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Osseointegrated Reconstruction and Rehabilitation of Transtibial Amputees: the Osseointegration Group of Australia surgical technique and protocol for a prospective cohort study

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Abstract

Introduction

Lower extremity amputation uniformly impairs a person's vocational, social, and recreational capacity compared to a healthy state, reducing their quality of life. Rehabilitation in Traditional Socket Prostheses (TSP) is associated with a spectrum of complications which includes minor skin abrasions, infected open wounds, poor proprioception with resultant frequent falls, excess sweating, and suboptimal fit. Osseointegration has recently emerged as a novel concept to overcome these complications by eliminating the socket-residuum interface and anchoring the prosthesis directly to bone. Though the complications of TSPs affect both transfemoral and transtibial amputees, Osseointegration has been predominantly performed in transfemoral ones assuming a greater benefit/risk ratio. However, as the safety of the procedure has been established, we intend to extend the concept to transtibial amputees and document the outcomes. The purpose of this paper is to describe the surgical technique of transtibial osseointegration, and formulate the protocol for a prospective study describing patient selection, surgical technique and rehabilitation, in order to report the clinical and functional outcomes and complications of transtibial osseointegration.

Methods and analysis

The inclusion criteria are age over 18 years, unilateral, bilateral and mixed transtibial amputation and experiencing socket-related problems. All patients receive Osseointegrated implants, the type of which depend on the length of the residuum and quality of bone, which are press-fitted into the residual bone. Objective functional outcomes and subjective patient-reported-quality-of-life outcomes are recorded preoperatively and at defined post-operative follow-up intervals up to 2 years, and compared to the pre-operative values and values recorded in transfemoral osseointegration patients. Adverse events are also recorded.

Ethics and dissemination

The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). The outcomes of this study will be disseminated by publications in peer-reviewed academic journals and scientific presentations at relevant orthopaedic and clinical conferences.

Strengths and Limitations of the study

- This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far.

- The findings of the study would not only underline the feasibility of osseointegration in terms of risks and benefits in transtibial amputees but also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations.
- The data may also help provide a foundation for estimating societal impact of transtibial osseointegration, particularly the true economic impact as compared to traditional socket prostheses by indirect means.
- It does not have a control group and therefore comparison of outcomes of transtibial osseointegration directly with traditional socket prostheses used by transtibial amputees is not possible.
- The study has a relatively short follow-up period of 2 years, which does not allow the examination of longer term outcomes and risk of adverse events.

Introduction

Amputation of a lower extremity not only causes changes in the anatomy and function of the limb but also almost inevitably results in major impairments of the person's vocational, social and recreational abilities and overall quality of life.[1] The focus of management of extremity amputations has evolved over time due to advancement of medical technology from prevention of mortality to overcoming these impairments and improving quality of life.[2] For centuries, the conventional way of rehabilitating such individuals has been via traditional socket mounted prostheses (TSP),[3] and despite significant technological innovations to both socket materials and design, there has been very little change to the overall prosthetic-residuum interface from a moulded compression cone to modern suction-based socket suspension.[4]

The use of TSP is associated with a spectrum of complications arising mainly out of the socket-residuum-interface that causes reduction in prosthesis use, ability to mobilize and quality of life.[1, 5-7] These include skin problems such as infections, and skin breakdown due to chronic irritation and thermal injury,[8-11] mechanical problems such as suboptimal fit, pain and pistoning[12] and lastly, problems with proprioception that leads to loss of balance and falling.[13] Socket prostheses users account for their poor quality of life mostly to physical disability, pain and decreased energy levels.[5, 14]

In order to overcome these complications, a significantly different concept has emerged over the past two decades, which circumvents the socket-residuum-interface completely by anchoring the prosthesis directly to the bone, popularly known as Osseointegration.[15] It involves insertion of porous metal implant in the medullary cavity of the bone in a screw or press-fit technique, over which compact cortical bone grows without any intervening soft tissue in a short course of time, integrating the implant structurally and functionally to the bone.[16]

This integration of nonvital component into living bone was first discovered serendipitously in 1950s in rabbit models[4] and has been well established in the field of dentistry for the

treatment of edentulous jaws for many years with a 10-year survival of dental implants in mandibular bone of 95%.[17-20] Since its first introduction in 1990s in individuals with amputations, osseointegration has been predominantly used for the treatment of individuals with transfemoral amputation demonstrating multiple potential advantages such as improved walking ability, daily prosthetic use, reduced energy consumption, sitting comfort and osseoperception.[7, 21, 22] This results in improved mobility and quality of life for individuals with amputations.[1, 7, 21, 23]

Over the last few years multiple studies have been published investigating the safety of this procedure, especially in individuals with transfemoral amputations, as incorporating a metal implant into the bone, whilst having an open connection with the outside environment can give rise to substantial concerns regarding the risk of ascending infection and concomitant implant loosening or sepsis.[24-30] Multiple studies reported that despite frequent colonization around the skin-implant interface, the implant system caused few infections leading to disability or implant removal (average 4%).[24-30] Most encountered complications were soft tissue infections or redundancy of soft tissue possibly influenced by learning curve and iteration of surgical technique and implant design.[24, 28]

Osseointegration has been predominantly used in transfemoral amputees (TFA) as compared to transtibial amputees (TTA), due to apparently greater benefit-risk ratio with the TFA being perceived to have more socket related problems and poorer mobility as compared to TTAs and the extent of risks or complications of the new procedure largely unknown. [14, 31-33] Due to the same reasons, commercial availability of approved standard implants for TFA only promoted its use. Furthermore, it is much easier to press-fit or insert a screw fixation implant in to a cylindrical cortical bone such as a femur as opposed to the reverse pyramid shaped cancellous bone of the proximal tibia[25]. It is very challenging to press fit an implant into cancellous bone and achieve immediate stability. The same principles apply to a screw fixation device.

With the establishment of safety of this procedure in literature, there is enough justification now for its use in individuals with TTA. Firstly, the prevalence of transtibial amputations is much higher than transfemoral amputations.[34, 35] Of these individuals using socket prostheses, 40% experience at least one skin problem, with the percentage substantially higher in individuals with TTA (TTA: 45.8%, TFA: 20%; OR: 4.1). Secondly, there is increased percentage of stump pain reported in patients with TTA.[8, 36]. Thirdly, suboptimal socket fit occurs in both individuals with TTA and with TFA (TTA: 59%, TFA: 78%)[37] and dissatisfaction with socket prostheses does not differ when comparing for level of amputation, with only 43% being satisfied with the comfort of their prosthesis.[38-40] These problems are inherently linked to intolerance of the prosthesis[12] and impact the ability of TTA to become independently mobile.[41]

Until recently, there is very little data assessing the protocol, techniques and results of Osseointegration in individuals with TTA. Only few papers with very small case series have been published with variable results.[25, 27, 42, 43]

The purpose of this paper is to describe the surgical technique of transtibial osseointegration, and formulate the protocol for a prospective study describing patient selection, surgical technique, rehabilitation, in order to report the clinical and functional outcomes and complications of the procedure in transtibial amputees.

Study objectives

The overall objective of this study is to assess the safety and efficacy of transtibial osseointegration procedure with at least 2 year follow-up and to compare the benefits and risks from pre-operative status and with the previously reported outcomes for transfemoral osseointegration. Specifically, this would involve:

1. Assessing the objective functional outcomes with the 6 Minute Walk Test (6MWT), Timed Up and Go (TUG) and K-levels, compared with preoperative data and with outcomes of TFA.
2. Assessing the subjective patient-reported quality-of-life outcomes with the Short Form Health Survey 36 (SF-36), compared with preoperative data and with outcomes of TFA.
3. Examining the prevalence of adverse events, including infection, revision surgery, fractures and implant failures, and compare with the adverse events after TFA.

Methods and analysis

The current prospective cohort study is designed to assess the safety and efficacy of Transtibial Osseointegration procedure with at least 2 years follow-up. Patients are evaluated by validated outcome measures preoperatively and postoperatively. Preliminary data has been obtained from an initial pilot study comprising 10 patients, which has been used to provide the sample size estimate for the current study. The outcomes of this study will be compared with those obtained using the previously for Transfemoral Osseointegration at the same follow-up time points.

Patient selection

Eligibility criteria

The inclusion criteria are age over 18 years, unilateral, bilateral, mixed transtibial amputation and experiencing socket-related problems or difficulties in using socket prostheses. Exclusion criteria included limb exposure to radiation, on-going chemotherapy, psychological instability, inability to comply with the rehabilitation program, residual tibia not suitable for osseointegration surgery and uncontrolled diabetes mellitus or peripheral vascular disease. All participants gave their informed consent. The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Patient screening and recruitment

Patients were either referred by general practitioners, rehabilitation physicians, specialists, prosthetists. All prospective patients were advised to complete an online form and were contacted over phone to carefully document their demography, medical and prosthetic history, issues with compliance, psychological and pain history and to understand their expectations. If the patients satisfied the inclusion criteria prima facie, they were invited to the multi-disciplinary clinic for evaluation. The clinic would usually comprise of specialist orthopaedic surgeons, orthopaedic fellows in training, rehabilitation specialist, prosthetists, psychologist, medical physician and nurse practitioner. Evaluation consisted of a screening interview, clinical and radiological examination to assess eligibility and recording of baseline values of outcome measures. Patients who were found to be suitable were counselled regarding the procedure, rehabilitation protocol and possible complications and enrolled for transtibial osseointegration surgery. The first patient who underwent the procedure was enrolled in April 2014. Enrolment is ongoing at the time of publication of this paper and is expected to be completed by April 2022 and expected to be more than 100 patients.

Study intervention

Preoperative management

All the patients were assessed with AP and lateral plain radiographs of the residuum to assess the bone quality and presence of any anomaly. Long leg standing radiographs were performed to assess the mechanical alignment of the lower limbs and to rule out pathologies in the contralateral limb. DEXA scans of the proximal femora and the spine to assess the bone mineral density which would help determine the speed of post-operative rehabilitation. Furthermore, CT scans of the residual bone was performed to plan for the type of implant and size that would be required.

All patients were assessed pre-operatively by the team physiotherapist was prescribed a training program for optimization of core strength, upper body strength, transfers, use of gait aids and loading.

Osseointegration Implant

Transtibial amputees are divided into two groups, the first being pre-existing amputation prior to osseointegration. For this group, the level of amputation is commonly at the metaphyseal level which is approximately one hand breadth below the tibial tubercle or around 10-14cm. For some patients, the amputation level is much higher. This group requires customization of implant considering the large variety of length, shape and diameter of the tibial residuum. The shorter the residuum the greater the complexity which is usually associated with a higher risk of failure.

The second group are the patients who require amputation where the surgeon has the luxury to control the level of amputation. Here, the ideal level of amputation is 25cm from the ground to allow enough clearance for prosthetic components. This will enable the implantation of a standard femoral implant of 160mm in length (Osseointegrated Prosthetic Limb (OPL, Permedica s.p.a., Milan, Italy) with excellent pressfit in the diaphysis of the tibial bone, similar to that of transfemoral implantation.

In our pilot project, we decided to choose the path of 3D printing with coarse surface structure and trialed several implant designs from CustoMed (South Africa), AQ implants (Germany), BresMedical (Australia) and also using a modified ILP/ESKA with a spongy metal surface. We also utilized a lesser rough surface coating with plasma spray for that cohort, every single one of which failed. Later down the track had two implant breakages of the 3D printed implant which made us more cautious of such implant design and technique especially in overweight males who are highly active. This resulted in the transition to machined implants with additive rough coating surface that give similar roughness of what a 3D implant can provide but much stronger core structure.

To summarise, the Transtibial Osseointegration implant used by us for, was designed by senior author (MAM) into mainly two types. For longer residuums with sufficient cortical bone, a standard titanium implant which was machine manufactured of 160mm length with plasma spraying on the surface was used (Figure 1). Alternatively, for short residuums with metaphyseal bone a custom-made short stem titanium implant with coarser surface structure was either machine manufactured or 3D printed. The surface of the implant is composed of a macroporous mesh-like structure allowing for bone ingrowth. Some implants contain longitudinal flanges for additional rotational stability. All implants are connected to a dual cone adapter with Morse-taper ends connecting the implant with the external prosthesis. The surface of the dual cone adapter is highly polished and coated with titanium-niobium oxide, an alloy known to have bacterial repellant properties[4], which also facilitates the excursion of the soft tissues and skin over it avoiding adhesions. A safety mechanism is built into the dual cone, with a safety pin that breaks to reduce the chance of periprosthetic fractures or implant breakage.

Surgical Technique

All patients received an osseointegrated implant in a single-stage surgery. Spinal and general anesthesia was used and 2grams of cephazolin was administered for infection prophylaxis. Patients were placed in supine position, side supports were applied, a padding bolster was placed under the hip and an uninflated tourniquet was applied to the affected leg. For disinfection alcoholic chlorhexidine was used, after which a disposable fenestrated extremity drape was applied.

At the level of the distal stump, a horizontal elliptical incision was made, the amount of soft tissue and muscle tissue was minimalized and all nerves were sharply severed and vessels were ligated or cauterized until hemostasis was achieved. The saphenous, tibial and common peroneal nerves were re-innervated to surrounding muscle branches if symptoms of nerve pain or excessive phantom pain existed pre-operatively (Figure 2). Alternatively,

the re-innervation of tibial and common peroneal nerves can be performed via a separate lateral distal thigh incision and posterior dissection.

Care was taken to preserve the periosteum at all times. If the distal end of the tibia needed to be re-cut, the periosteum was elevated and re-sutured to the end of the bone after using an oscillating saw for the distal tibia osteotomy. The fibula was usually cut 2-3 cm shorter than the tibia using the saw.

The intramedullary canal was prepared depending on the length of the residuum. If the amputation was at the diaphysisal level with good cortical bone distally then reaming up to 0.5 mm larger than the definite implant anticipated to be used after cortical chatter is heard (Figure 3) followed by sequential broaching up to the size of the desired implant (Figure 4). If the tibial stump was at the metaphyseal level with poor quality bone then no reaming was done and only impaction broaching was performed usually stopping at 2 mm smaller than the definite size of the implant. Both reaming and broaching is performed under image intensifier guidance to ensure accurate positioning in the centre of the tibia on the AP and lateral planes. Finally, the distal edge of the tibia was smoothened with use of a face-reamer (Figure 5).

Final implantation of the osseointegration intramedullary component was done using press-fit technique up to the subchondral bone of the proximal tibia (Figure 6). To stabilize the implant in shorter residual stumps, multiple locking screws were initially used, before it was abandoned due to increased risk of loosening and no added benefits.

Closure was initiated by suturing the fascia to the periosteum all around at the distal end of the tibial stump in a 'purse-string' fashion. The anterior and posterior soft tissue sleeves were refashioned to remove subcutaneous fat. A flap would be created-preferably anterior, to cover the end of the stump and to begin closure in layers. A sharp corer was used to make a stoma in the flap to communicate to the exact diameter of the implant, before progressing to close the rest of the wound in layers. Alternatively, the anterior and posterior flaps were closed around the implant in a 'fish-mouth' fashion (Figure 7). After this step, the dual cone component of the osseointegration device was inserted and secured with an internal locking screw, followed by fixing the taper sleeve and bushing to the dual cone using an external screw, all the time securing the implant to prevent rotation using a special device (Figure 8 and 9).

