**Study Title**

Efficacy of single versus split dose enoxaparin post elective neurointervention in prevention of thromboembolic events – a randomised study

**Short Title:** EPPICS II Study

**Researchers**

**Professor Alan Coulthard**

*Principal Investigator*

Roles: Interventional Neuroradiologist, supervisor, expert adviser, study design, medical imaging analysis

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*Associate Investigator*

Roles: Senior House Officer Medical Imaging Research. Data collection, co-ordination, and write up

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Roles: Director of ICU

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**Site**

Department of Medical Imaging, Royal Brisbane & Women’s Hospital, Brisbane, QLD, Australia

**Grant Considerations**

A research grant application was lodged with the Royal Australian and New Zealand College of Radiologists (RANZCR) 2020.

**Background**

Thromboembolic events are frequent adverse events in neurointerventional procedures. Intracranial thromboembolic events occur intraprocedurally at a rate of 8% (standard deviation +/-5.7%)1. Intravenous unfractionated heparin(UFH) is recommended during endovascular aneurysm treatment, with a monitored activated clotting time(ACT) of between 200-3002,3. Most ischaemic strokes occur between 4 and 12 hours post-procedure4.The risk of thromboembolic events increases after stenting perioperatively and in the 48hrs post treatment by 10%2. A cumulative analysis of endovascular coiling demonstrated a reduction in postoperative thromboembolic events with heparin use compared with no heparin use (5.9 vs. 9.3%)5. In practice many operators adopt an ad hoc case-by-case approach to post-procedure anticoagulation, based on perceived risk of thromboembolic events.

In addition, there is a risk of developing clinically silent ischaemic lesions (CSILs), which can be identified as ‘bright spots’ on diffusion weighted imaging (DWI). The overall incidence of DWI lesions post endovascular cerebral aneurysm treatment has been reported as 49-60%6. The majority appear asymptomatic. However a long-term follow-up study of healthy volunteers by Vermeer et al suggested that CSILs increased the risk of dementia and cognitive decline over a 5-year period7. Conversely Kang et al. (n=40) did not find a significant difference between mean cognitive scores between patients with and without CSILs at 1 and 4 weeks8.

There are conflicting opinions on the risk factors for DWI lesions post neurointervention. A meta-analysis found that flow diversion was associated with a higher rate of thromboembolic complications compared to coiling6. The limitations of many studies in post-procedure DWI lesions include being retrospective and non-randomised9, and lacking pre-procedure imaging.

Our randomised prospective trial (EPPICS) comparing standard of care unfractionated heparin infusion (UFH) post procedure with either enoxaparin 1.5mg/kg at T=0 or enoxaparin 1.5mg/kg at T=0 and T=12h had a primary outcome measure of therapeutic anticoagulation at T=4hrs. Only 11% of the UFH group were within the therapeutic range compared with the two enoxaparin arms (p<0.001). For the secondary outcome of puncture site complications there were no differences between UFH and the lower dose of enoxaparin, but the higher dose had an odds ratio of developing puncture site complications of 3 compared with UFH. Fewer new DWI lesions were noted in the higher dose enoxaparin group compared to UFH (p<0.01).

There is a clear and significant benefit to using enoxaparin over unfractionated heparin in terms of therapeutic anticoagulation. The purpose of this study is to determine whether the two dose regimes of enoxaparin differ in terms of post procedural DWI lesions (thromboembolic events) and puncture site complications.

**Aims / Objectives**

Patients undergoing elective endovascular aneurysm treatments will be divided into two anticoagulation ‘arms’, each with a differing anticoagulation regimen. Outcomes between these groups will be assessed with respect to the following outcomes:

*Primary outcome*

The proportion of patients per group who develop thromboembolic events detected as lesions on DWI MRI within 48 hours post endovascular treatment of intracranial aneurysms

* Thromboembolic events will be further characterised as clinically evident or clinically silent
  + Clinically evident ischaemic lesion (CEIL) – Defined as the presence of new DWI brain lesions AND an acute event of cerebrovascular origin causing focal or global neurological dysfunction, lasting either <24 hours (TIA) or >24 hours
  + Clinically silent ischaemic lesion (CSIL) – Radiological evidence of ischaemic intracranial lesions without overt neurological dysfunction

*Secondary outcome*

1. The proportion of patients who experience a puncture site complication

*Tertiary outcomes*

1. Frequency of new parenchymal susceptibility weighted imaging (SWI) lesions in the brain (which may signify microbleeds)
2. Frequency of haemorrhage (major and minor)
   1. Major haemorrhage – A clinically overt haemorrhage resulting in a fall of more than 30 g/L in haemoglobin; or a retroperitoneal, intracranial or intraocular haemorrhage
   2. Episodes of bleeding that were clinically overt but do not meet these criteria are considered minor haemorrhages

**Hypothesis**

**Primary**

* In patients who have elective endovascular treatment of unruptured intracranial aneurysms randomised to receive anticoagulation post procedure of either enoxaparin 1.5mg/kg at T=0 OR enoxaparin 1mg/kg at T=0 and T=12hrs there is no difference in the number of thromboembolic events post procedure (new DWI lesions at T=48hrs MRI).

