ISRCTN12961998 https://doi.org/10.1186/ISRCTN12961998

A Dehydroepiandrosterone and Pharmacokinetics in Trauma study (ADaPT)

Submission date
30/05/2018

Recruitment status
No longer recruiting

Registration date
04/06/2018

Overall study status
Completed

Last Edited
12/07/2022

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Hormones, such as dehydroepiandrosterone (DHEA), play an important role in the body helping to maintain muscle mass and the immune system. The immune system helps the body recover from injury and fight off infection. Immediately after an injury DHEA levels have been shown to drop quickly and if DHEA levels are already low, as seen in older people, this puts them at increased risk of infection and reduces their chance of a full recovery. Research has shown in both young and old men and women that DHEA levels are below normal levels for as long as 3 months after injury. As a result, giving trauma patients DHEA to boost DHEA levels in the blood could improve the immune response and speed up recovery. The aim of this study is to work out what dose of DHEA (50, 100 or 200mg per day) will increase patient's DHEA levels to those seen in a healthy young adult male. The study will also work out what is the best method of delivering the DHEA into the body, either by an oral tablet that is swallowed or a tablet that is placed under the tongue and dissolves.

Who can participate?
Male and female trauma patients aged 16 – 50, and female hip fracture patients aged 50 or older admitted to University Hospital Birmingham.

What does the study involve?
A blood sample is taken within 24 hours of the injury if the patients are admitted within this time frame. This sample is used to assess the acute response of DHEA and immune markers to injury. Participants are randomly allocated to receive doses of DHEA via either oral tablets or sublingual tablets for the 3-day treatment period. The dose is increased if the treatment is seen to be ineffective, i.e. it does not restore serum DHEA to at least 15 nmol/L. Once a sufficient dose to restore DHEA levels has been established the dose is still increased to investigate if higher doses are optimal for enhancing the immune response. Research has demonstrated that complications such as infection commonly occur 1-2 weeks post trauma. Due to these findings, supplementation for the male trauma and female trauma cohorts begins on day 8; DHEA is administered once daily for three days at 08:00. On day 7 after injury ten blood samples are taken at regular intervals across the day. On day 8 these samples are repeated after the first dose of DHEA has been administered. On day 9, 10 and 11 blood samples are taken once daily to assess DHEA levels, immune function and systemic inflammation. Urine samples are collected 24

hours a day from day 7 to day 11 to assess DHEA and other hormones in urine. Follow up is completed on day 12 as this covers a period of 48 hours after the last dose.
For the hip-fracture cohort, supplementation is flexible and depends on the patients' hospital stay. DHEA is administered once daily for three days at 08:00. The day before DHEA is administered (Pre-dosing day), ten blood samples are taken at regular intervals across the day. On the first dosing day, these samples are repeated after the first dose of DHEA has been administered. On dosing days 2 and 3, and 1 day after the last dose (post-dosing day 1), blood samples are taken once daily to assess DHEA levels, immune function and systemic inflammation. Urine samples are collected 24 hours a day from pre-dosing day to post-dosing day 1 to assess DHEA and other hormones in urine. Follow up is completed on 2 days after the last dose (post-dosing day 2) as this covers a period of 48 hours after the last dose.

What are the possible benefits and risks of participating?
The benefits for participants are small, there will be increased monitoring of their progress throughout the study period. It is unknown how beneficial DHEA supplementation is in trauma patients, but it is unlikely that three doses of DHEA will have any enhanced effect on rate and/or degree of recovery. The main benefit of participating in this study is that this work will help to develop future studies exploring the effects of DHEA supplementation on healing, recovery and rehabilitation in severely injured patients. There is a minimal risk of side effects associated with the doses of DHEA and length of treatment in this study. A few studies have reported rare side effects associated with DHEA including: acne, mood swings, altered liver function, and in extremely rare occasions increased facial hair growth in women. However, these side effects are all related to long-term use of DHEA and it is extremely unlikely the participants will experience any of these side effects after 3 days of treatment. The risks associated with participation in the study are minimal. Blood samples and urine collection are a routine part of hospital medical care. The drawing of a blood sample, where possible, will be taken as an additional sample in routine blood sampling for clinical necessity. It is likely that some study sampling will be performed when there is no clinical need. A mid-line or cannulation will be used in all patients who do not have an A-line in situ to reduce the discomfort of multiple samples on day 7 and 8 for the trauma cohorts and on pre-dosing day 1 and dosing day 1 for the hip fracture cohort. Nevertheless, the sample will be drawn by medical personnel well trained in this procedure and care will be taken to ensure that any discomfort is kept to a minimum.