Postoperative Rehabilitation

Postoperative rehabilitation for transtibial osseointegration is carried out in two phases. Phase one is just after surgery and comprises of applying static axial load for twenty minutes twice per day. Loading commences on Day One, starting with 5kg and with progressive increments of 5kg per day for those with longer residuums and a standard 160mm implant and 5kg per week for those patients with shorter residuums that require customized

implants. The loading phase continues until either 50% of patient's body weight or 50 kg is reached. Phase two comprises of fitting the external prosthetic limb and performance core muscle strengthening, gait and balance exercises. By this point daily weight-bearing is initiated two weeks post-surgery for long residuums with sufficient cortical bone and by six weeks for short residuums.

Further Rehabilitation

Following the fitting of a prosthetic limb (Figure 10), patients are encouraged to weight-bear daily on their prosthesis using two crutches for six weeks and then one crutch on the opposite side for a further six weeks and then unaided thereafter. All this time home based physiotherapy to improve gait, balance, and negotiation of obstacles, slopes and staircase is continued.

Outcome

Demographics and functional outcomes

At baseline, data was obtained including patient characteristics; such as demographics, cause of amputation, age at amputation and previous medical history. Functional outcome measures and conventional radiographs were also taken at baseline as well as at 12, 24 and yearly follow-up thereafter. Functional outcomes comprised of 1) objective functional outcomes measuring 6 Minute Walk Test (6MWT)[44], Timed up and Go (TUG) [45] and K levels[46], 2) subjective patient-reported-outcome-measure Short-form 36 (SF-36)[47] and 3) prevalence of adverse events.

Adverse events

Adverse events were reported which included infection that required hospitalization for administration of intravenous antibiotics or surgical intervention, periprosthetic fracture, implant breakage, aseptic loosening, need for revision surgery or additional amputation and death. Severity of infections was assessed and graded into Al Muderis et al. classification system.[24] During the study, all patients would be contacted to ensure that all adverse events are recorded. Patients would also be asked whether, after their current experience with osseointegration, they would choose osseointegration again.

Data analysis

A p value of < 0.05 was considered to be significant in this study. Demographic and functional data were compared using IBM SPSS software, version 22 0 (IBM Corp., Armonk, New York, USA). Continuous variables would be summarized with mean and SE and the distribution of the data would be checked for normality using Kolmogorov-Smirnov Test. Variations in parameters due to demography would be tested for statistical significance using the Chi-square test. Depending on normality, parametric (like ANOVA) or non-parametric tests (like Wilcoxon test) would be used for comparison of functional scores pre and post-operatively. Fisher's exact test would be used to test significance of K-levels pre

and post-operatively. Correlation analysis would also done using the Spearman's test when ordinal and scale data were involved and Pearson's test when only scale data was involved. Cumulative implant survival would be assessed using a Kaplan-Meier Estimator.

Discussion

This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far. The findings of the study would not only underline the feasibility of osseointegration in terms of risks and benefits in transtibial amputees but also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations. As evidenced by literature, transtibial amputees using TSP suffer from same difficulties involving skin breakdown[8], suboptimal fit[48] and pain[4] as do the transfemoral ones, which ultimately affect their prosthetic use, mobility and overall quality of life. As the dramatically different concept of osseointegration proved life-changing in management of transfemoral amputees with established safety, it is only logical to extend the science to transtibial amputees and document the outcomes.