**Secondary**

* In patients who have elective endovascular treatment of unruptured intracranial aneurysms randomised to receive anticoagulation post procedure of either enoxaparin 1.5mg/kg at T=0 OR enoxaparin 1mg/kg at T=0 and T=12hrs there is no difference in the frequency of puncture site complications.

**Method**

Patients presenting for an aneurysm coiling who fit the inclusion criteria will be recruited for the study pre-operatively. Informed consent will be obtained. A brain MRI will be obtained pre-operatively, utilising DWI, SWI and Axial FLAIR sequences in addition to standard of care imaging. Patients will undergo the endovascular coiling/stenting procedure as per local protocol and will subsequently be randomised into one of two categories of enoxaparin administration (see below). Outcomes will be assessed starting from removal of the vascular sheath and extending until 48 hours post procedure or ICU discharge, whichever happens later. Patients will undergo an additional brain MRI with identical imaging sequences within 48 hours post procedure. Data will be collected (as per Variables section) throughout the patient’s admission.

The primary outcome, thromboembolic events, will be assessed through identifying new DWI lesions on post-procedure MRI and clinical examination for neurological deficit (indicating CEIL) or the lack thereof (CSIL). The number of DWI brain lesions will be interpreted by an experienced radiologist on both sets of brain MRI. Both trial arms will be compared.

The secondary outcome, puncture site complications, will be assessed through clinical observation. Puncture site complications may include 1) haematoma; 2) requiring a vascular compression device such as Femstop; or 3) surgical intervention.

Additional complications will also be assessed between these groups, especially major haemorrhage and microbleeds.

The decision to anticoagulate or not is made at the end of the endovascular procedure, depending on the assessment by the operator that the patient is at higher risk of thromboembolic events. The indicators for post procedural anticoagulation include placement of an endovascular device such as a stent, coil or loop protrusion into the parent vessel, large area of coil exposure at the aneurysm neck and intraprocedural platelet aggregation. These are detailed in our inclusion criteria. From our experience approximately 70-90% of the consented subjects who have had baseline MRI will require post procedural anticoagulation. This higher risk group will be randomised for either enoxaparin 1.5mg/kg at T=0, or enoxaparin 1mg/kg at T=0 and T=12hrs. It is intended that the remaining participants (no anticoagulation, “lower risk” group) form a separate study group adding data to our group’s research on thromboembolic outcomes after neuroendovascular procedures. They will be assessed for thromboembolic complications by neurological examination at 24 hours and MRI at 48 hours.

*Study Type*

Randomised prospective single-centre study

Population

Patients presenting with unruptured intracranial aneurysms who are scheduled to undergo endovascular treatment, such as elective coiling, stent assisted coiling, balloon assisted coiling or flow diverting stents

*Inclusion criteria*

Patients deemed fit for an elective endovascular aneurysm treatment

Patients who require post procedure anticoagulation after intracranial endovascular aneurysm treatment. The criteria for post procedural anticoagulation are any of the following:

1) Placement of an Endovascular Device

2) Presence of procedural platelet aggregation

3) Increased risk of thromboembolic events due to

(3a) large area of coil exposure at aneurysm neck

(3b) loop protrusion into parent artery

Able to understand the project and provide voluntary consent and continued participation

*Exclusion criteria*

Patients under 18 years of age (i.e. paediatric population)

Patients presenting with acute subarachnoid haemorrhage

Patients with significantly impaired renal function (eGFR < 30)

Patients not suitable for 3T MR imaging (e.g. pacemakers)

Pregnant women

*Patients deemed not to require anti-coagulation (see Method section)*

*Recruitment*

Preadmission clinic and/or prior to procedure

*Number of participants*

The sample size calculations are based on the comparison between enoxaparin 1mg/kg (given at T=0 and T=12hrs) and enoxaparin 1.5mg/kg (given at T=0) for the primary outcome, which is the proportion of patients experiencing a new DWI lesion post procedure. Sample size calculations were performed using a two-sided pooled Z test based on 80% power and equal number allocation to each group. An estimate of the proportion of patients with a new DWI lesion post procedure was derived from the EPPICS I study performed at the Royal Brisbane and Women’s Hospital (RBWH) between 2016-2020. EPPICS found 0.64 of patients experienced a new DWI lesion post procedure in the enoxaparin 1mg/kg group. With a clinically meaningful absolute decrease of 0.25 and a type I error rate (α) of 0.05, 62 participants are required for each of the two arms. Therefore we aim to recruit a total of 124 participants.

