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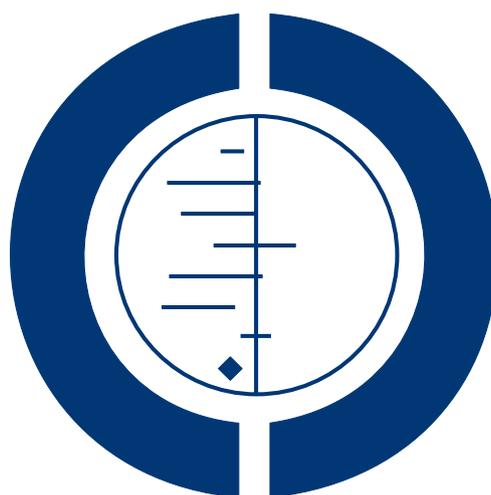
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Anabolic steroids for rehabilitation after hip fracture in older people (Protocol)

Farooqi V, Cameron ID, Chapman I, Couzner L, Crotty M



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[Intervention Protocol]

Anabolic steroids for rehabilitation after hip fracture in older people

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To examine the effects of anabolic steroids on functional outcome (independence, mobility and activities of daily living) after surgical treatment of hip fracture in older people.

The following main comparisons are intended, set in the context of usual or conventional care:

- Anabolic steroids versus no or placebo intervention
- Anabolic steroids with other intervention (either nutrition or exercises or both) versus no or placebo intervention

BACKGROUND

Description of the condition

Fracture of the proximal femur (known widely as hip fracture) is a common cause of morbidity and mortality in the elderly population. Age specific incidence curves for women and for men showed similar patterns of increase in risk with age, with risks approximately doubling every five years after the age of 50 (Farmer 1984). By the age of 90, one third of women and one sixth of men will have sustained a hip fracture (Riggs 1986). Surgical management is the mainstay of the treatment for hip fracture. This is generally

followed by inpatient rehabilitation, with or without extension to an outpatient rehabilitation program. Despite treatment, functional recovery after hip fracture is often incomplete, with many patients who were walking independently before their hip fracture losing their independence (Koval 1996; Lyons 1997). This negatively impacts on their health-related quality of life (Adachi 2001). By six to 12 months after a hip fracture, between 22% and 75% of people have not recovered their pre-fracture ambulatory or functional status (Cummings 1988; Koval 1995). Patients sustaining hip fracture require extensive health system resources (Ray 1997), and many patients require continued supportive services. After their initial treatment, people who have had a hip fracture

are at high risk for re-hospitalisation (Wolinsky 1997), refracture (Johnell 1985) and institutionalisation (Bonar 1990; Rosell 2003). With the rise in life expectancy, the prevalence of hip fracture is expected to rise (Gullberg 1997).

Description of the intervention

Following surgical treatment of hip fracture, a wide range of therapies are used to assist functional recovery (SIGN 2009). Some of these have specific goals such as restoration of mobility, and independence in basic activities of daily living. This review focusses on the use of anabolic steroids for restoring function after hip fracture surgery.

Anabolic steroids are a group of synthetic hormones, related to the male hormone testosterone, that promote the storage of protein and the growth of tissue (anabolism) (Dorland 2007). Their use has been demonstrated to have a positive effect in the treatment of diverse clinical conditions, including the treatment of anaemia in renal disease patients (Navarro 2002; Teruel 1996), osteoporosis (specifically bone density), cachexia in people with chronic illness (Johns 2009), and improving muscle mass and strength in older people (Snyder 1999). Women show an age-related decline in endogenous androgen levels which might influence the development of osteoporosis (Zofkova 2000). A double-blind study showed better mobility and less pain in people with vertebral fractures after treatment with anabolic steroids compared with alfacalcidol (Lyritis 1994).

Anabolic steroids come in different preparations, which can be given various ways (e.g. orally, skin patches, intramuscular injections), start at different times (prior to surgery, or at any stage of recovery after hip fracture surgery) and can be administered for different lengths of time.

How the intervention might work

Patients with hip fractures are often elderly, frail and undernourished (Bachrach-Lindström 2000; Lumbers 2001). They may undergo a catabolic state (Patterson 1992), which leads to chronic muscle wasting and reduced muscle strength. This can affect mobility and result in falls. Loss of muscle mass and lean body weight contribute to generalised weakness, an impaired immune response and slower wound healing. Anabolic steroids have shown some benefit in conditions with increased catabolic rates such as burns, chronic obstructive airway disease and acquired immune deficiency syndrome (AIDS) (Berger 1996).