The clinical application of osseointegration was first seen in the field of dentistry[18], and as its efficacy was established, the concept was extended to transfemoral amputees more than two decades back.[20] The challenges posed by TSP were overcome by direct anchorage of the implant to the bone that enabled physiological weight bearing[16], increased flexibility and range of motion[49], sitting comfort[50], mechanoreception-based sensory feedback (osseoperception)[22], improved donning and doffing[23], better mobility[7] and improved prosthetic use[23], body image[48] and quality of life[23]. The safety of the implant was established in subsequent studies in terms of stability and risk of infection.[24]

Although largely unreported in literature so far, the further application of osseointegration to transtibial amputees has been done in pilot project by our group to suitable patients as well as some other surgeons worldwide. Prospective outcomes at 12 months of five patients with peripheral vascular disease who underwent transtibial osseointegration was published recently by Al Muderis et al.[42] Results showed that all the patients enrolled in the study were able to mobilize unaided at final follow-up. There was notable improvement of objective functional measures of 6MWT and TUG as well as subjective functional measures, while only two superficial infections were noted which resolved with conservative treatment and no implant loosening or other adverse event documented. However, two previous studies from Germany[25, 27] reporting on nine individuals with transtibial amputations treated with their custom cobalt chrome implants reported an explantation rate of 43% and rates of both septic and aseptic loosening of 22% each, though patient eligibility, rehabilitation and follow-up is unclear.

Recently, another study comprising of a small number of nine transtibial patients having a follow-up of only 12 months has been reported from The Netherlands.[43] The cohort was a mixed one with majority (31 patients) being transfemoral patients. Comparison of outcomes between transtibial and transfemoral osseointegrated patients revealed higher overall baseline values in transtibial patients except walking distance in daily life and prosthetic comfort. Improvement in the outcome measures was also greater in transtibial patients (except hip abductor strength and prosthesis wearing time), and at final follow-up lesser transtibial patients experienced stump pain as compared to transfemoral patients (transfemoral: 20/31 (65%), transtibial: 2/9 (22%)). Major adverse events related to implants was recorded as 8% which included both groups and included three dual-cone breakages and four bone fractures (due to fall), which were all managed successfully. However, a lower uneventful course was noted in transtibial patients (44%) compared to transfemoral ones (61%). The authors concluded that transtibial osseointegration was both efficacious and safe at 12 months follow-up. On a different note, the author's claim to be the first study reporting outcomes of transtibial osseointegration patients is obviously erroneous as there has been other studies including one from our group previously.[25, 27, 42]

Conclusion

The proposed study would comprise the largest cohort of Transtibial amputees undergoing Osseointegration with a substantial follow-up time. The clinical outcomes and adverse events noted in this study would help considerably to set the standard of care in transtibial amputee patients and provide directions of further research in terms of implant design, surgical technique, rehabilitation or management of complications.

AUTHORS' CONTRIBUTIONS

R Haque: Study design; patient care and surgical team; manuscript preparation.

S Al-Jawazneh: Data collection; patient care and surgical team

J Hoellwarth: Data collection; patient care and surgical team

M A Akhtar: Data collection; patient care and surgical team

K Doshi: Data collection; patient care and surgical team

Y Tan: Data collection, statistical evaluation

W. Lu: Data collection; manuscript preparation.

Claudia Roberts: Patient care; data collection; manuscript preparation.

M Al Muderis: Study design; patient care and surgical procedure; manuscript preparation.

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COMPETING INTERESTS STATEMENT

M. Al Muderis receives royalties for design contributions for the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a; Milan, Italy) implant system. All other authors listed in this study declare no competing interests.

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Figure 1: The Standard Implant for longer residuums. The parts include: 1, proximal cap screw. 2, Intramedullary body. 3, internal safety screw. 4, dual cone transcutaneous abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector.

