ISRCTN69942081 https://doi.org/10.1186/ISRCTN69942081

Tetanus vaccine safety in patients taking anti-coagulants: can it be administered intramuscularly instead of subcutaneously, as usually recommended?

Submission date
06/02/2012

Recruitment status
No longer recruiting

Registration date
16/02/2012

Overall study status
Completed

Last Edited
09/01/2023

Condition category
Haematological Disorders

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

Plain English summary of protocol

Background and study aims
When patients are treated with oral anticoagulants (that is, medicines taken by mouth that stop the blood from clotting), anti-tetanus vaccinations just under the skin (subcutaneous) are usually recommended to reduce the risk of bleeding. This is in spite of the fact that, to date, only injections of the vaccine that go directly into the muscle (intramuscular) have been shown to work. This study will compare the safety and effectiveness of subcutaneous injections of tetanus-diphtheria vaccine compared with intramuscular injections in patients treated with oral anticoagulants.

Who can participate?
Patients treated with oral anticoagulants who need to be vaccinated against tetanus and have had at least one dose of vaccine, may participate in the study.

What does the study involve?
A test to check how well the participants blood is clotting (an INR test) is performed at the beginning of the study. This is followed by intramuscular or subcutaneous injections of tetanus-diphtheria vaccine and then a blood analysis. There are then follow-up visits at 1, 2, 14 and 30 days after each dose of the vaccine to detect any side effects and, finally, a blood analysis 30 days after the last vaccination dose.

What are the possible benefits and risks of participating?
There may be adverse, but rare, side effects due to the vaccination. It is also possible that participants will experience an allergic reaction at the injection site.

Where is the study run from?
The study takes place in 15 Primary Care Health Centres in Vigo, Spain. Sárdoma Health Centre leads the study.

When is the study starting and how long is it expected to run for?
The study ran from January 2009 until November 2012.

Who is funding the study?
Department of Health of Galicia (Spain).

Who is the main contact?
Dr Fernando Lago Deibe
flagod@mundo-r.com

Contact information

Type(s)
Scientific

Contact name
Dr Fernando I Lago-Deibe

Contact details
Health Center of Sárdoma
Vigo Primary Care Region
Galician Health Service
Baixada a Laxe 76
Vigo
Spain
36204
-
flagod@mundo-r.com

Additional identifiers

EudraCT/CTIS number
2007-001073-29

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
2007-001073-29

Study information

Scientific Title
Prospective clinical trial, phase IV, controlled randomized, double-blind, parallel-group for evaluate the safety and efficacy of Tetanus vaccination in patients taking oral anticoagulants. Comparing the subcutaneous versus intramuscular injection of Tetanus vaccination.

Study objectives

In patients treated with oral anticoagulants, subcutaneous injections of anti-tetanus vaccination are usually recommended to reduce the risk of bleeding, although their effectiveness has been proven only for intramuscular injection.

The objective of this study is to compare the security and the efficacy of intramuscular and subcutaneous injections of tetanus-diphtheria vaccine in patients treated with oral anticoagulants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Clinical Research Ethics Committee of Galicia, Spain, 07/06/2009, ref: 2007/089

Study design
Prospective double blinded phase IV trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Patients treated with oral anticoagulants for whom at least one dose of anti-tetanus vaccine was indicated

Interventions
We present a prospective, double-blind, phase IV clinical trial with layered randomized assignment. For allocation of the participants, a computer-generated list of random numbers was used. The three layers were defined by the doses of the corresponding anti-tetanus injections, one, two or three, with two parallel groups in each layer, each of which was given doses of the corresponding tetanus vaccine either intramuscularly (Group 1), or subcutaneously (Group 2).

Interventions
Patients were recruited in the primary care consultancies by their family doctors. The doctor in this first visit assessed the vaccinal state of the patient, taking into account the vaccinal records in the clinical history, or in case of absence of information in the records by interviewing the patient. In this way the doctor determined, according to the number of doses received and the date of the last dose if the patient was properly vaccinated, in which case they were excluded

from the study, or whether they needed to be given a booster dose or to start or complete the adult primovaccination. The guidelines for applicable vaccination were those recommended by the Ministry of Health until 2008.

Briefly, an INR test and a blood analysis to detect antitetanus antibodies will be performed at the beginning, followed by intramuscular injections of tetanus-diphtheria vaccine in one intervention arm and subcutaneous injection in the other one. In both arms, there will be follow-up visits at 1, 2, 14 and 30 days after each dose of the vaccine to detect any side effects and a blood analysis 30 days after the last vaccination dose. Total duration of treatment is variable, depending on the number of vaccine doses needed by each patient.

1. For complete primovaccination and less than 10 years since the last dose: nothing (not included in the study).
2. In the case of complete primovaccination and more than 10 years since the last dose: 1 booster dose.
3. In case of no previous vaccination: complete primovaccination with three doses separated by 1-2 months between the first two and 6-12 months between the second and third, with subsequent booster doses every 10 years. If the primovaccination had been started prior to starting the study the patient was administered doses according to the standard schedule.
4. In the case of incomplete primovaccination:
4.1. 1 dose if the patient already had been administered 2, and the latter was more than a year earlier.
4.2. 2 doses, separated by six months, if the patient had 1 dose administered more than a month earlier.

