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Reversal of over-anticoagulation with vitamin K

Submission date
10/11/2011

Recruitment status
No longer recruiting

Registration date
10/11/2011

Overall study status
Completed

Last Edited
25/05/2018

Condition category
Haematological Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background & study aims?
Warfarin is a blood thinning drug. It is very useful for treating and preventing blood clots. The blood thinning property of warfarin is measured by a blood test called INR (International Normalised Ratio); the finger-prick test each time a patient visits the anticoagulant clinic. The INR value needs to be maintained within a narrow target range (2.0-3.0 for most types of clotting disorders) for safe and effective treatment. The INR value can sometimes go above the set target range which can increase the risk of bleeding. As such vitamin K is used as an antidote to reverse INR. Patients with an INR value equal or greater than 6.0 with no signs of bleeding or with symptoms of mild bleeding are normally given a fixed oral dose of vitamin K in order to bring their INR back to the target range. However, this fixed dose regimen is not very accurate in reversing the INR. In nearly half of patients the INR is still outside the target range 24 hours after being given vitamin K, making them likely to either bleed if the INR is still above the target range or to develop clots if the INR is over-corrected (below the target range). In a previous study we have shown that an individualised dose of vitamin K based on the patients INR value was more accurate in bringing the INR down to the target range than the fixed dose regimen. We have now improved the original individualised dose regimen. The new regimen estimates vitamin K dose based on INR value as well as body surface area. We now want to test the new improved individualised dose regimen against the fixed dose regimen in 186 patients in a study called a randomised clinical trial. We will also measure physical features and activities of two genes which control warfarins activity to see if using these could make individualised dosing even more accurate.

Who can participate?
To participate you need to be: Aged 18 years and over (male or female). On warfarin therapy and with an INR of 6.0 or greater on one of your clinic visits.

What does the study involve?
For the purposes of this study you will make a total of 4 visits to the anticoagulant clinic over a 2 week period. Some of the study visits may overlap with your routine anticoagulant clinic visits in the hospital if you are already attending these clinics. At the first visit we will ask you about your age, measure your height and weight, reason you take warfarin, what other medications you take and your medical history. We will take a blood sample (6 ml; about 1 teaspoonful) for INR testing and later genetic analysis for VKORC1 and CYP2C9 genes. You will then be randomly allocated to receive either an individualised dose or a fixed dose of vitamin K (as per routine

local clinic practice). We will compare the two groups in terms of the number of people whose INR returns to their target range at 24 hours. We will ask you to return to the clinic 24 (+/- 3) hours later in order to check your INR. A further blood sample (1ml or less than half a teaspoonful) will be taken. If your INR is below the target range at 24 hours, the need for an injectable blood thinning drug (low molecular weight heparin) will be assessed by the clinic doctor and prescribed if considered necessary, according to routine practice. You will be asked about any problems with your treatment since your were given vitamin K using a standard questionnaire. A member of the research team will fill in the questionnaire in discussion with you. You will be followed-up at two more clinic visits [day 7 (+/-2 days) & day 14 (+/-2 days)] so that the study nurse can check your INR by taking a blood sample (1ml; less than half a teaspoonful) and ask as before if you have had any problems with your treatment since you were given vitamin K using a standard questionnaires.

What are the possible benefits and risks of participating?
A high INR increases the risk of bleeding. That is why vitamin K is given routinely to reverse high INR and to minimise the risk of bleeding. We hope that the individualised dose regimen is more accurate at returning INR to within the target range than the fixed dose regimen. However, the risk of bleeding remains with both treatments (as well as the risk of clotting if INR is over-corrected) if INR reversal is not properly controlled. We hope that giving vitamin K on an individual basis is more accurate in bringing the INR back to the target range than the fixed dose regimen which is the current practice. We anticipate that the information we get from this study will help us to establish this either way. We will also look at the impact of other factors such as age, sex, medication and genetics and how this affects the vitamin K dose needed. These results may lead to further improvement of the existing individualised vitamin K dosing regimen.

Where is the study run from?
The study will take place at the outpatient warfarin clinic, Freeman Hospital and the Haematology Unit, Royal Victoria Infirmary, The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK).