There is also good reason to combine the use of anabolic steroids with nutritional supplementation. Protein energy malnutrition occurs in 30% to 50% of people who sustain a hip fracture (Lumbers 1996; Ponzer 1999). Postoperative hip fracture rehabilitation is facilitated by improving the nutritional intake of the patient (Delmi 1990). A Cochrane review concluded that some evidence exists

for the beneficial effects of nutritional supplementation after hip fracture, although adherence can be a problem (Avenell 2006). Chapman 2009 provides some evidence that combining testosterone and nutritional supplementation for undernourished older people reduces both the number of people hospitalised and the duration of hospital admissions.

Adverse effects, often dose related, from anabolic steroids include growth of facial hair in women, hair loss, acne, oedema and liver damage.

Why it is important to do this review

Hip fractures are a major cause of hospital admission. Despite advances in surgical treatment these fractures continue to have a large impact on older people and society because they result in high rates of disability and institutionalisation. Anabolic steroids may have a role in improving outcomes and restoring a greater degree of independence in these patients. It is important to assess the evidence for the use of these drugs in this predominantly elderly and frail population.

OBJECTIVES

To examine the effects of anabolic steroids on functional outcome (independence, mobility and activities of daily living) after surgical treatment of hip fracture in older people.

The following main comparisons are intended, set in the context of usual or conventional care:

- Anabolic steroids versus no or placebo intervention
- Anabolic steroids with other intervention (either nutrition or exercises or both) versus no or placebo intervention

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of anabolic steroids treatment following surgical treatment of hip fracture. Trials that used a quasi-randomisation (e.g. allocation by date of birth or hospital record number) or cluster (e.g. by hospital ward) randomisation will be included as will trials that were not analysed on an intention-to-treat basis.

Types of participants

The main study population will be older people with any type of hip fracture that has been surgically treated. It is anticipated that a large proportion of these patients will be older than 65 years of age. Trials that include younger participants will be included if the mean age, minus one standard deviation, is greater than 65 years. Participants younger than 65 years, or with multitrauma or pathological fractures, will be included as long as they make up less than 25% of the total sample size and there was adequate randomisation of these participants to intervention and control groups.

Types of interventions

The intervention assessed will be anabolic steroids, which come in different preparations and can be given enterally (orally, nasogastric or via percutaneous gastrostomy tubes) or parenterally (via transdermal, intramuscular routes, etc). The intervention can start prior to surgery, or at any stage of recovery after hip fracture surgery, but interventions that are pre-surgical only will be excluded. The duration of administration may vary and can last until the end of the rehabilitation phase. The administration of anabolic steroids will be compared with the provision of no intervention or a placebo intervention. It is envisaged that usual or conventional care will be provided to all trial participants. Studies that compare the effects of anabolic steroids, alone or in conjunction with other interventions, namely nutrition or exercise or both, versus no intervention or the administration of a placebo will be included.

The following comparisons are intended, set in the context of usual or conventional care:

1. Anabolic steroids versus no or placebo intervention
 2. Anabolic steroids with other intervention, where this is either nutrition or exercises or both, versus no or placebo intervention
- The second comparison will be analysed and presented separately from the first, and main, comparison.

Types of outcome measures

Primary outcomes

The primary outcome will be function: for example, independence in mobility and activities of daily living. Preference will be given to validated, patient-reported outcome measures. Data on adverse events including mortality, hospital readmission and complications from the use of anabolic steroids will also be sought.

Secondary outcomes

Secondary outcomes will be patients' perceived quality of life, adherence and acceptability of the intervention, objective assessments of body composition, nutritional indices, muscle strength and use of resources such as length of hospital stay.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials (*The Cochrane Library* current issue), MEDLINE (1950 onwards), and EMBASE (1980 onwards). We will also search [Current Controlled Trials](#) and the [WHO international Clinical Trials Registry Platform](#) for ongoing and recently completed trials. We will apply no restrictions based on language or publication status.

In MEDLINE (OvidSP), the subject specific search will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (Lefebvre 2009) (Appendix 1), and will be modified for use in other databases.

