified as the main regulators of the inflammatory phase of tissue repair.[3] This same mechanism may also influence the proliferation and differentiation phase of healing tissues.[3] Hence platelet-rich therapy has been used in an attempt to optimise healing by delivering supra-physiological levels of platelet-derived growth factors to the site of injury.[4]

At present, good quality evidence to support the use of platelet-rich therapy in the clinical setting remains sparse. The National Institute of Health and Clinical Excellence (NICE) has advised that its use should be restricted to research settings.[5] One exciting area of research is the use of platelet-rich therapy to enhance healing in osteoporotic fractures.[6]

Intracapsular fractures of the proximal femur are a good example. Failure of internal fixation for these hip fractures is common, with up to 35% of displaced fractures requiring revision surgery.[7-9] Therefore, any adjunct that can accelerate fracture healing and reduce the rate of failure of fixation has the potential to change patient care.

We conducted a randomised controlled trial to quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip. Specifically, we sought to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

METHODS

This study was a single centre, parallel group, participant blinded, randomised standard-of-care controlled trial with a 1:1 allocation to main treatment groups. Full details of the protocol have been published elsewhere.[10] The trial was given ethical approval on 6th July 2009 by Coventry Research Ethics Committee (09/H1210/22).

PARTICIPANTS

All patients aged 65 years and above with an intracapsular hip fracture were eligible, including those with cognitive impairment. Patients were excluded if they were managed non-operatively, presented late following their injury, had serious injuries to either lower limb that interfered with rehabilitation of the hip fracture, or had extant local disease precluding fixation, e.g. local tumour deposit, symptomatic ipsilateral hip osteoarthrosis.

RECRUITMENT AND ALLOCATION OF PARTICIPANTS

Participants were recruited between September 2009 and April 2011 from the acute trauma admissions to University Hospitals Coventry and Warwickshire NHS trust, in Coventry, UK. This is a major trauma centre that serves a population of two million people. Approximately 650 patients per year with a fracture of the proximal femur are treated in the centre.[11] Participants with capacity gave written consent; for those who lacked capacity, written consent was given by a consultee in accordance with the Mental Capacity Act 2005.

Participants were randomly allocated to one of two groups: standard of care fixation or standard of care fixation and platelet-rich therapy injection. Treatment allocation was determined using a computer generated, randomised number sequence administrated by an independent Clinical Trials Unit via a secure online programme. The randomisation code was stratified by displacement of the fracture[12] and split into unequal block sizes. Stratification ensured that the approximately 20% of fractures that were minimally displaced, that are associated with a very substantially improved outcome, were distributed evenly between groups. The code was only broken at the end of the trial once the trial statistician had locked and analysed the dataset.

Allocation to treatment group took place intra-operatively, only after the operating surgeon confirmed a successful reduction of the fracture. Those patients in whom a reduction could not be achieved underwent hip arthroplasty, which reflects standard clinical practice.

INTERVENTIONS

All participants underwent closed reduction of their fracture; where the leg was manipulated until the bones were 'reduced' back into their normal anatomical position. The lower limb was supported on a fracture table. Internal fixation of the fracture was achieved through a standard lateral approach with peri-operative antibiotic cover in accordance with hospital protocol. Post-operative care was the same for both groups of patients with early active mobilisation and immediate full weight-bearing with a standardised physiotherapy rehabilitation regime. All participants received routine prophylaxis against deep vein thrombosis.

Standard of care fixation was with two or three parallel cannulated screws. The number and exact configuration was left to the discretion of the operating surgeon to ensure that the results could be easily generalised. For those participants allocated to platelet-rich therapy, each screw was advanced up to but not beyond the fracture such that no compression was achieved before the platelet-rich plasma was injected. The guidewire of one screw was then removed and 3ml of platelet-rich plasma, harvested in accordance with the manufacturer's recommendations (GenesisCS Component Concentrating System, EmCyte Corporation, Fort Myers, FL), was injected without an activator through the cannulated screw directly into the fracture site under image intensifier guidance. This is a Mishra[13] Type 1A platelet-rich plasma, details of the bioactivity of which are available elsewhere.[14,15] The guidewire was immediately replaced and the screws advanced across the fracture site. No attempt was made to blind the operating surgeon.

OUTCOME MEASUREMENTS

PRIMARY

The proportion of participants undergoing re-operation for failure of fixation within one year of sustaining the fracture.

SECONDARY

- Radiographic non-union at one year. Non-union was defined as "failure of the fracture to show signs of bony union on the anteroposterior or lateral radiograph one year after surgery".[8]
- Radiographic evidence of avascular necrosis at one year
- The EQ-5D index (York A1 value set)[16] at 6, 12 and 52 weeks
- Length of index hospital stay
- Mortality
- Adverse events

SAMPLE SIZE

Very few data were available with which to estimate the possible size of a treatment effect of platelet-rich therapy.[17,18] The minimum clinically important treatment effect of platelet-rich therapy was agreed in discussion with several expert orthopaedic trauma surgeons. Although the figures varied by surgeon, all agreed that an absolute risk reduction (ARR) of between 15% and 25% in fixation failure would be clinically important. The overall rate of fixation failure of all intracapsular fractures of the femur is reported to be 25% and 35%.[7-9] Sample sizes were determined using the PS power and sample size software.[19] Selecting a power of 90%, and the most plausible estimate of fixation failure rate (30%) and an intermediate value for the minimum clinically important ARR of 20% gives a treatment group size of 82. Adding 20% on to the total trial sample size estimate to account for expected patient mortality gives a recruitment target of 200 participants that should provide a good margin for unanticipated recruitment problems and loss to follow-up.

