END OF STUDY REPORT

The effect of transdermal GTN on spasm, arterial size and procedure outcomes in transradial coronary angiography – A pilot study

Protocol Number	6
Chief Investigator	Dr Alun Harcombe
EudraCT Number	2007-000510-37
REC Reference Number	08/H0408/35
Sponsor Reference Number	08CA001
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Funder(s)	None
Sponsor(s)	Nottingham University Hospitals NHS Trust

Name of Test Drug/Investigational Product	**Nitro-Dur (Schering-Plough)** Glycerol Trinitrate, 10mg Transdermal patch
Indication Studied	

Report Author: _____ Date: 05th March 2020
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Sponsor Authorisation: _____ Date: 05th March 2020
[Name] [Title]

This study was carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures

List of Abbreviations and Definition of Terms

GTN	Glycerol Trinitrate

1. Summary of Study

Transradial coronary angiography is an alternative to the transfemoral approach and the benefits of lower hospital costs and improved patient satisfaction have been demonstrated; however, the a complication is arterial spasm. This can cause pain and sometimes for the procedure to be abandoned. Glycerol Trinitrate (GTN) is known to dilate arteries and a patch applied to the wrist before the procedure may offer a simple, effective method of reducing the incidence of spasm. If this technique is to become the method of choice then this issue needs to be addressed; otherwise this may limit the application of this technique to the large number of patients undergoing coronary angiography every year. The study was pilot prospective cohort study that recruited adult patients undergoing a transradial coronary angiogram. It was initially designed to recruit 30 patients, but due to recruitment issues only 18 were recruited.

2. Objectives

This project was designed as a pilot prospective cohort study, as there were no published data on this indication of GTN patches. It was designed as a single group observational study, as no placebo patches or historical controls could be used.

The main aim was to obtain data to inform a proposed Randomised Controlled Trial (RCT) to be carried out in the future. The proposed future RCT would involve comparing GTN patches to placebo and possibly other vasodilatory agents.

This pilot study aimed to enable us to:

- measure a number of outcome variables
- determine whether these are achievable and quantifiable
- identify the most appropriate primary outcome measure
- provide data to inform the sample size calculation for the future RCT
- collect data on spasm and other outcomes measures, such as procedure and access time
- measure arterial diameters to determine effect of GTN patch

This pilot study enabled the integrity of the protocol to be examined, for the evaluation of data measurement and collection techniques and identify recruitment issues.

3. Ethical Review

The study was given a favourable opinion by a Nottingham Research Ethics Committee 2 on 25th April 2008. It was conducted in accordance with GCP principles and NUH processes. The study was initiated after the protocol, informed consent forms and participant and GP information sheets had received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research

Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department.

4. Investigational Plan

The study recruited adult patients who were referred for non-emergency coronary angiography from either cardiology clinics or in-patients ward.
We collected data on the change in size of the upper limb arteries when GTN patches were applied to the wrist, prior to transradial angiography. We collected data on complications, particularly spasm, experienced during the angiography. There were no controls as all patients received the active GTN patches, as per normal routine clinical practice at Nottingham.

5. Selection of Study Population

Inclusion Criteria

- Any adult that undergoes a non-emergency coronary angiogram via the Radial artery.
- Patent (open) Radial and Ulnar artery as determined by a modified Allen's test

Exclusion Criteria

- Participants unable to attend for the ultrasound scans.
- Any known adverse reaction to GTN.
- Unable to give informed consent
- Extensive co-morbidities or pregnancy.

6. Study Settings

Data collection took place at Nottingham University Hospitals NHS Trust. It is a teaching hospital with appropriate Cardiology and Catheter Laboratory facilities, as well as a suitable vascular studies unit for ultrasound scanning.

Dr Harcombe was the Chief Investigator and had overall responsibility for the study, he also performed some of the coronary angiograms. Richard Simpson was a co-investigator and MSc. student and I ran the entire study; including study design; writing the protocols and study documents; gaining approvals; identifying and recruiting the patients; performing the ultrasound; data collection; performing the image and data analysis and drawing the conclusions.

7. Interventions (if applicable)

1. Pre-assessment clinic appointment letter sent out, including invitation letter, PIS and consent form.

2. Pre-assessment visit (about 1 week before the procedure)

a. Pilot study is discussed with the patient and they have the opportunity to ask questions.

3. On the day of the procedure
    a. The patients are admitted to the cardiology ward
    b. If patient was not consented for the study at pre-assessment then this was done before ultrasound scan was performed.
    c. Patients had the pre-application ultrasound scan
    d. GTN patch is prescribed as per normal clinical procedure and then applied to the wrist
    e. Post-application ultrasound scan after 30 mins wait
    f. Transradial coronary angiogram performed
    g. Data collection sheet and patient questionnaire completed
    h. Patient discharged home

The GTN patch used: Nitro-Dur (Schering-Plough), a 10mg Glycerol Trinitrate, transdermal patch. The dose regimen: One 10mg (0.4mg/h) transdermal GTN patch place over the radial artery at the wrist before the angiogram
Drug supplies were kept in a secure, limited access storage area under the storage conditions specified by Pharmacy; a locked drug cupboard on the cardiology ward at room temperature.

8. Changes in the Protocol from Initial Approval

There were no changes to the protocol from initial approval and no therefore no amendments were submitted.

9. Protocol Deviations

Of the 18 patients included in the study and had the GTN patch applied, 3 patients had a transfemoral procedure, due to contraindications to the transradial approach at the time of the procedure. At the time of the recruitment, all the patients were deemed to be suitable for the study. One patient had a previous shoulder surgery and the other two had their procedures carried out by different operators at very short notice.

All patients did not undergo the 1 month follow-up duplex ultrasound, as originally planned, but had normal routine clinical follow-up 1-2 months after the procedure. This was due to organisational changes at the Hospital.

10. Patient Information & Consent

A study invitation letter, PIS and consent form was sent out with the pre-assessment clinic appointment letter, about 1-2 weeks before the procedure. Full consent was taken when the patient was admitted if the patient did not do this at the pre-assessment visit.
Three other additional pateitns that were considered, for the study but were not recruited due to falling outside of the inclusion and exclusion criteria.

11. Randomisation (if applicable)

There was no randomisation procedure needed for this study

12. Safety Reporting

The risk of side-effects of the GTN patch were low and since the adverse events were anticipated to be mild, participants were followed-up as per the routine clinical practice in the Department of Cardiovascular Medicine. Side effects and adverse events were recorded when they occurred. A Consultant Cardiologist was present at all coronary angiograms.
The GTN patch (0.4mg/h) was applied for approximately two or three hours on the day of the coronary angiogram. Therefore the patient was exposed to GTN for a short period on the day of the procedure.
Research meetings were held on a 2 monthly basis to review adverse events and data collection.

13. Statistical Analysis

Continuous data were summarised using means and standard deviation or median and inter-quartile range if not considered to come from normal distribution. The unpaired t-test was used to compare two independent groups of continuous data if the assumptions were met and the Mann-Whitney U-test was used as the non-parametric alternative.
For paired data (pre- vs. post- GTN patch measurements) which conformed to normality, the paired t-test was used to compare the results. The Wilcoxon matched pairs signed rank test was employed if a non-parametric test was indicated.
Categorical variables were summarised using frequencies and percentages and comparisons were made using the Chi-squared test or Fishers exact test if the assumptions were not met.

There was not deviation from the statistical plan.

All patients received the same dose for the procedure and therefore the relationship to response could not be analysed.

14. Main Findings of the Study

Two (13.3%) patients experienced spasm during the study, one mild and one severe (this patient was converted to transfemoral angiogram). Younger patients were more likely to experience spasm (P=0.019).

Gender (P=0.10) and arterial diameter (P values ranged from 0.22 for the contralateral brachial artery to 0.66 for the distal ipsilateral ulnar artery) were not found to be associated with presence of spasm. Females had significantly smaller arteries than the male patients (P<0.05). GTN patches significantly increased the arterial diameter by a mean of 9.75% across all arteries.

15. Conclusions

Despite various limitations, including small sample size and no comparison group, this study has found that GTN patches may offer a simple alternative to a spasmolytic cocktail, as when compared to no treatment it reduces spasm and it also dilates arteries.