Where is the study run from?
Queen Elizabeth Hospital Birmingham (UK)

When is the study starting and how long is it expected to run for?
March 2017 to April 2022

Who is funding the study?
1. AO Foundation (Switzerland)
2. NIHR Surgical Reconstruction and Microbiology Research Centre (SRMRC) (UK)
3. University Hospitals Birmingham Charity (UK)

Who is the main contact?
1. Gurneet Sur
g.sur@bham.ac.uk
2. Lt Col Mark Foster
m.foster@bham.ac.uk

Contact information

Type(s)
Public

Contact name
Ms Gurneet Sur

Contact details
D3B Team (Drugs, Devices, Diagnostics and Biomarkers)
5th Floor, Open Plan EAST, ITM
Heritage Building
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TH
+44 (0)121 371 8492
G.Sur@bham.ac.uk

Type(s)
Scientific

Contact name
Mr Mark Foster

Contact details
NIHR SRMRC
Institute for Translational Medicine Research & Development
University Hospitals Birmingham NHS Foundation Trust
Heritage Building (Queen Elizabeth Hospital)
Birmingham
United Kingdom
B15 2TH
+44 (0)121 371 4926
m.foster@bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2016-004250-15

Protocol serial number
38158

Study information

Scientific Title
A prospective, phase II, single centre, cross-sectional, randomised trial investigating dehydroepiandrosterone and its pharmacokinetics in trauma

Acronym

ADaPT

Study objectives
Hormones, such as Dehydroepiandrosterone (DHEA), play an important role in the body helping to maintain muscle mass and the immune system. The immune system helps the body recover from injury and fight off infection. Immediately after an injury DHEA levels have been shown to drop quickly and if DHEA levels are already low, as seen in older people, this puts them at increased risk of infection and reduces their chance of a full recovery. Previous research has shown in both young and old men and women that DHEA levels are below normal levels for as long as 3 months after injury. As a result, the trialists believe giving trauma patients DHEA to boost DHEA levels in the blood could improve the immune response and speed up recovery. The aim of this trial is to work out what dose of DHEA (50, 100 or 200mg per day) will increase patient's DHEA levels to those seen in a healthy young adult male. It will also work out what is the best method of delivering the DHEA into the body either by an oral tablet that is swallowed or a tablet that is placed under the tongue and dissolves.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/06/2018, West Midlands – Coventry and Warwickshire Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; Tel: +44 (0)207 104 8101; Email: NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net), ref: 18/WM/0102

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe trauma injury

Interventions
Current interventions as of 12/10/2021:

This is an efficacy dose-finding trial with two objectives. Firstly, to establish a dose sufficient to raise DHEA levels to those seen in healthy young adult males. Secondly, to establish an optimal dose for enhancing the immune response post trauma. This trial is investigating 3 doses of DHEA: 50, 100 and 200 mg and 2 methods of delivery (oral and sublingual tablets). The patient population will be generated from male and female patients attending the Major Trauma Centre (MTC) and Critical Care Unit (ITU) at University Hospital Birmingham Foundation Trust (UHBFT) with a traumatic injury and an additional patient group of older (>50 years old) female patients with a hip fracture. Patients will be randomised to receive the doses of DHEA via either oral tablets or sublingual tablets for the 3 day treatment period. This creates six cohorts: oral–male trauma, sublingual-male trauma, oral–female trauma, sublingual–female trauma, oral–hip fracture, sublingual-hip fracture. Up to 15 patients in each cohort will be treated and assessed. Thus, a maximum of 270 patients will receive DHEA supplementation. However, an adaptive

design will be used with regular analyses to stop early in any particular cohort of 15 and dose escalate if the treatment is seen to be inactive, i.e. it does not restore serum DHEA to at least 15 nmol/L. Once a sufficient dose to restore DHEA levels has been established the dose will still be escalated to investigate if higher doses are optimal for enhancing the immune response. Due to the nature of the injuries, informed consent is likely to be obtained from professional legal representatives or personal legal representatives in the first instance, consent from the patient will be obtained as soon as they have capacity.

A blood sample will be taken within 24 hours of the injury if the patients are admitted within this time frame. This sample will be used to assess the acute response of DHEA and immune markers to injury. Patients will be randomised before day 7 for the trauma cohorts and before pre-dosing day for the hip-fracture cohorts to receive the dose of DHEA via either oral tablets or sublingual (under the tongue) tablets. Randomisation will occur on the electronic Clinical Research Tool (CREST) system. A 1:1 allocation ratio will be used. Research has demonstrated that post injury complications such as infection commonly occur 1-2 weeks post trauma. Due to these findings, supplementation for the male trauma and female trauma cohorts begins on day 8; DHEA is administered once daily for three days at 08:00. On day 7 after injury ten blood samples are taken at regular intervals across the day. On day 8 these samples are repeated after the first dose of DHEA has been administered. On day 9, 10 and 11 blood samples are taken once daily to assess DHEA levels, immune function and systemic inflammation. Urine samples are collected 24 hours a day from day 7 to day 11 to assess DHEA and other hormones in urine. Follow up is completed on day 12 as this covers a period of 48 hours after the last dose.
For the hip-fracture cohort, supplementation is flexible and depends on the patients' hospital stay. DHEA is administered once daily for three days at 08:00. The day before DHEA is administered (Pre-dosing day), ten blood samples are taken at regular intervals across the day. On the first dosing day, these samples are repeated after the first dose of DHEA has been administered. On dosing days 2 and 3, and 1 day after the last dose (post-dosing day 1), blood samples are taken once daily to assess DHEA levels, immune function and systemic inflammation. Urine samples are collected 24 hours a day from pre-dosing day to post-dosing day 1 to assess DHEA and other hormones in urine. Follow up is completed on 2 days after the last dose (post-dosing day 2) as this covers a period of 48 hours after the last dose.

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Previous interventions:

This is an efficacy dose-finding trial with two objectives. Firstly, to establish a dose sufficient to raise DHEA levels to those seen in healthy young adult males. Secondly, to establish an optimal dose for enhancing the immune response post trauma. This trial is investigating 3 doses of DHEA: 50, 100 and 200 mg and 2 methods of delivery (oral and sublingual tablets). The patient population will be generated from male and female patients attending the Major Trauma Centre (MTC) and Critical Care Unit (ITU) at University Hospital Birmingham Foundation Trust (UHBFT) with a traumatic injury and an additional patient group of older (>50 years old) female patients with a hip fracture. Patients will be randomised to receive the doses of DHEA via either oral tablets or sublingual tablets for the 3 day treatment period. This creates six cohorts: oral–male trauma, sublingual-male trauma, oral–female trauma, sublingual–female trauma, oral–hip fracture, sublingual-hip fracture. Up to 15 patients in each cohort will be treated and assessed. Thus, a maximum of 270 patients will receive DHEA supplementation. However, an adaptive design will be used with regular analyses to stop early in any particular cohort of 15 and dose escalate if the treatment is seen to be inactive, i.e. it does not restore serum DHEA to at least 15 nmol/L. Once a sufficient dose to restore DHEA levels has been established the dose will still be escalated to investigate if higher doses are optimal for enhancing the immune response. Due to

the nature of the injuries, informed consent is likely to be obtained from professional legal representatives or personal legal representatives in the first instance, consent from the patient will be obtained as soon as they have capacity.

A blood sample will be taken within 24 hours of the injury if the patients are admitted within this time frame. This sample will be used to assess the acute response of DHEA and immune markers to injury. Patients will be randomised before day 7 to receive the dose of DHEA via either oral tablets or sublingual (under the tongue) tablets. Randomisation will occur on the electronic Clinical Research Tool (CREST) system. A 1:1 allocation ratio will be used. Research has demonstrated that post injury complications such as infection commonly occur 1-2 weeks post trauma. Due to these findings, supplementation will begin on day 8; DHEA will be administered once daily for three days at 08:00. On day 7 post injury ten blood samples will be taken at regular intervals across the day to observe the time course of serum DHEA, the sulphated form DHEAS will also be measured. On day 8 these bloods will be repeated after the first dose of DHEA has been administered. On day 9, 10 and 11 blood samples will be taken once daily to assess DHEA levels, immune function and systemic inflammation. Urine samples will be collected 24 hours a day from day 7 to day 11 to assess DHEA and other hormones within urine. Follow up will be completed on day 12 as this will cover a period of 48 hours post the last IMP dose.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Dehydroepiandrosterone