When the vaccination status was unknown or doubtful primovaccination was started. After assessing whether the patient fulfilled the inclusion criteria, and none of the exclusion criteria, they were invited to participate in the study, and if they agreed to sign informed consent, were included in one of the tiers according to the vaccine dose (one, two or three) that corresponded (allocation ratio 1:1). They were given an appointment to perform an INR test and if it was less than 4 extraction for anti-tetanus antibodies was performed and a dose of the vaccine was immediately administered so that the patient could pass to the corresponding nursing consultancy. The nurse was responsible for requesting, from the randomization centre, by telephone, the administration route to which the patient had been assigned. The patient was not informed of the administration route used. Patients needing to receive more than one dose were dosed via the same route for all doses and were given appointments as a function of the interval and number of corresponding doses. The doctor was blinded to the administration route and performed follow-up, visits 1, 2, 14 and 30 days after each dose of the vaccine to detect any side effects. On the first visit, before administering the vaccine, and at 30 days after the last dose of ATV,
the antibody titre was determined for all patients using enzymatic immunoanalysis.

Physical examination performed systematically on each visit was:
1. General appearance
2. Arterial blood pressure.
3. Measurement of the brachial perimeter at the height of the deltoid on the first visit and at the site of inoculation after vaccination.

Inspection and palpation of the injection site looking for basic injuries.
1. Homolateral axillary palpation of the injection site.
2. All the examinations which are required due to the emergence of a general and/or unexpected side effect

Laboratory analysis:
1. Determination of INR through the capillary technique with a reflectometer.
2. Determination of antitoxoid tetanus antibodies by enzymatic immunoanalysis in a centralized Laboratory (Barcelona).

Intervention Type
Biological/Vaccine

Phase
Phase IV

Primary outcome measure
The main efficacy analysis variable was the increase in anti-tetanus antibodies before/after, each route of administration (UI/ml).

Secondary outcome measures
1. Measurement of the brachial perimeter in centimetres.
2. Appearance of elementary injuries (redness, swelling, heat, granulomas, hematoma) in the area of administration of the vaccine, axillary node, and the appearance of pain measured with the visual analogue pain scale.
3. The emergence of general symptoms (fever, malaise, headache, weakness, arthralgias)
4. The appearance of any serious adverse effect: one that was fatal or posed danger to the life of the patient, ended in disabilities or required hospitalization.

Follow-up visits at 1, 2, 14 and 30 days after each dose of the vaccine to detect any side effects.

Overall study start date
19/01/2009

Completion date
01/06/2019

Eligibility

Key inclusion criteria
1. All patients, whose control were being performed at 15 Health Centres (Vigo Primary Care Area)
2. Patients treated with oral anticoagulants, where administering at least one dose of anti-tetanus vaccine was indicated. This was for those whose vaccination status was unknown, uncertain or if they were clearly not vaccinated.
3. Patients giving written consent to be vaccinated and participate in the study after being duly informed.

Participant type(s)
Patient

Age group
Adult

Sex

Both

Target number of participants
135 patients in each group are required

Total final enrolment
234

Key exclusion criteria
1. Severe local reaction to previous doses with affection of the whole circumference of the injected limb
2. Peripheral neurological disorders due to previous doses
3. Severe anaphylactic reaction due to previous doses or any of the components
4. Bad haematologic control (INR>4) in the last 2 months
5. Serious illness, terminal stages of diseases, immobilized, adversely affected chronic pathology or immunosuppressive states
6. Pregnant or breast-feeding women

Date of first enrolment
19/01/2009

Date of final enrolment
01/06/2018

Locations

Countries of recruitment
Spain

Study participating centre
Health Center of Sárdoma
Vigo
Spain
36204

Sponsor information

Organisation
Department of Health of Galicia (Spain)

Sponsor details
Consellería de Sanidade, Xunta de Galicia
Ed. Adm. San Lázaro s/n
Santiago de Compostela
Spain

15703
-
investigacion.docencia.innovacion@sergas.es

Sponsor type
Government

Website
http://www.sergas.es

ROR
https://ror.org/0181xnw06

Funder(s)

Funder type
Government

Funder Name
Department of Health of Galicia [Consellería de Sanidade of Galicia] (Spain) ref: PS07/114

Funder Name
The Vigo Primary Care Research Network (Spain)

Funder Name
Galician Ministry of Innovation and Industry [Consellería de Innovación e Industria] (Spain) ref: INCITE08ENA9104079ES

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
01/06/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available, due to several reasons: the researchers do not have the infrastructure for this,

the study was designed many years ago (2008) and at that time the transfer of data was not foreseen, nor do they have authorization from the CEIC (Ethical Committee for Clinical Research) and the patients for it.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	28/08/2014		Yes	No
Basic results		30/11/2019	03/12/2019	No	No
Results article		09/01/2023	09/01/2023	Yes	No