Searching other resources

The proceedings of the American Orthopaedic Trauma Association's annual meetings will be searched. This will be performed by handsearching the table of contents of the meeting proceedings (1996-2009). We will also search reference lists of relevant articles.

Data collection and analysis

Selection of studies

Two review authors (MC and VF) will independently screen records identified from database searches for possible inclusion. From the full text, trials which appear meet the selection criteria will be selected for inclusion. Further information will be sought from the trial authors if necessary. A third author (IDC) will moderate any disagreement. Reasons for exclusion will be documented.

Data extraction and management

Data extraction of the included studies will be completed, using a piloted form, by combinations of two authors acting independently. The data collected will include study design characteristics, the study population, interventions, outcome measures, and length of follow-up. Trial authors will be contacted for clarification when necessary. Disagreements will be resolved by the other review authors.

Assessment of risk of bias in included studies

Combinations of two authors will independently assess risk of bias using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2008a) (see Appendix 2). We will assess generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance, early stopping, and other sources of bias. The risk of bias will be rated for each domain and will be expressed as "Yes", implying a low risk of bias, "Unclear", implying the risk of bias is unclear, or "No", implying a high risk of bias.

After piloting the 'Risk of bias' tool for two trials, the review authors responsible for data extraction will discuss any modifications that may be required to enhance the assessment of risk of bias.

Measures of treatment effect

Results will be analysed at both short term (six months or less) and longer term intervals. Risk ratios with 95% confidence intervals will be calculated for dichotomous outcomes. Mean differences with 95% confidence intervals will be calculated for continuous outcomes.

Unit of analysis issues

The unit of randomisation in these trials is usually the individual patient. However, we will also consider randomised trials where the unit of randomisation is another entity such as a hospital ward. If possible, appropriate adjustments will be made before presenting data from such trials if the trialists have not adjusted for clustering. We will seek advice on the interpretation and presentation of the results from such trials from the statistical editors of the Cochrane Bone, Joint and Muscle Trauma Review Group.

Dealing with missing data

Where appropriate, we will perform intention-to-treat analysis to include all people randomised. However where drop-outs have been identified, the actual denominator of participants contributing data at the relevant outcome assessment will be used. We will investigate the effect of drop-outs and exclusions by conducting worst- and best-case scenario sensitivity analyses. The 'best-case' scenario is when all participants with missing outcomes in the experimental intervention group are assigned a good outcome, and all those with missing outcomes in the control intervention group a bad outcome; the 'worst-case' scenario is the converse. We will be alert to potential mislabelling or non identification of standard errors and standard deviations. Unless missing standard deviations can be derived from confidence intervals, P values or standard errors, we will not assume values in order to present these in the analyses.

Assessment of heterogeneity

Heterogeneity will be assessed by visual inspection of the forest plot (analysis) along with consideration of the χ^2 test for heterogeneity and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

If sufficient data are available, we will attempt to assess publication bias by preparing a funnel plot. We will also investigate selective outcome reporting by comparing the study outcomes with those routinely presented for similar studies and also by comparing the methods section of trial reports with the results reported.

Data synthesis

If considered appropriate, results of comparable groups of trials will be pooled. Initially we will use the fixed-effect model and 95% confidence intervals. We will also consider using the random-effects model, especially where there is unexplained heterogeneity. It is anticipated that we will pool data even if heterogeneity remains high. For continuous outcomes, if outcomes are reported from different scales or instruments assessing the same dimension, the results will be pooled using standardised mean difference. Mindful of unit of analysis issues, we will pool the data from cluster randomised trials using the generic inverse variance. Studies that are using anabolic steroids in conjunction with another intervention such as nutritional supplementation will be analysed separately.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, subgroup analysis will be performed to determine whether primary outcomes vary according to gender and route of administration.