STATISTICAL METHODS

The primary outcome measure, the proportion of patients requiring re-operation for failure of fixation (revision) within one year of sustaining the fracture, was compared between treatment groups (fixation and fixation plus platelet-rich therapy) using a chi^2 test, where data from participants were analysed by treatment allocation. Treatments were considered to differ significantly if p-values were less than 0.05. The primary analysis was an available case analysis where deaths without revision were excluded from the analysis. If mortality differed between the treatment groups, this had the potential to bias the effect estimate, so additional *post hoc* analyses were undertaken with deaths imputed as both revisions and non-revisions to assess the sensitivity of the primary analysis to the decisions regarding handling of the missing data.
Fisher's exact test was used to assess the significance of observed differences for the secondary proportional outcome measures. For continuous outcomes, which were approximately normally distributed, mean differences were tested using a two-tailed t-test; for non-parametric data (length of stay) differences were tested with the Mann Whitney U test. A planned subsidiary analysis used a multiple linear regression model to investigate the relationship between each participant's EQ-5D score at one year post operation and the treatment group, after appropriate adjustment for age, sex and fracture displacement for each participant. The incidences of adverse events were reported for each treatment group stratified by the type of event. Planned subgroup analyses were undertaken only for pre-specified subgroups. Explanatory variables of sex, fracture displacement, dementia and age were entered into a

logistic regression model with associated interaction terms with the treatment arm for each.

In addition to the primary analysis comparing risks of revision between groups, the Data Monitoring Committee recommended that a *post hoc* time-to-event analysis was also undertaken to assess temporal differences in revision post operation. In this setting, where failure of the fixation was the event of interest, death was regarded as a competing risk. In the presence of competing risks, the standard cause-specific Cox proportional hazards model is not appropriate as it treats the competing risk (death) as a censored observation. Therefore the approach adopted here was the proportional hazards model proposed by Fine and Gray,[20] based on direct regression modelling of covariates on the cumulative incidence function (CIF). The CIF, the proportion of trial participants at time t who had event j (death or revision), was used to compare treatments and the R software[21] package cmprsk[21] was used to implement the Fine-Gray model using a stepwise fitting algorithm.

RESULTS

PARTICIPANTS

A summary of the flow of participants through the study is at Fig. 1. Of the 388 patients admitted with an intracapsular hip fracture during the recruitment period, 52% underwent trial treatments, which represented 83% of all eligible patients assessed. This was largely due to recruitment only taking place during the working week.

Two hundred and eleven participants were enrolled into the study, of whom 200 were randomly allocated to treatments. Ninety-nine participants were allocated to the control group of whom 76 completed the trial protocol; 101 were allocated to the test group of whom 81 completed the protocol. In the latter group there were three protocol violations leading to three crossovers. Of the 43 participants who died, 3 underwent revision surgery prior to death, so in total 160 participants were available for the primary analysis. The numbers of participants unavailable at each of the four time-points for the EQ-5D score are reported in the trial flow diagram (Fig. 1). Similar proportions of other secondary outcomes were unavailable at different follow-up time-points due to death, co-existing chronic confusional states at the time of recruitment, new onset co-morbidities and participant withdrawals.

The baseline characteristics of the trial participants are described in Table 1. There were no apparently substantial between-group differences for any of the recorded baseline characteristics.

TREATMENTS

Both the test and control treatments were successfully delivered as described previously, under the supervision of 18 Consultant Trauma Surgeons and performed by a total of 21 specialist trainees.

OUTCOMES AND ESTIMATION

Table 2 shows counts and estimated risks of revision surgery by treatment group. There was an ARR of 5.6% (95% CI -10.6 to 21.8%) in favour of platelet-rich therapy (χ^2 test, p=0.569).

Deaths were also approximately balanced between treatment groups (control n=23 and test n=20). Imputing all the deaths as 'revisions' increased overall estimates of revision risks, but due to the balance across groups had little impact on effect estimates (control risk 52.5%; ARR in favour of platelet-rich therapy 6.0%, 95% CI -8.8 to 20.8%; χ^2 test p=0.480). Similarly, an equivalent analysis re-coding deaths as 'non-revisions' did not modify the conclusions of the primary analysis (control risk

31.3%; ARR in favour of platelet-rich therapy 3.6%, 95% CI -10.0 to 17.2%; chi^2 test p=0.688).

Logistic regression analysis, with a binary response variable (1=revised and 0=unrevised), was used to assess the effect of treatment group allocation on revision after adjustment for sex, fracture displacement, dementia and age. This model gave an adjusted estimated odds ratio of 0.71 (95% CI 0.36 to 1.40), which was marginally smaller than the unadjusted odds ratio of 0.79 from Table 2, and provided no evidence for a significant treatment effect (z-test from logistic regression p=0.325). In addition to the planned variables used for the adjusted analysis, other baseline variables (e.g. diabetes) were also entered into the regression model, but proved not to be significant. Interaction terms were added to the model to test for pre-specified subgroup effects; that is additional terms were included in the model that tested to see if the treatment effect was changed (moderated) by fracture displacement, dementia or age group. Appropriate interaction terms were added individually to the base model to give three separate analyses; none of the interaction terms significantly improved the model fit, providing no evidence for substantial subgroup effects.

There was no significant difference in unadjusted mean EQ-5D score at one year between the control and treatment groups (mean control group EQ-5D=0.588, mean difference (MD)=0.018 in favour of the control group, t-test p=0.799). After adjusting for age, sex and fracture displacement this was maintained. A summary of the other secondary outcomes is presented in Table 3. There was no significant difference between treatment groups in any of the measures excepting length of stay. The number and distribution of complications were similar in both treatment groups (Table 4).

Estimated cumulative incidence function (CIF) curves, the probability that the event of interest occurs before a given time, are shown for death and revision as competing events for each treatment group in Figure 2. Estimates of hazard ratios (HR) for the competing risks regression model are reported in Table 5. Estimates indicated an increased risk of revision surgery for participants with a pre-existing diagnosis of osteoporosis and a significantly lower risk for participants with minimally displaced fractures or dementia. There was no evidence for a significant treatment effect (HR 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy). An analogous time-to-event analysis using the more conventional Cox proportional hazards model gave very similar results (HR 0.819, 95% CI 0.489 to 1.372, p=0.449 in favour of platelet-rich therapy).

DISCUSSION

PRINCIPAL FINDINGS

This trial has found no evidence of a difference in the risk of revision surgery between participants receiving platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur. However, we have been unable to definitively exclude a clinically important difference. A sensitivity analysis to explore the effect of decisions regarding the handling of the missing data and the competing risks of death and revision surgery found similar estimates of the effect size.

The majority of secondary outcomes, including radiographic, mortality and patient-reported health related quality-of-life measures, demonstrated effects that were concordant with the primary outcome. The length of inpatient stay was significantly shorter in the group treated with platelet-rich therapy. We are unable to provide a biologically plausible explanation for this difference. There was no evidence of any subgroup interaction effects.

STRENGTHS AND LIMITATIONS OF STUDY

This was a pragmatic trial. Although only conducted at a single centre, a large number of surgeons were involved in the administration of both the interventions. The consequent variety in reduction and fixation strategies probably reflects wider surgical practice in a well recognised cohort of patients. The corollary of this, that the case number for any one surgeon was comparatively low, might have reduced the assay sensitivity of the trial. However, each surgeon was either trained to perform the intervention or supervised suitably. Additionally, since each individual surgeon preformed only a small number of interventions the impact of the 'surgeon effect', related to both experience and technical expertise, was likely to have been small.

The hypothesis of the trial concerned the incidence of fixation failure. Since this is difficult to define a surrogate outcome of revision surgery was chosen. It is possible that other considerations, such as patient comorbidity, may have influenced any decision to undertake revision surgery. However, it is unlikely that such considerations differed between the treatment groups.

Only 80% of the available population was screened for eligibility since the trial staff was often not available outside the working week. This might have produced a sampling bias. However, review of the admission and screening data revealed no substantial differences in the crucial confounders of age, sex, fracture displacement and chronic cognitive impairment between the unscreened and recruited samples.

Some participants were being treated with anti-platelet drugs at the time of recruitment into the trial. These participants were not excluded since the trial was pragmatic and there is no evidence that the mechanism of release of the platelet derived growth factors during platelet-rich therapy administration are dependent on the pathways inhibited by aspirin and other anti-platelet drugs.

COMPARISON WITH OTHER STUDIES

Few data exist from other similar studies with which to compare these findings.[17] Indeed, to our knowledge this is the first trial of this size to be conducted exploring platelet-rich therapy in bone healing.[2]

Our modelling demonstrated that fracture displacement and a pre-existing diagnosis of osteoporosis were significant predictors of revision risk. This is consistent with clinical experience and previous authors' findings.[8] The cohort study reported by Parker et al[8] recruited more participants than this trial and identified risk factors with smaller effect sizes. Interestingly our model found that dementia was a protective factor. It is difficult to develop a biologically plausible explanation for this observation. It may rather reflect the reluctance to embark upon major revision arthroplasty surgery in this group of particularly frail patients.

CONCLUSIONS AND IMPLICATIONS

How does our work contribute to the current debate concerning platelet-rich therapy?

Very little evidence exists to support any routine clinical applications of platelet-rich therapy. NICE have recommended that its use in the treatment of tendonopathy is limited to research settings.[5] To our knowledge this trial is the first to explore the clinical effectiveness of platelet-rich therapy in osteoporotic bone healing.

New NICE guidance for the management of fractures of the proximal femur suggests arthroplasty, with a risk of revision of approximately 5%, as opposed to internal fixation for this group of patients with displaced fractures.[23] We have been unable to definitively exclude an important treatment effect for platelet-rich therapy but in the absence of an approximately 20% reduction in the risk of revision surgery following internal fixation with platelet-rich therapy, the standard of care will remain arthroplasty.

Future work might investigate the effectiveness of platelet-rich therapy in different fracture types such as incomplete fractures or those in bone of normal density.

ADDITIONAL INFORMATION

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Conflict of interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that (1) none has support from companies for the submitted work; (2) none has any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none has any non-financial interests that may be relevant to the submitted work.

Trial registration: Current Controlled Trials, ISRCTN49197425. The trial registration is dated on this database as 23 April 2010. However, the registration process was begun prospectively. An initial application was made to Current Controlled Trials on 8 Jan 2009. However, at this time the study was also being adopted onto the UKCRN Portfolio. Coincidentally a change in registration policy occurred such that adopted studies would be registered with Current Controlled Trials through UKCRN. This process led to a delay such that registration was not completed until April 2010.

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Data: All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Additional data are available via the corresponding author (x.griffin@warwick.ac.uk).

Contributions: All authors participated in the design and management of the study. XLG and NP analysed and interpreted the data. XLG and JA managed the recruitment and follow-up of the patients. XLG and NP planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. The Trial Steering Committee authorised the release of the manuscript XLG is the guarantor.

ARTICLE SUMMARY

Article Focus

- to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

Key Messages

- no evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not
- a clinically meaningful difference cannot be definitively excluded

Strengths and Limitations

- pragmatic trial
- includes participants with chronic cognitive impairment

Table 1: Baseline characteristics for each group		
Characteristic	Group	
	Control (n=99)	Test (n=101)
Age (years)	83 (7.8)	83 (8.2)
Female (%)	73	69
Minimally displaced fractures (%)	22	21
Demented (AMT<8) (%)	31	34
Pre-morbid EQ-5D	0.63 (0.34)	0.69 (0.30)
Previously diagnosed CRF (%)	4.0	4.9
Previously diagnosed diabetes mellitus (%)	6.1	16
Previously diagnosed osteoporosis (%)	18	18
Currently prescribed anti-platelet drug (%)	32	27
Previously or currently prescribed systemic steroid (%)	6.1	6.9
Currently prescribed NSAID (%)	4.0	3.9
Currently smoking (%)	8.1	7.9
Time to theatre (hours)	34 (33)	30 (26)

Key:
Summary statistics: mean (standard deviation)
Data are presented as absolute values (%)

AMT: Abbreviated mental test score
CRF: Chronic renal failure
EQ-5D EuroQoL 5 Dimensions Index
NSAID: Non-steroidal anti-inflammatory drug
n/a: not applicable
n/r: not recorded

Table 2: Revision at 12 months post index operation				
Group	Unrevised	Revised	Total	Risk (%)
Control	47	31	78	39.74
Test	54	28	82	34.15
Total	101	59	160	36.88

Table 3: Between group differences in secondary outcome measures				
Outcome	Treatment group		Test	Significance
	Control (n=78)	Test (n=82)		
Radiographic non-union at one year (%)	1	2	Fisher Exact	1.00
Radiographic avascular necrosis at one year (%)	1	2	Fisher Exact	1.00
Length of index hospital stay (days)	23 (10-41)	15 (7-27)	Mann Whitney	0.03
Mortality (%)	23	20	Fisher Exact	0.61

Key:
Proportions are expressed as percentages; summary statistics as median and IQR

Table 4: Between group differences in complications		
Complication	Absolute number of events	
	Control group (n=99)	Test group (n=101)
Wound infection	3	1
Pulmonary embolus	2	0
Pneumonia	12	9
Urinary tract infection	6	5
Blood transfusion	2	0
Cerebrovascular accident	1	0
Myocardial infarction	1	0
Deep vein thrombosis	2	2
Death	23	20

Key:
Events are not mutually exclusive

Table 5: Estimates of hazard ratios for competing risks model				
Covariate		Hazard Ratio	95% CI	p-value
Displacement	*Minimally displaced*	0.303	0.126 to 0.730	0.008
	Displaced	1	-	-
Steroids	*Yes*	0.165	0.022 to 1.217	0.077
	No	1	-	-
Previously diagnosed osteoporosis	*Yes*	2.207	1.153 to 4.223	0.017
	No	1	-	-
Demented	*Yes*	0.496	0.263 to 0.937	0.031
	No	1	-	-
Treatment	*Test*	0.895	0.533 to 1.504	0.680
	Control	1	-	-

Figure 1: CONSORT flow diagram

Notes:

a 2 participants underwent revision prior to death

b 1 participant underwent revision prior to death

c 31 unavailable at baseline

d 35 unavailable at baseline

Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group

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PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL.

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ABSTRACT

Objective To quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip.

Design Single centre, parallel group, participant blinded, randomised controlled trial.

Setting UK Major Trauma Centre.

Participants 200 of 315 eligible patients aged 65 years and over with any type of intracapsular fracture of the proximal femur. Patients were excluded if their fracture precluded internal fixation.

Interventions Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of platelet-rich plasma into the fracture site or not.

Main outcome measures Failure of fixation within 12 months, defined as any revision surgery.

Results Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to test and control groups respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6% (95% CI -10.6 to 21.8%) favouring treatment with platelet-rich therapy (chi^2 test, p 0.569). An adjusted effect estimate from a logistic regression model was similar (odds ratio=0.71, 95% CI 0.36 to 1.40, z-test p=0.325). There were no significant differences in any of the secondary outcomes measures excepting length of stay favouring treatment with platelet-rich therapy (median difference 8 days, Mann Whitney U p=0.03). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (hazard ratio 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy).

Conclusions No evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not. However, we cannot definitively exclude a clinically meaningful difference.

Trial registration Current Controlled Trials, ISRCTN49197425, www.controlled-trials.com/ISRCTN49197425

INTRODUCTION

Platelet-rich therapies are autologous blood products with a greater concentration of platelets than physiological whole blood.[1] These preparations have been used since the early 1990s to promote bone and soft tissue healing.[1] Promising preliminary studies have led to the use of platelet-rich therapy in both sports medicine, rheumatology and orthopaedic surgery with the aim of promoting and enhancing soft tissue and bone healing.[2]

Platelet-rich therapies can be produced at the bedside by either centrifugation or filtering of autologous whole blood mixed with an anti-coagulant. Both these processes produce a plasma fraction that has a supra-physiological concentration of platelets. Platelets have long been identified as the main regulators of the inflammatory phase of tissue repair.[3] This same mechanism may also influence the proliferation and differentiation phase of healing tissues.[3] Hence platelet-rich therapy has been used in an attempt to optimise healing by delivering supra-physiological levels of platelet-derived growth factors to the site of injury.[4]

At present, good quality evidence to support the use of platelet-rich therapy in the clinical setting remains sparse. The National Institute of Health and Clinical Excellence (NICE) has advised that its use should be restricted to research settings.[5] One exciting area of research is the use of platelet-rich therapy to enhance healing in osteoporotic fractures.[6]

Intracapsular fractures of the proximal femur are a good example. Failure of internal fixation for these hip fractures is common, with up to 35% of displaced fractures requiring revision surgery.[7-9] Therefore, any adjunct that can accelerate fracture healing and reduce the rate of failure of fixation has the potential to change patient care.

We conducted a randomised controlled trial to quantify and draw inferences on the clinical effectiveness of platelet-rich therapy in the management of patients with a typical osteoporotic fracture of the hip. Specifically, we sought to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

METHODS

This study was a single centre, parallel group, participant blinded, randomised standard-of-care controlled trial with a 1:1 allocation to main treatment groups. Full details of the protocol have been published elsewhere.[10] The trial was given ethical approval on 6th July 2009 by Coventry Research Ethics Committee (09/H1210/22).

PARTICIPANTS

All patients aged 65 years and above with an intracapsular hip fracture were eligible, including those with cognitive impairment. Patients were excluded if they were managed non-operatively, presented late following their injury, had serious injuries to either lower limb that interfered with rehabilitation of the hip fracture, or had extant local disease precluding fixation, e.g. local tumour deposit, symptomatic ipsilateral hip osteoarthrosis.

RECRUITMENT AND ALLOCATION OF PARTICIPANTS

Participants were recruited between September 2009 and April 2011 from the acute trauma admissions to University Hospitals Coventry and Warwickshire NHS trust, in Coventry, UK. This is a major trauma centre that serves a population of two million people. Approximately 650 patients per year with a fracture of the proximal femur are treated in the centre.[11] Participants with capacity gave written consent; for those who lacked capacity, written consent was given by a consultee in accordance with the Mental Capacity Act 2005.

Participants were randomly allocated to one of two groups: standard of care fixation or standard of care fixation and platelet-rich therapy injection. Treatment allocation was determined using a computer generated, randomised number sequence administrated by an independent Clinical Trials Unit via a secure online programme. The randomisation code was stratified by displacement of the fracture[12] and split into unequal block sizes. Stratification ensured that the approximately 20% of fractures that were minimally displaced, that are associated with a very substantially improved outcome, were distributed evenly between groups. The code was only broken at the end of the trial once the trial statistician had locked and analysed the dataset.