Primary outcome(s)
Current primary outcome measure as of 12/10/2021:

Serum DHEA after DHEA supplementation; assessed by mass spectrometry of blood samples collected at:
- 2-4 hours post dose, 4-8 hours post dose and 10 hours post dose on day 8 for trauma cohorts and dosing day 1 for hip-fracture cohort
- 2-4 hours post dose on day 9 for trauma cohorts and dosing day 2 for hip-fracture cohort
- 2-4 hours post dose on day 10 for trauma cohorts and dosing day 3 for hip-fracture cohort
- 24 hours post last dose on day 11 for trauma cohorts and post-dosing day 1 for hip-fracture cohort
- 48 hours post last dose on day 12 for trauma cohorts and post-dosing day 2 for hip-fracture cohort

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Previous primary outcome measure:

Serum DHEA after DHEA supplementation; assessed by mass spectrometry of blood samples collected at:
- 2-4 hours post dose, 4-8 hours post dose and 10 hours post dose on day 8
- 2-4 hours post dose on day 9
- 2-4 hours post dose on day 10

- 24 hours post last dose on day 11
- 48 hours post last dose on day 12

Key secondary outcome(s)
Current secondary outcome measures as of 12/10/2021:

1. Neutrophil function such as superoxide production and phagocytosis measured using blood samples collected at the following timepoints:
- Within 24 hours of trauma (Day 0, if possible)
- 08:00 on days 7-12 for trauma cohorts and pre-dosing day – post-dosing day 2 for hip-fracture cohort
2. Pro and anti-inflammatory cytokines measured using blood samples collected at the following timepoints:
- Within 24 hours of trauma (Day 0, if possible)
- 08:00 on days 7-12 or trauma cohorts and pre-dosing day – post-dosing day 2 for hip-fracture cohort
3. Tolerance, measured by gastric residual volumes (GRV) collected at 08:00 on the days where a nasogastric or nasojejunal tube is in situ

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Previous secondary outcome measures:

1. Neutrophil function such as superoxide production and phagocytosis measured using blood samples collected at the following timepoints:
- Within 24 hours of trauma (Day 0, if possible)
- 08:00 on days 7-12
2. Pro and anti-inflammatory cytokines measured using blood samples collected at the following timepoints:
- Within 24 hours of trauma (Day 0, if possible)
- 08:00 on days 7-12
3. Tolerance, measured by gastric residual volumes (GRV) collected at 08:00 on the days where a nasogastric or nasojejunal tube is in situ

Completion date
30/04/2022

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/01/2021:

Trauma patients:
1. 16 - 50 years of age
2. Severe trauma injury (Injury severity score (ISS) ≥16 and ≤50)
3. Admitted to University Hospital Birmingham within 6 days of trauma
4. Anticipated to be an inpatient for the 12 day trial period

Hip fracture patients:
1. 50 years or age and older
2. Female

3. Neck of Femur fracture
4. Admitted to University Hospital Birmingham within 6 days of fracture
5. Anticipated to be an inpatient for the 12 day trial period

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Previous inclusion criteria:

Trauma patients:
1. 16 - 50 years of age
2. Severe trauma injury (Injury severity score (ISS) ≥16 and ≤50)
3. Admitted to University Hospital Birmingham within 6 days of trauma
4. Anticipated to be an inpatient for the 11 day trial period

Hip fracture patients:
1. 50 years or age and older
2. Female
3. Neck of Femur fracture
4. Admitted to University Hospital Birmingham within 6 days of fracture
5. Anticipated to be an inpatient for the 11 day trial period

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
68

Key exclusion criteria
Current exclusion criteria as of 12/10/2021:

Trauma patients:
1. Ages 51 years of age
2. ISS 50
3. Isolated brain injury
4. Unlikely to survive the trial period
5. Previous or known hormone-sensitive malignancy
6. Known Prostatic hypertrophy (M)
7. Female patients taking Hormonal Replacement Therapy medication or Oral Contraceptives
8. Intake of any drug that has a major or moderate effect on the steroid synthesis or metabolism (see list in appendix 1) in the last 3 months
9. Pre-existing liver impairment or chronic liver failure
10. Previous or current malignancy or invasive cancer diagnosed within the past 3 years except

for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
11. Pregnant and/or breastfeeding females (Serum pregnancy tests to be carried out on women of childbearing potential)
12. Known hypersensitivity to the active substance or excipient
13. Known thromboembolic events in the last 12 months and any predisposition to thrombosis e. g. factor V Leiden