Sensitivity analysis

Where possible, the review authors will perform sensitivity analyses to examine the effects of important sources of bias, such as whether allocation was concealed, in the included studies.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

APPENDICES

Appendix 1. Search strategies

MEDLINE (OvidSP interface)

1 exp Femoral Fractures/
 2 ((hip* or pertrochant* or intertrochant* or trochanteric or subtrochanteric or extracapsular* or ((femur* or femoral*) adj3 (neck or proximal or head))) adj4 fracture*).mp.
 3 1 or 2
 4 exp Steroids/
 5 exp Androgens/
 6 exp Anabolic Agents/
 7 (anabolic adj1 steroid*).mp.
 8 (androgen* adj1 anabolic).mp.
 9 (etiocholanolone or androst* or prasterone or stanolone or testosterone or methyltestosterone or metribolone or ethylestrenol or fluoxymesterone or mesterolone or methandriol or methandrostenolone or methenolone or nandrolone or norethandrolone or oxandrolone or oxymetholone or stanozolol or trenbolone or amafolone or atomid or benorterone or boldenone or calusterone or danazol or drostanolone or etiocholanone or mestanolone or mibolerone or testololactone or hydroxyandrost* or epiandrosterone or oxotestosterone or oxoandrostenedione).mp.
 10 or/4-9
 11 3 and 10
 12 Randomized Controlled Trial.pt.
 13 Controlled Clinical Trial.pt.
 14 randomized.ab.
 15 placebo.ab.
 16 Drug Therapy.fs.
 17 randomly.ab.
 18 trial.ab.
 19 groups.ab.
 20 or/12-19
 21 exp Animals/ not Humans/
 22 20 not 21
 23 11 and 22

Appendix 2. Risk of bias assessment tool

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated? The judgement for Yes , Unclear or No will be based on criteria listed in Table 8.5.c in the Handbook (Higgins 2008b)

(Continued)

<p>Allocation concealment</p>	<p>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment</p>	<p>Was allocation adequately concealed? The judgement for Yes, Unclear or No will be based on criteria listed in Table 8.5.c in the Handbook (Higgins 2008b)</p>
<p>Blinding of participants, personnel and outcome assessors <i>Assessments should be made for each main outcome (or class of outcomes).</i></p>	<p>Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective</p>	<p>Was knowledge of the allocated intervention adequately prevented during the study? The judgement for Yes, Unclear or No will be based on criteria listed in Table 8.5.c in the Handbook (Higgins 2008b)</p>
<p>Incomplete outcome data <i>Assessments should be made for each main outcome (or class of outcomes).</i></p>	<p>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors</p>	<p>Were incomplete outcome data adequately addressed? The judgement for Yes, Unclear or No will be based on criteria listed in Table 8.5.c in the Handbook (Higgins 2008b)</p>
<p>Selective outcome reporting</p>	<p>State how the possibility of selective outcome reporting was examined by the review authors, and what was found</p>	<p>Are reports of the study free of suggestion of selective outcome reporting? The judgement for Yes, Unclear or No will be based on criteria listed in Table 8.5.c in the Handbook (Higgins 2008b)</p>
<p>Other sources of bias: Baseline imbalance</p>	<p>State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry Prespecified source of bias</p>	<p>Was the study apparently free of problems relating to imbalances in baseline characteristics that could put it at a high risk of bias? Yes: There was no major imbalance in important baseline characteristics. Unclear: The baseline characteristics were not reported. No: There was a major baseline imbalance in at least one important baseline characteristics</p>
<p>Other sources of bias: Early stopping</p>	<p>State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry Prespecified source of bias</p>	<p>Was the study apparently free of problems relating to early stopping that could put it at a high risk of bias? Yes: Sample size calculation was reported and the trial was not stopped or the trial was stopped early by formal stopping rules at a point where the likeli-</p>

(Continued)

		hood of observing an extreme intervention effect due to chance was low. Unclear: Sample size calculation was not reported. It is unclear whether the trial was stopped early or not. No: The trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool	Was the study apparently free of other problems that could put it at a high risk of bias? Yes, Unclear or No.

HISTORY

Protocol first published: Issue 12, 2010

CONTRIBUTIONS OF AUTHORS

Dr Vaqas Farooqi conceived and wrote the protocol. All authors reviewed and approved the text.

Professor Maria Crotty is the guarantor of this review.

DECLARATIONS OF INTEREST

It is possible that some or all authors may be involved in a study potentially eligible for this review. In this case, the trial will be appraised independently by other review authors.

SOURCES OF SUPPORT

Internal sources

- Repatriation General Hospital, Australia.
Infrastructure to support the review authors affiliated with this institution.
- Rehabilitation Studies Unit, Sydney Medical School, The University of Sydney, Australia, Australia.
Infrastructure to support the review author affiliated with this institution.
- The University of Adelaide, Australia.
Infrastructure to support the review author affiliated with this institution.

External sources

- No sources of support supplied