Allocation to treatment group took place intra-operatively, only after the operating surgeon confirmed a successful reduction of the fracture. Those patients in whom a reduction could not be achieved underwent hip arthroplasty, which reflects standard clinical practice.

INTERVENTIONS

All participants underwent closed reduction of their fracture; where the leg was manipulated until the bones were 'reduced' back into their normal anatomical position. The lower limb was supported on a fracture table. Internal fixation of the fracture was achieved through a standard lateral approach with peri-operative antibiotic cover in accordance with hospital protocol. Post-operative care was the same for both groups of patients with early active mobilisation and immediate full weight-bearing with a standardised physiotherapy rehabilitation regime. All participants received routine prophylaxis against deep vein thrombosis.

Standard of care fixation was with two or three parallel cannulated screws. The number and exact configuration was left to the discretion of the operating surgeon to ensure that the results could be easily generalised. For those participants allocated to platelet-rich therapy, each screw was advanced up to but not beyond the fracture such that no compression was achieved before the platelet-rich plasma was injected. The guidewire of one screw was then removed and 3ml of platelet-rich plasma, harvested in accordance with the manufacturer's recommendations (GenesisCS Component Concentrating System, EmCyte Corporation, Fort Myers, FL), was injected without an activator through the cannulated screw directly into the fracture site under image intensifier guidance. This is a Mishra[13] Type 1A platelet-rich plasma, ~~D~~details of the bioactivity of which ~~this platelet rich plasma~~ are available elsewhere.[1~~3~~4,1~~5~~4] The guidewire was immediately replaced and the screws advanced across the fracture site. No attempt was made to blind the operating surgeon.

OUTCOME MEASUREMENTS

PRIMARY

The proportion of participants undergoing re-operation for failure of fixation within one year of sustaining the fracture.

SECONDARY

- Radiographic non-union at one year. Non-union was defined as "failure of the fracture to show signs of bony union on the anteroposterior or lateral radiograph one year after surgery".[8]
- Radiographic evidence of avascular necrosis at one year
- The EQ-5D index (York A1 value set)[1~~5~~6] at 6, 12 and 52 weeks
- Length of index hospital stay
- Mortality

- Adverse events

SAMPLE SIZE

Very few data were available with which to estimate the possible size of a treatment effect of platelet-rich therapy.[176,178] The minimum clinically important treatment effect of platelet-rich therapy was agreed in discussion with several expert orthopaedic trauma surgeons. Although the figures varied by surgeon, all agreed that an absolute risk reduction (ARR) of between 15% and 25% in fixation failure would be clinically important. The overall rate of fixation failure of all intracapsular fractures of the femur is reported to be 25% and 35%.[7-9] Sample sizes were determined using the PS power and sample size software.[189] Selecting a power of 90%, and the most plausible estimate of fixation failure rate (30%) and an intermediate value for the minimum clinically important ARR of 20% gives a treatment group size of 82. Adding 20% on to the total trial sample size estimate to account for expected patient mortality gives a recruitment target of 200 participants that should provide a good margin for unanticipated recruitment problems and loss to follow-up.

STATISTICAL METHODS

The primary outcome measure, the proportion of patients requiring re-operation for failure of fixation (revision) within one year of sustaining the fracture, was compared between treatment groups (fixation and fixation plus platelet-rich therapy) using a chi^2 test, where data from participants were analysed by treatment allocation. Treatments were considered to differ significantly if p-values were less than 0.05. The primary analysis was an available case analysis where deaths without revision were excluded from the analysis. If mortality differed between the treatment groups, this had the potential to bias the effect estimate, so additional *post hoc* analyses were undertaken with deaths imputed as both revisions and non-revisions to assess the sensitivity of the primary analysis to the decisions regarding handling of the missing data. Fisher's exact test was used to assess the significance of observed differences for the secondary proportional outcome measures. For continuous outcomes, which were approximately normally distributed, mean differences were tested using a two-tailed t-test; for non-parametric data (length of stay) differences were tested with the Mann Whitney U test. A planned subsidiary analysis used a multiple linear regression model to investigate the relationship between each participant's EQ-5D score at one year post operation and the treatment group, after appropriate adjustment for age, sex and fracture displacement for each participant. The incidences of adverse events were reported for each treatment group stratified by the type of event. Planned subgroup analyses were undertaken only for pre-specified subgroups. Explanatory

variables of sex, fracture displacement, dementia and age were entered into a logistic regression model with associated interaction terms with the treatment arm for each.

In addition to the primary analysis comparing risks of revision between groups, the Data Monitoring Committee recommended that a *post hoc* time-to-event analysis was also undertaken to assess temporal differences in revision post operation. In this setting, where failure of the fixation was the event of interest, death was regarded as a competing risk. In the presence of competing risks, the standard cause-specific Cox proportional hazards model is not appropriate as it treats the competing risk (death) as a censored observation. Therefore the approach adopted here was the proportional hazards model proposed by Fine and Gray,[2019] based on direct regression modelling of covariates on the cumulative incidence function (CIF). The CIF, the proportion of trial participants at time t who had event j (death or revision), was used to compare treatments and the R software[219] package cmprsk[21] was used to implement the Fine-Gray model using a stepwise fitting algorithm.

RESULTS

PARTICIPANTS

A summary of the flow of participants through the study is at Fig. 1. Of the 388 patients admitted with an intracapsular hip fracture during the recruitment period, 52% underwent trial treatments, which represented 83% of all eligible patients assessed. This was largely due to recruitment only taking place during the working week.

Two hundred and eleven participants were enrolled into the study, of whom 200 were randomly allocated to treatments. Ninety-nine participants were allocated to the control group of whom 76 completed the trial protocol; 101 were allocated to the test group of whom 81 completed the protocol. In the latter group there were three protocol violations leading to three crossovers. Of the 43 participants who died, 3 underwent revision surgery prior to death, so in total 160 participants were available for the primary analysis. The numbers of participants unavailable at each of the four time-points for the EQ-5D score are reported in the trial flow diagram (Fig. 1). Similar proportions of other secondary outcomes were unavailable at different follow-up time-points due to death, co-existing chronic confusional states at the time of recruitment, new onset co-morbidities and participant withdrawals.

The baseline characteristics of the trial participants are described in Table 1. There were no apparently substantial between-group differences for any of the recorded baseline characteristics.

TREATMENTS

Both the test and control treatments were successfully delivered as described previously, under the supervision of 18 Consultant Trauma Surgeons and performed by a total of 21 specialist trainees.

OUTCOMES AND ESTIMATION

Table 2 shows counts and estimated risks of revision surgery by treatment group. There was an ARR of 5.6% (95% CI -10.6 to 21.8%) in favour of platelet-rich therapy (χ^2 test, p=0.569).

Deaths were also approximately balanced between treatment groups (control n=23 and test n=20). Imputing all the deaths as 'revisions' increased overall estimates of revision risks, but due to the balance across groups had little impact on effect estimates (control risk 52.5%; ARR in favour of platelet-rich therapy 6.0%, 95% CI -8.8 to 20.8%; χ^2 test p=0.480). Similarly, an equivalent analysis re-coding deaths as 'non-revisions' did not modify the conclusions of the primary analysis (control risk

31.3%; ARR in favour of platelet-rich therapy 3.6%, 95% CI -10.0 to 17.2%; chi^2 test p=0.688).

Logistic regression analysis, with a binary response variable (1=revised and 0=unrevised), was used to assess the effect of treatment group allocation on revision after adjustment for sex, fracture displacement, dementia and age. This model gave an adjusted estimated odds ratio of 0.71 (95% CI 0.36 to 1.40), which was marginally smaller than the unadjusted odds ratio of 0.79 from Table 2, and provided no evidence for a significant treatment effect (z-test from logistic regression p=0.325). In addition to the planned variables used for the adjusted analysis, other baseline variables (e.g. diabetes) were also entered into the regression model, but proved not to be significant. Interaction terms were added to the model to test for pre-specified subgroup effects; that is additional terms were included in the model that tested to see if the treatment effect was changed (moderated) by fracture displacement, dementia or age group. Appropriate interaction terms were added individually to the base model to give three separate analyses; none of the interaction terms significantly improved the model fit, providing no evidence for substantial subgroup effects.

There was no significant difference in unadjusted mean EQ-5D score at one year between the control and treatment groups (mean control group EQ-5D=0.588, mean difference (MD)=0.018 in favour of the control group, t-test p=0.799). After adjusting for age, sex and fracture displacement this was maintained. A summary of the other secondary outcomes is presented in Table 3. There was no significant difference between treatment groups in any of the measures excepting length of stay. The number and distribution of complications were similar in both treatment groups (Table 4).

Estimated cumulative incidence function (CIF) curves, the probability that the event of interest occurs before a given time, are shown for death and revision as competing events for each treatment group in Figure 2. Estimates of hazard ratios (HR) for the competing risks regression model are reported in Table 5. Estimates indicated an increased risk of revision surgery for participants with a pre-existing diagnosis of osteoporosis and a significantly lower risk for participants with minimally displaced fractures or dementia. There was no evidence for a significant treatment effect (HR 0.895, 95% CI 0.533 to 1.504, p=0.680 in favour of platelet-rich therapy). An analogous time-to-event analysis using the more conventional Cox proportional hazards model gave very similar results (HR 0.819, 95% CI 0.489 to 1.372, p=0.449 in favour of platelet-rich therapy).

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DISCUSSION

PRINCIPAL FINDINGS

This trial has found no evidence of a difference in the risk of revision surgery between participants receiving platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur. However, we have been unable to definitively exclude a clinically important difference. A sensitivity analysis to explore the effect of decisions regarding the handling of the missing data and the competing risks of death and revision surgery found similar estimates of the effect size.

The majority of secondary outcomes, including radiographic, mortality and patient-reported health related quality-of-life measures, demonstrated effects that were concordant with the primary outcome. The length of inpatient stay was significantly shorter in the group treated with platelet-rich therapy. We are unable to provide a biologically plausible explanation for this difference. There was no evidence of any subgroup interaction effects.

STRENGTHS AND LIMITATIONS OF STUDY

This was a pragmatic trial. Although only conducted at a single centre, a large number of surgeons were involved in the administration of both the interventions. The consequent variety in reduction and fixation strategies probably reflects wider surgical practice in a well recognised cohort of patients. The corollary of this, that the case number for any one surgeon was comparatively low, might have reduced the assay sensitivity of the trial. However, each surgeon was either trained to perform the intervention or supervised suitably. Additionally, since each individual surgeon preformed only a small number of interventions the impact of the 'surgeon effect', related to both experience and technical expertise, was likely to have been small.

The hypothesis of the trial concerned the incidence of fixation failure. Since this is difficult to define a surrogate outcome of revision surgery was chosen. It is possible that other considerations, such as patient comorbidity, may have influenced any decision to undertake revision surgery. However, it is unlikely that such considerations differed between the treatment groups.

Only 80% of the available population was screened for eligibility since the trial staff was often not available outside the working week. This might have produced a sampling bias. However, review of the admission and screening data revealed no substantial differences in the crucial confounders of age, sex, fracture displacement and chronic cognitive impairment between the unscreened and recruited samples.

Some participants were being treated with anti-platelet drugs at the time of recruitment into the trial. These participants were not excluded since the trial was pragmatic and there is no evidence that the mechanism of release of the platelet derived growth factors during platelet-rich therapy administration are dependent on the pathways inhibited by aspirin and other anti-platelet drugs.

COMPARISON WITH OTHER STUDIES

Few data exist from other similar studies with which to compare these findings.[176] Indeed, to our knowledge this is the first trial of this size to be conducted exploring platelet-rich therapy in bone healing.[2]

Our modelling demonstrated that fracture displacement and a pre-existing diagnosis of osteoporosis were significant predictors of revision risk. This is consistent with clinical experience and previous authors' findings.[8] The cohort study reported by Parker et al[8] recruited more participants than this trial and identified risk factors with smaller effect sizes. Interestingly our model found that dementia was a protective factor. It is difficult to develop a biologically plausible explanation for this observation. It may rather reflect the reluctance to embark upon major revision arthroplasty surgery in this group of particularly frail patients.