When is study starting and how long is it expected to run for?
The study is to start in January 2012 and is to last for 2 years. The study will recruit suitable patients for the first 20 months.

Who is funding the study?
The study is funded by the National Institute for Health Research (NIHR), UK.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Protocol serial number
10934

Study information

Scientific Title
Reversal of over-anticoagulation using a tailored vitamin K dosing regimen: towards a better management of anticoagulation therapy

Study objectives
Warfarin (a blood-thinning drug) is used to treat blood clotting disorders. The blood-thinning action of warfarin is gauged by a blood test called the INR. The INR value for each patient needs to be maintained within a narrow therapeutic range for safe and effective treatment. Despite improvements in the management of warfarin therapy about 50% of patients fail to stabilise within their target INR range and are thus prone to the drugs adverse effect of bleeding if INR exceeds the therapeutic range. Current guidelines advocate the administration of a fixed-dose of vitamin K, the antidote to warfarin, as a way of reversing high INR values. However patients present with a wide range of high INR values and therefore response to a fixed dose of vitamin K is unsatisfactory. Consequently, on average, about 45% of patients with high INR remain outside their target INR range 24 hours after vitamin K administration and are prone to either bleeding (if INR is still high) or blood clots (if INR reversal is overcorrected). In a recent pilot study we investigated the effectiveness of an individualised vitamin K dosing regimen in reversing excessive INR. The individualised dosing algorithm performed significantly better than the fixed-dose regimen. We have since developed a new improved tailored dosing regimen which calculates vitamin K dose based on the patients INR on presentation, target INR and body surface area. The proposed project will compare the performance of the new improved dosing algorithm with the fixed-dose regimen in 186 patients in a randomised trial. We will also measure physical features and activities of 2 genes which control warfarins activity to see if using these could make tailored dosing even more accurate. We envisage that the new dosing regimen will produce a more accurate reversal of excessive INR, increasing the proportion of patients whose INR is corrected to within their target range and save the NHS costs associated with treatment failure.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East Newcastle & North Tyneside ref: 11/NE/0249

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Non-malignant haematology

Interventions
Eligible participants will be randomly allocated to receive a vitamin K "tailored" dose, or "fixed-dose" vitamin K regimen as per routine clinical practice (control arm).

All eligible patients will receive an oral dose of vitamin K (Konakion MM) based on venous INR value on admission (index INR). The appropriate dose of vitamin K (either the fixed-dose regimen or the tailored dose based on the patient's INR) will be dispensed, diluted and administered immediately in a small cup of water.

Length of study: 24 months, with patients will each be followed up for 2 weeks only after study intervention.

Intervention Type
Supplement

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Vitamin K

Primary outcome(s)
The proportion of patients reaching the target INR range within 24 hours of receiving oral vitamin

Key secondary outcome(s))
The need for repeated doses of vitamin K, temporary resistance to warfarin

Completion date
31/12/2013

Eligibility

Key inclusion criteria
1. Patients on chronic therapy on warfarin presenting with an INR equal or greater than 6.0
2. Patient has provided written informed consent for participation in the study prior to any study

specific procedures
3. 18 years of age or over
4. Male & female particpants

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Younger than 18 years
2. Life expectancy less than 10 days
3. Presence of major bleeding requiring immediate and complete correction of anticoagulation
4. A history of thromboembolic / major haemorrhagic event in the previous 3 months
5. nown bleeding disorder
6. Known sensitivity to vitamin K
7. Liver disease
8. Indication for acute normalisation of INR (such as imminent surgery)
9. Scheduled discontinuation of warfarin therapy
10. Receiving thrombolytic therapy within 48 hours
11. A platelet count less than 50x10 x 9 (superscript) cells/L
12. Unable to take oral medication
13. Unable to return to the clinic the next day for laboratory/clinical assessment
14. Participation in any other investigational study/trial within the past month

Date of first enrolment
01/01/2012

Date of final enrolment
31/12/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Newcastle University
Institute of Cellular Medicine
The Medical School
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
NIHR - Research for Patient Benefit (RfPB) (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2017		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes