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Randomised Controlled Trial comparing Metatarsal Method of Transection using Bone Cutters or Bone Saw on Outcomes after Ray Amputation

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Abbreviations

ABPI Anke Brachial Pressure Index

CRP C Reactive Protein

eGFR Estimated Glomerular Filtration Rate

PAD Peripheral Arterial Disease

TMA Transmetatarsal Amputation

TPI Toe Pressure Index

1. Background and Study Rationale:

Toe amputation is a common minor vascular procedure and is increasingly performed in the context of irretrievable diabetic foot infection, with and without concurrent ischaemia. Approximately 422 million people worldwide have diabetes mellitus and peripheral arterial disease (PAD) affects approximately 200 million people(1). The intersection between diabetes, neuro-ischaemic foot ulceration and lower limb amputations is well established(2). Recently published data from the United States reported overall rates of lower limb amputations in diabetic patients rose between 2000 and 2015, in part due to a 62% increase in the rate of minor (foot and toe) amputations(3). It is estimated that 6% of Irish adults are diabetic; from this, we can extrapolate the burden of managing diabetic foot complications(4). Resource utilisation notwithstanding, the financial costs of managing diabetic foot complications are estimated to outstrip some cancers(5). As the prevalence of diabetes mellitus rises amongst an ageing Irish population, the importance of achieving durable functional outcomes after partial foot amputation is paramount.

Re-ulceration, re-infection, re-amputation and hospital re-admission after partial foot amputation for digital gangrene is well documented in the literature in both diabetic and PAD cohorts(6). Across the literature, rates of re-amputation at five years post-index surgery for diabetic foot complications range from 45-65% (6, 7). A recent study by Collins et al reported that, out of 146 Irish patients undergoing minor amputations, 43% (n=63) required further ipsilateral amputation, 21 (14.4%) of which were trans-tibial or trans-femoral(8). Chronic kidney disease, diabetes with or without poor gylcaemic control, peripheral neuropathy, peripheral arterial disease, ongoing tobacco smoking, obesity (BMI >30), concurrent sepsis at the time of index operation have all been identified as independent risk factors for amputation failure and the need for revision(9-11). While numerous studies have investigated patient-dependent factors predictive of amputation failure, there is a dearth of evidence examining the impact of surgical technique on this commonly performed procedure.

An exhaustive search of the literature surrounding surgical technique and outcomes after ray amputation yielded several papers on the benefits of various soft tissue flaps for covering wound defects but just one detailing a particular methods of bone transection. However, Moodley et al focused on the use of a Gigli saw, which is beyond the scope of this feasibility

study(12). There have been no randomised controlled trials evaluating the impact of metatarsal transection method on outcomes after ray amputation, specifically whether a manual bone cutter or an electric/oscillating/pneumatic bone saw were used. We hypothesise that utilising a manual bone cutter is more subject to inter-user variability, as it depends on the physical strength of the operating surgeon; improperly applied forces are liable to fracture the remaining bone, leaving small comminuted fragments that may become necrotic and act as a nidus for further infection within the wound bed. Furthermore, using an oscillating microsaw has the advantage of providing a clean bony transection regardless of the physical strength of the operator, however it may cause more damage to the surrounding connective tissues and disturb microvascular periosteal supply, which could also lead to osteonecrosis. We propose a pilot randomised controlled trial to test the feasibility and to generate sufficient data to permit sample size calculation for a trial designed to evaluate the outcomes after ray amputation using either a bone cutter or a bone saw.

4. **Objectives:**

The principal research question for this trial is as follows:

2.1 Primary Objective

The primary objective of this feasibility study is to collect sufficient data to enable an accurate power calculation for a future randomised controlled trial.

2.2 Secondary Objectives

1. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on rates of surgical reintervention at six months;
2. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on re-infection rates;
3. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on time to surgical wound healing;

4. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on wound-related hospital readmissions at six months;
5. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on ulcer healing;
6. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on ulcer recurrence;
7. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on osteomyelitis recurrence in the affected foot;
8. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on resection specimen margin culture positivity;
9. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on patient-reported post-operative pain, as measured by the Verbal Rating Scale (VRS)(13, 14);
10. To determine the effect of oscillating microsaw compared to bone cutters for toe amputation on patient-reported health-related quality of life (HR-QoL) at 6 weeks and 6 months post-operatively, as measured by the EQ-5D-5L tool(15)

3. Study Design and Endpoints:

3.1 Statement of Design

This is a prospective, randomised controlled, assessor-blinded, feasibility study with participants allocated to one of two parallel groups in a 1:1 fashion using randomisation by minimisation. The operating surgeon will be aware of the type of operation performed. The nature of the intervention (metatarsal amputation using either a bone saw or a bone cutter) ensures that both the patient and the assessor can be blinded, so long as the assessor is not the operating surgeon. Patients who are undergoing toe amputation via spinal or local anaesthesia, will be provided with headphones to ensure they do no overhear what equipment is requested. Evaluation of the post-operative x-rays will be performed by a designated trial radiologist who will be blinded to the intervention. The statistical analysis will be blinded. The primary trial centre will be University Hospital Galway, Ireland, with other centres also evaluated for inclusion. Appropriate patients shall be recruited from both the out-patient and in-patient setting. The procedures may be classed as Emergent, Urgent or Elective.

3.2 Endpoints

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the number of patients in each group who underwent surgical reintervention at twelve months post-operatively.

3.2.2 Primary Safety Endpoint

The primary safety endpoint is the rate of vascular-related post-operative complications in each group.

4. Study Participants:

4.1 Inclusion Criteria

Consenting patients, aged 18 and over, undergoing transmetatarsal amputation of one of more toes. Patients will be stratified by pulse status (at least one pedal palpable vs both pedal pulses impalpable) and chronic kidney disease (eGFR >60 and eGFR <60 mL/min/1.73m^2), considering both are significant factors in predicting wound healing.

4.2 Exclusion Criteria

1. Patients with significant peripheral arterial disease, as defined by ABPI <0.4 or digital pressures of <50mmHg, not undergoing concurrent revascularisation;
2. Patients unfit for surgery;
3. Patients unable to provide informed consent.

4.3 Informed consent of the in-patient

The process of obtaining informed consent will be conducted in compliance with the principles of good clinical practice and within the rules set down by the approving Research Ethics Committee. Prior to consenting to the study, each participant will be provided with a full written and verbal explanation, and sufficient time will be given for full consideration. Any queries they have will be answered. The participant will then, if they agree, sign the consent form and a copy of this given to them. At any time, the participant may withdraw from the study without prejudice or without effect on their treatment.

4.3.1 Informed consent of the out-patient

In relation to patients seen in out-patients who are eligible; the study will be discussed verbally with them and documentation provided. They will be asked at that time to give their consent, and they will be asked again on day of surgery.

4.4 Randomisation

As this is a multicentre trial and considering the myriad of factors impacting healing after toe amputation, randomisation by minimisation will be generated centrally by third-party computer software (Sealed Envelope) to ensure equal distribution of patients in each cohort across the sites. Patients will be randomised in a 1:1 ratio. On the day of surgery, a nominated, independent member of the surgical team will access the randomisation software and show the operating surgeon. Of note, randomisation will be per patient and not per toe amputation; as such, a single patient undergoing two or more toe amputations simultaneously will only be randomised once.

4.5 Baseline patient data

Patients will have a full medical history taken and clinical examination as part of their standard care. The following will be recorded:

1. Weight;
2. Height;
3. Blood pressure;
4. Heart rate;
5. ECG findings;
6. Gender;

7. Ethnicity;
8. Date of birth;
9. Diabetes mellitus and glycaemic control, defined as the most recent HbA1c;
10. Insulin requirement for diabetic patients;
11. Hypercholesterolaemia;
12. Hypertension;
13. Previous myocardial infarction;
14. Previous coronary revascularisation;
15. Previous stroke;
16. Atrial fibrillation;
17. Peripheral arterial disease;
18. Smoking history;
19. Recent ipsilateral lower limb re-vascularisation;
20. ABPI +/- TPI in the index limb;
21. Chronic kidney disease, as defined by eGFR;
22. Baseline bloods at hospital admission, including white cell count, neutrophil count, haemoglobin, mean corpuscle volume, CRP, creatinine and urea, albumin, total protein
23. Baseline x-ray findings, including degree of osteomyelitis, osteopenia and soft tissue gas

5. Interventions

All procedures will be carried out by a vascular consultant or trainee with significant experience in the procedure. This will a transmetatarsal amputation performed using either a bone cutter or a bone saw. The aim is for a successful healing of the wound, and no further re-interventions or re admission within a year. All patients will receive saline wound lavage. Wounds with extensive contamination will receive washout with 50% hydrogen peroxide solution. The most proximal specimen of bony resection will be sent for culture and sensitivity to the microbiology laboratory. The used of a drain and closure material are left to the discretion of the operating surgeon.

Continuation of antibiotics will be as per local microbiology guidelines and cultures and sensitivities will be followed. Patients will be followed up with x-ray within 48 hours of surgery to assess for bony fragments. Use of VAC or wound adjuncts will be documented.

6. Schedule of Events:

6.1 Follow up

All patients will be followed up with an x-ray at 6 months post-operatively to assess for bony healing, as is common practice in orthopaedic surgery. Any recurrence of symptoms, post-operative complications or concerns will be recorded. As per usual vascular practice, patients will be followed up in the community post-discharge and receive regular wound care from public health nurses. In order to determine approximate time from surgery to wound healing, sequential wound pictures will be sent on a fortnightly basis by the PHN to a secure HSE email account used by the trial investigators.

6.2 Withdrawals during follow up

At any time, the participant may withdraw from the trial with no bearing on any further management or intervention. The investigators may decide to remove anyone at any time if this is in the best interest of the patient.

6.3 Loss to follow-up

Any loss to follow up will be documented and explained to the best ability of the investigator. During consent, the importance of follow-up will be impressed upon, and any non-attendance to clinic or imaging will be followed up by a member of the team and the patient will be encouraged to attend if possible. Any reasons not able to attend will be recorded.

6.4 Protocol Violations

The following will be deemed a protocol violation and the participant will be removed from the trial:

1. Non-adherence to repeat imaging;
2. Withdrawal of consent for procedure or inclusion in study.

	Screening	Enrolment	Intervention	Follow up 6 weeks	Follow op 6 months	Follow up 1 year
Consent		X				
History and Exam	x	X				
Imaging	x		x		x	x
Intervention			x	x	x	x
Clinical follow-up				x	x	x

7. Safety Parameters:

7.1 Potential adverse events related to intervention

The risk of any significant adverse event occurring is deemed unlikely. All reasonable measures to avoid these events will be undertaken. Any adverse events (as described below) that occur will be recorded and reported in any trial data:

1. Bleeding requiring takeback to theatre for haemostasis or requiring transfusion of >1 unit packed red cells with corresponding drop in Hb >1g/dl ;
2. Venous thrombo-embolism;
3. Myocardial infarction;
4. Adverse reaction to local anaesthetic;
5. Major ipsilateral amputation, either below-knee amputation or above-knee amputation

7.2 Definition of an adverse event

Any untoward medical event related directly or indirectly to an intervention as a result of participation in the trial.

7.3 Definition of a serious adverse event

Any unexpected event that results in death; a life-threatening adverse event; in-patient hospitalisation or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect is deemed a serious adverse event.

7.4 Event Reporting

All adverse events will be reported directly to the either the site or principal investigator. Recurrent adverse events or serious adverse events in isolation will be reported in turn to the local Ethical Committee and the risk assessment department for risk analysis.

8. Statistical considerations:

Post intervention, all patient outcomes will be recorded and assessed on intention to treat basis. We expect a certain degree of crossover from the bone cutter trial arm to bone saw trial arm, as is reflected in daily surgical practice. Furthermore, we expect a small number of patients may ultimately not undergo treatment as initially planned. Any losses to follow up will be reported. There are no studies investigating this particular trial question, as such there is no data on which to base a power calculation. For this pilot trial, we aim to recruit 20 patients into each arm i.e. 40 patients in total. All analyses will be preformed on an intention to treat basis. The statistical analysis will be blinded. Binary outcomes will be analysed using the Chi-Square test. Non-parametric continuous variables will be compared using Mann-Whitney U Test. The time between surgery and measurable endpoints will be compared using Kaplan-Meier Survival Curves.

9. Ethical Considerations:

9.1 Ethical approval

Ethical approval will be processed by the Research Ethics Committee at the University Hospital Galway Medical Ethics Committee.

9.2 Data Protection

All data shall be managed in the strictest confidence by approved trial investigators in accordance with Irish data-protection law. Datasets will be anonymous, encrypted and stored in a secure centralised sever (REDCap).

10. Discussion:

At present, ray amputation can be performed using a bone cutters or a bone saw to transect the metatarsal shaft, depending on institutional availability and surgeon preference. There is a dearth of published literature comparing outcomes achieved between the two techniques.

Certainly, there has been no randomised controlled trials published. This randomised controlled feasibility study aims to provisionally compare the value and safety profile of two different surgical techniques. An initial feasibility study was selected as a significant number of patients are needed to power a full study. We plan to recruit from multiple sites after the initial cohort has been selected.

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