CONCLUSIONS AND IMPLICATIONS

How does our work contribute to the current debate concerning platelet-rich therapy?

Very little evidence exists to support any routine clinical applications of platelet-rich therapy. NICE have recommended that its use in the treatment of tendonopathy is limited to research settings.[5] To our knowledge this trial is the first to explore the clinical effectiveness of platelet-rich therapy in osteoporotic bone healing.

New NICE guidance for the management of fractures of the proximal femur suggests arthroplasty, with a risk of revision of approximately 5%, as opposed to internal fixation for this group of patients with displaced fractures.[232] We have been unable to definitively exclude an important treatment effect for platelet-rich therapy but in the absence of an approximately 20% reduction in the risk of revision surgery following internal fixation with platelet-rich therapy, the standard of care will remain arthroplasty.

Future work might investigate the effectiveness of platelet-rich therapy in different fracture types such as incomplete fractures or those in bone of normal density.

ADDITIONAL INFORMATION

We thank Becky Kearney, Katie McGuinness, Helen Richmond, Kate Dennison, Zoe Buckingham, Troy Douglin, Filo Eales, Gail McCloskey and Catherine Richmond for their assistance in recruitment and data collection during the trial; Philip Roberts, Ceri Jones, Peter Kimani and Steve Drew for their clinical, trials, and regulatory expertise in the trial steering committee and data monitoring committee for this trial; and all the patients for their time and effort in participating in this trial.

Conflict of interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that (1) none has support from companies for the submitted work; (2) none has any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none has any non-financial interests that may be relevant to the submitted work.

Trial registration: Current Controlled Trials, ISRCTN49197425. The trial registration is dated on this database as 23 April 2010. However, the registration process was begun prospectively. An initial application was made to Current Controlled Trials on 8 Jan 2009. However, at this time the study was also being adopted onto the UKCRN Portfolio. Coincidentally a change in registration policy occurred such that adopted studies would be registered with Current Controlled Trials through UKCRN. This process led to a delay such that registration was not completed until April 2010.

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Data: All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Additional data are available via the corresponding author (x.griffin@warwick.ac.uk).

Contributions: All authors participated in the design and management of the study. XLG and NP analysed and interpreted the data. XLG and JA managed the recruitment and follow-up of the patients. XLG and NP planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. The Trial Steering Committee authorised the release of the manuscript XLG is the guarantor.

ARTICLE SUMMARY

Article Focus

- to explore the difference in the risk of fixation failure at one year after index fracture between patients treated with platelet-rich therapy and those not as an adjunct to internal fixation of an intracapsular fracture of the proximal femur.

Key Messages

- no evidence of a difference in the risk of revision surgery within one year in participants treated with platelet-rich therapy compared with those not
- a clinically meaningful difference cannot be definitively excluded

Strengths and Limitations

- pragmatic trial
- includes participants with chronic cognitive impairment

Table 1: Baseline characteristics for each group		
Characteristic	Group	
	Control (n=99)	Test (n=101)
Age (years)	83 (7.8)	83 (8.2)
Female (%)	73	69
Minimally displaced fractures (%)	22	21
Demented (AMT<8) (%)	31	34
Pre-morbid EQ-5D	0.63 (0.34)	0.69 (0.30)
Previously diagnosed CRF (%)	4.0	4.9
Previously diagnosed diabetes mellitus (%)	6.1	16
Previously diagnosed osteoporosis (%)	18	18
Currently prescribed anti-platelet drug (%)	32	27
Previously or currently prescribed systemic steroid (%)	6.1	6.9
Currently prescribed NSAID (%)	4.0	3.9
Currently smoking (%)	8.1	7.9
Time to theatre (hours)	34 (33)	30 (26)

Key:
Summary statistics: mean (standard deviation)
Data are presented as absolute values (%)

AMT: Abbreviated mental test score
CRF: Chronic renal failure
EQ-5D EuroQoL 5 Dimensions Index
NSAID: Non-steroidal anti-inflammatory drug
n/a: not applicable
n/r: not recorded

Table 2: Revision at 12 months post index operation				
Group	Unrevised	Revised	Total	Risk (%)
Control	47	31	78	39.74
Test	54	28	82	34.15
Total	101	59	160	36.88

Table 3: Between group differences in secondary outcome measures				
Outcome	Treatment group Control (n=78)	Test (n=82)	Test	Significance
Radiographic non-union at one year (%)	1	2	Fisher Exact	1.00
Radiographic avascular necrosis at one year (%)	1	2	Fisher Exact	1.00
Length of index hospital stay (days)	23 (10-41)	15 (7-27)	Mann Whitney	0.03
Mortality (%)	23	20	Fisher Exact	0.61

Key:
Proportions are expressed as percentages; summary statistics as median and IQR

Table 4: Between group differences in complications		
Complication	Absolute number of events	
	Control group (n=99)	Test group (n=101)
Wound infection	3	1
Pulmonary embolus	2	0
Pneumonia	12	9
Urinary tract infection	6	5
Blood transfusion	2	0
Cerebrovascular accident	1	0
Myocardial infarction	1	0
Deep vein thrombosis	2	2
Death	23	20

Key:
Events are not mutually exclusive

Table 5: Estimates of hazard ratios for competing risks model				
Covariate		Hazard Ratio	95% CI	p-value
Displacement	*Minimally displaced*	0.303	0.126 to 0.730	0.008
	Displaced	1	-	-
Steroids	*Yes*	0.165	0.022 to 1.217	0.077
	No	1	-	-
Previously diagnosed osteoporosis	*Yes*	2.207	1.153 to 4.223	0.017
	No	1	-	-
Demented	*Yes*	0.496	0.263 to 0.937	0.031
	No	1	-	-
Treatment	*Test*	0.895	0.533 to 1.504	0.680
	Control	1	-	-