*Consent / Privacy*

A process of informed consent will be utilized for this study. Patients will be provided with all relevant details of the study to a level of their understanding. No identifiable patient information will be published. All data will be kept securely at the Royal Brisbane and Women’s Hospital (RBWH) and handled as per the Data Security protocol (see below).

*Process*

* Patients will initially be identified after referral to the Interventional Neuroradiology Service for consideration of treatment
* Discussion of the research project may initially be done here and patients will be provided with an information sheet
* Alternatively, patients may be recruited after confirmation booking for their procedure
* A letter of invitation and patient information and consent form (PICF) will be mailed out to patients at this time for their consideration
* Patients will attend an anaesthetic pre-admission appointment prior to their scheduled intervention. A researcher/resident from the RBWH Department of Medical Imaging will attempt to liaise with the patient between this time and the day of the procedure. Contact may be in person in the Department or over the telephone
* On the day of the procedure they will undergo initial MRI (DWI, SWI, FLAIR)
* The coiling/stenting procedure will be performed according to operator discretion and local protocol
* Intraoperative anticoagulation will be administered in the form of heparin with a target ACT of 200-300s
* At the conclusion of the procedure the femoral/radial catheter sheath will be removed
* Patients will then be randomized into one of the two aforementioned post-operative anticoagulation groups
  + A randomised database will be generated using a Microsoft Excel spreadsheet randomise function
  + 124 physical packets will be generated containing the randomised group (62 per group), in addition to important research instructions (e.g. forms detailing required observations etc)
  + The operating interventional neuroradiologist will be given the next packet in sequence
* Patients will be kept for at least 24-48 hours in the Intensive Care Unit (ICU) for observation [standard of care]
* Patients will receive a neurological examination day 1 post-procedure
* Post-operative complications will be documented in the patient’s chart
* Medical Emergencies will be dealt with according to the local protocols and practitioner experience
* At post-operative day 1 or 2, patients will receive an additional MRI
* Patients who were deemed not to require post-operative anti-coagulation will follow the same pathway, but will not have any anticoagulation. They will still receive their Day 1-2 MRI scan.
* Patients will be discharged home once medically stable

**Image Analysis (pre- and post- procedure MR-DWI, SWI and FLAIR)**

* All acquired images will be reviewed by an experienced radiologist and compared.
* DWI lesions
  + Location (intra or extra-territorial to treated aneurysm)
  + Size : <20mm or >20mm
  + Number
* Positive lesions defined as area of high signal on DWI with corresponding low signal on ADC (i.e. suggestive of restricted diffusion of H2O). In the unlikely event that additional opinion is needed, it will be obtained from another neuroradiologist within the medical imaging department.
* Pre- and post- images will be reviewed for evidence of new ischaemic lesions and compared
* SWI lesions - Pre- and post- images will be reviewed for evidence of new SWI lesions and compared
* FLAIR – pre-procedural FLAIR images will be assessed for previous infarcts or cerebral microangiopathy. The white matter will be graded using Swieten’s scale10.

*Variables*

Anticoagulation dosing regime

* Single Dose – 1.5 mg/kg subcutaneous enoxaparin given immediately post operatively (T=0)
* Split Dose – 1.0 mg/kg subcutaneous enoxaparin given immediately post operatively(T=0), followed by another 1.0 mg/kg at 12 hours(T=12h)
* Maximum dose will be capped at 150mg as per local guidelines11,12

*All complications will use the “Common Terminology Criteria for Adverse Event (CTCAE) 4.0” for definition and grading – Severe Adverse Events are defined as CTCAE Grade 4 of greater.*

Thromboembolic events (CTCAE ‘Stroke’)

* Clinical events (CEIL [CTCAE Grade 2-5], CSIL [CTCAE Grade 1])
* Post-procedural MRI will be assessed as detailed in Imaging Analysis

Table 1 - Variables

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| --- | --- | --- |
| Anticoagulation | Arm A(enoxaparin 1mg/kg at T=0 and T=12h) ; or  Arm B (enoxaparin 1.5mg/kg at T=0) | Dose administered (mg) |
| Medical History | Hypertension (0,1)  Diabetes mellitus (0,1) |  |
| Demographics | Age  Gender (m/f)  Ethnicity | Weight (kg), Height (cm), BMI  Current Smoker (0,1) |
| Relevant Medications | Aspirin (pre-op) (0,1)  P2Y12 inhibitor (pre-op) (0,1)  Proton pump inhibitor (0,1) |  |
| Procedure | Procedure Type (coil, BAC, SAC, FDS)  Number of aneurysms treated during procedure  Operator rating of procedure complexity | Procedure Time (minutes)  Mean ACT (intra-op)  Highest ACT (intra-op)  Inpatient Duration (days)  Reason for Anti-coagulation |
| Aneurysm | Aneurysm Location (vessel, right/left/midline)  Aneurysm Size (largest dimension [mm]) |  |
| Bloodwork | P2Y12 Reaction Unit (pre-op value)  Haemoglobin (Hb) (pre-op and post-op) |  |
| Complications | Intracranial Thromboembolism (0 [no], 1 [yes])   * Intraoperative (0,1) * Post-operative (0,1)   CSIL (CTCAE Grade 1)  CEIL (CTCAE Grade 2-5)  Puncture site (normal, haematoma, Femstop, surgical intervention) | Major Bleed (clinically overt with Hb drop >30g/L, intracranial, intraocular, retroperitoneal)  Minor Bleed  Other Complication (e.g. hydrocephalus, DVT, PE) |
| Imaging | Ischaemic Lesions (Pre and post op MRI)   * Location (intra or extra-territorial to treated aneurysm) * Number of lesions and size (<20mm, >20mm)   Pre-op FLAIR   * White matter hyperintensity Swietens grading * Previous infarct | Microbleed SWI lesions (Pre and post-op MRI within 48 hours)   * Number of lesions |

*Data Collection and Security*

Data will be entered into a spreadsheet kept in a password-protected drive at RBWH during review of patient imaging and medical records. Patients will be assigned a participant identification number. This will be recorded and referred to in all data during analysis. Patient MRI scans will be stored on the password protected picture archiving and communications system (PACS) at RBWH. Images used in publications will be de-identified and show only the region of interest.

A file with the unit record (UR) number and name of participants linking them to the participant identification numbers will be stored on a password-protected drive at RBWH. Only the principal investigators will have access to data files.

To preserve participant privacy, de-identified data will be sent to the biostatistician for analysis at the QIMR Berghofer Research Institute. The completed analysis will be returned to the principal investigators and remaining files at QIMR Berghofer will be promptly destroyed.

Deletion of electronic files in accordance with RBWH Information Technology Service's data disposal protocol will occur at the end of a 15-year period ending 31/09/2038. Printed documents will be held in the Department of Medical Imaging Research Office, Level 3, Ned Hanlon Building, Royal Brisbane and Women's Hospital (RBWH). Printed documents will be destroyed through RBWH secure document disposal service.

An interim review of cases will occur at 6 months, or when half of the participants have been recruited.

*Statistical Analysis*

This will be done in collaboration with the QIMR Berghofer Medical Research Institute Statistics Unit.

The primary endpoint will be the proportion of patients with new DWI lesions detected on post procedure MRI for each arm. We will further determine whether there are differences between the arms with respect to the secondary endpoints of the proportion of patients who experience puncture site or haemorrhagic complications. Characteristics of each arm will be summarised using frequency and percent, mean and standard deviation for normally distributed continuous variables and median and interquartile range for non-normally distributed continuous variables. Chi-square tests will be used to compare randomised groups for categorical outcomes (includes primary outcome), t-tests for continuous normally distributed outcomes and Mann-Whitney U tests for continuous non-normally distributed outcomes. Statistical significance will be set at α<0.05. As a secondary analysis to improve effect size estimates, a meta-analysis will also be performed with data from the previous EPPICS study.

*Timeline*

The project aims to start recruitment in 4Q 2020. Recruitment of 124 participants is expected to complete between 4Q 2022 to 1Q 2023. Records from 2019 suggest about 50 patients per year meeting inclusion criteria. Statistical analysis and manuscript development, in addition to other administrative duties will likely take an additional 3-4 months to complete. Factoring in patient drop-out and unforeseen delays, the anticipated duration of this project is 3 years.

*Dissemination*

The results of the trial will reported locally at RBWH, including the Department of Medical Imaging Interventional Neuroradiology Service. We also aim to communicate the findings to the wider medical community through scientific meetings such as the RANZCR Annual Scientific Meeting and publication. Participants can also indicate their interest in receiving a summary of the key findings of the study as part of the consent process.

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