Hip fracture patients:
1.
2. Unlikely to survive the study period
3. Previous or known hormone-sensitive malignancy
4. Intake of any drug that has a major or moderate effect on the steroid synthesis or metabolism (see list in appendix 1) in the last 3 months
5. Known pre-existing liver impairment or chronic liver failure
6. Previous or current malignancy or invasive cancer diagnosed within the past 3 years except for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
7. Pregnant and/or breastfeeding (Serum pregnancy tests to be carried out on women of childbearing potential)
8. Known hypersensitivity to the active substance or excipient
9. Patients on Hormonal Replacement Therapy medication or Oral Contraceptives
10. Known thromboembolic events in the last 12 months and any predisposition to thrombosis e. g. factor V Leiden

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Previous exclusion criteria as of 12/01/2021:

Trauma patients:
1. Ages 51 years of age
2. ISS 50
3. Isolated brain injury
4. Unlikely to survive the study period
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7. Female patients taking Hormone Replacement Therapy medication
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11. Pregnant and/or breastfeeding females (Serum pregnancy tests to be carried out on women of childbearing potential)
12. Known hypersensitivity to the active substance or excipient
13. Known thromboembolic events in the last 12 months and any predisposition to thrombosis e. g. factor V Leiden

Hip fracture patients:
1. <50 years of age
2. Unlikely to survive the study period

3. Previous or known hormone-sensitive malignancy
4. Intake of any drug that has a major or moderate effect on the steroid synthesis or metabolism (see list in appendix 1) in the last 3 months
5. Known pre-existing liver impairment or chronic liver failure
6. Previous or current malignancy or invasive cancer diagnosed within the past 3 years except for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
7. Pregnant and/or breastfeeding (Serum pregnancy tests to be carried out on women of childbearing potential)
8. Known hypersensitivity to the active substance or excipient
9. Patients on Hormone Replacement Therapy medication
10. Known thromboembolic events in the last 12 months and any predisposition to thrombosis e.g. factor V Leiden

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Previous exclusion criteria:

Trauma patients:
1. Ages <16 or >51 years of age
2. ISS <16 or >50
3. Isolated brain injury
4. Unlikely to survive the study period
5. Previous or known hormone sensitive malignancy
6. Known Prostatic hypertrophy (M)
7. Female patients taking Hormone Replacement Therapy medication
8. Intake of any drugs that is likely to influence the metabolism of steroids, in particular inducers and inhibitors of the drug-metabolising enzyme CYP3A4 in the last 3 months
9. Pre-existing liver impairment or chronic liver failure
10. Previous or current malignancy or invasive cancer diagnosed within the past 3 years except for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
11. Prescribed antipsychotic medication
12. Pregnant and/or breastfeeding females
13. Known hypersensitivity to the active substance or excipient
14. Known thromboembolic events in the last 12 months and any pre-disposition to thrombosis e.g. factor V leiden

Hip fracture patients:
1. <50 years of age
2. Unlikely to survive the study period
3. Previous or known hormone sensitive malignancy
4. Intake of any drugs that is likely to influence the metabolism of steroids, in particular inducers and inhibitors of the drug-metabolising enzyme CYP3A4 in the last 3 months
5. Known pre-existing liver impairment or chronic liver failure
6. Previous or current malignancy or invasive cancer diagnosed within the past 3 years except for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
7. Prescribed antipsychotic medication
8. Pregnant and/or breastfeeding
9. Known hypersensitivity to the active substance or excipient
10. Patients on Hormone Replacement Therapy medication

11. Known thromboembolic events in the last 12 months and any pre-disposition to thrombosis e. g. factor V leiden

Date of first enrolment
01/10/2018

Date of final enrolment
31/07/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2WB

Sponsor information

Organisation
University Hospitals Birmingham NHS Foundation Trust

ROR
https://ror.org/014ja3n03

Funder(s)

Funder type
Charity

Funder Name
AO Foundation

Alternative Name(s)
AO Trauma, AO

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Funder Name
NIHR Surgical Reconstruction and Microbiology Research Centre (SRMRC)

Funder Name
University Hospitals Birmingham Charity

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		26/07/2021	28/07/2021	Yes	No
HRA research summary			28/06/2023	No	No