Figure 1: CONSORT flow diagram

Notes:

a 2 participants underwent revision prior to death

b 1 participant underwent revision prior to death

c 31 unavailable at baseline

d 35 unavailable at baseline

Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group

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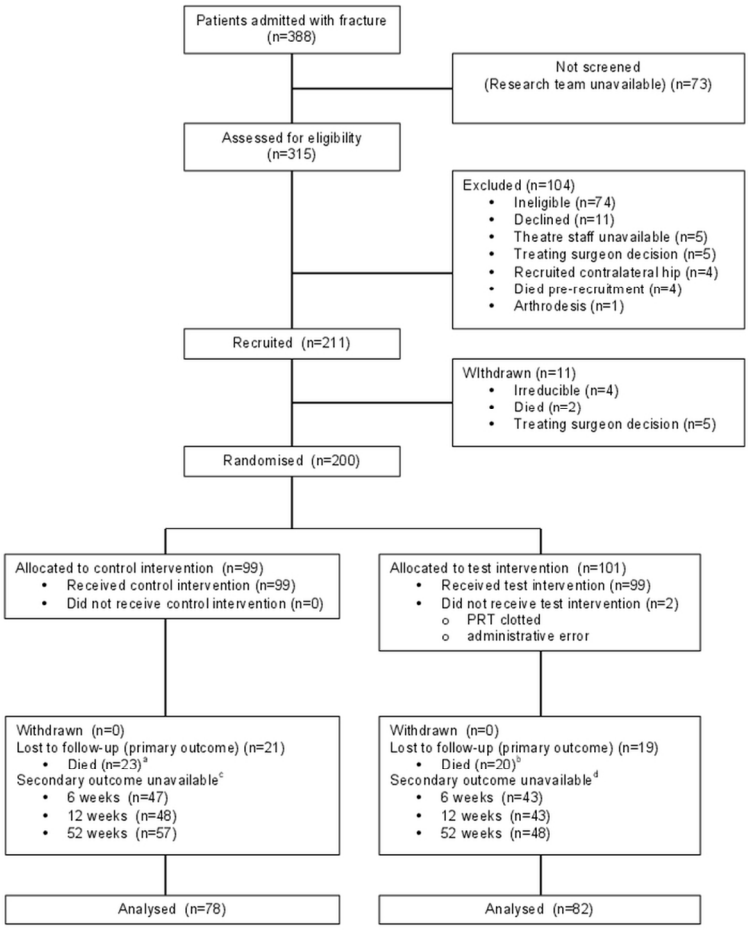

Figure 1
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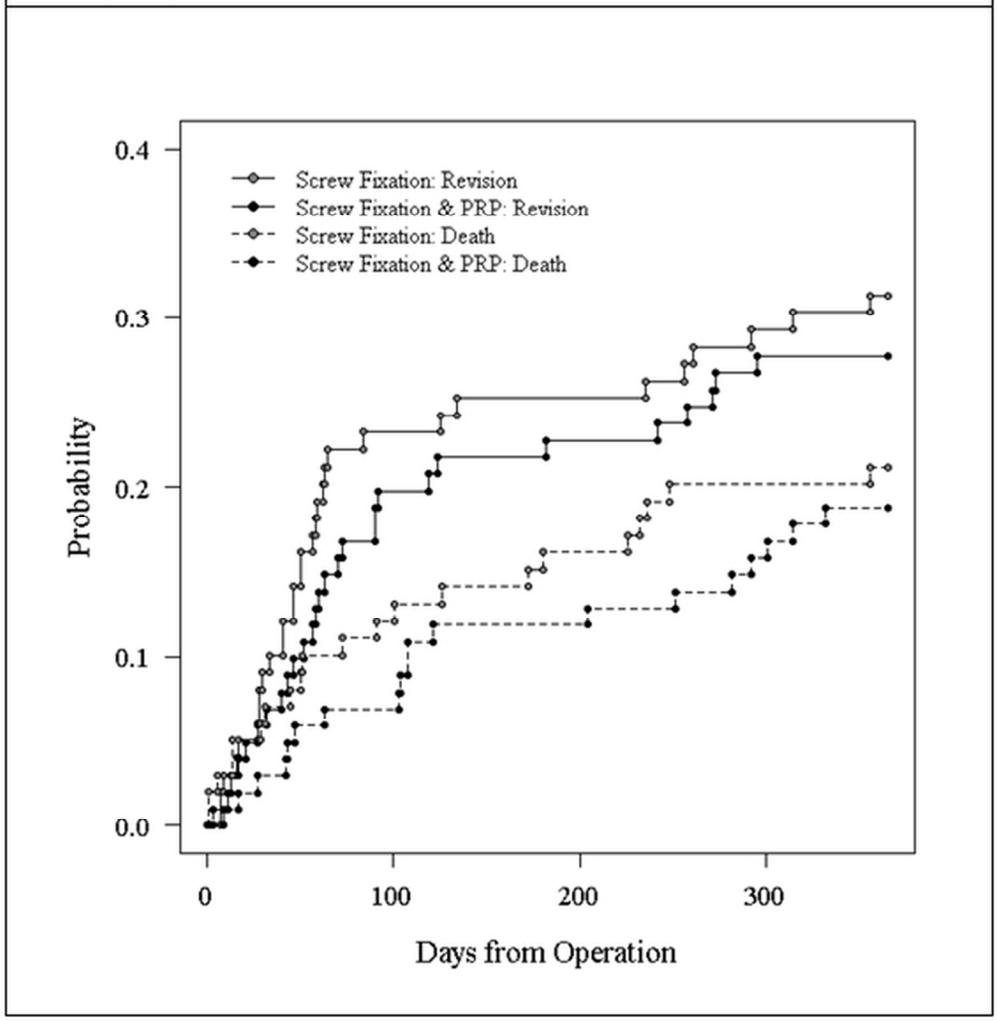
Figure 2: Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group



Estimated cumulative incidence function (CIF) curves death and revision as competing events for each treatment group
90x99mm (300 x 300 DPI)

CONSORT 2010 checklist - WHiT Study

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5 & 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4 & 5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6 & 7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6 & 7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	80
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8 & 9 Table 2-5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10 & 11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.