176x412mm (72 x 72 DPI)

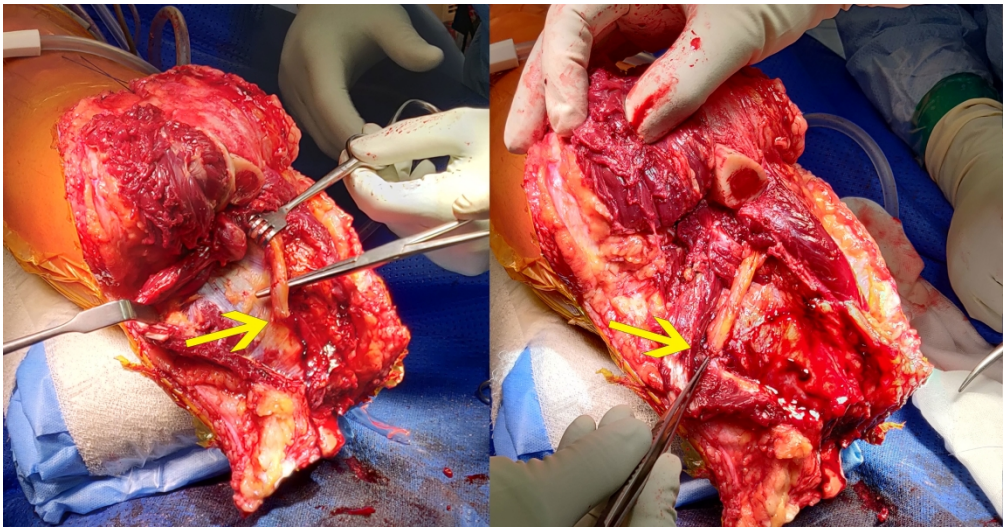

Figure 2: Targeted re-innervation of nerves (posterior tibial nerve highlighted) to surrounding muscular branches

1365x714mm (72 x 72 DPI)

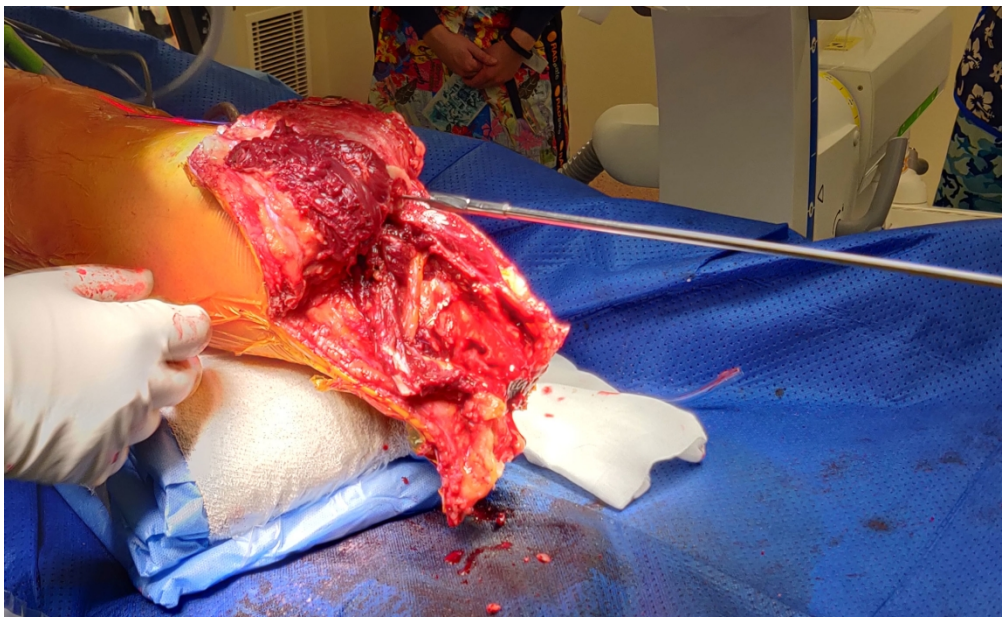

Figure 3: Reaming was done for longer residuums to 0.5 mm more than the diameter of implant expected to be used

817x499mm (72 x 72 DPI)

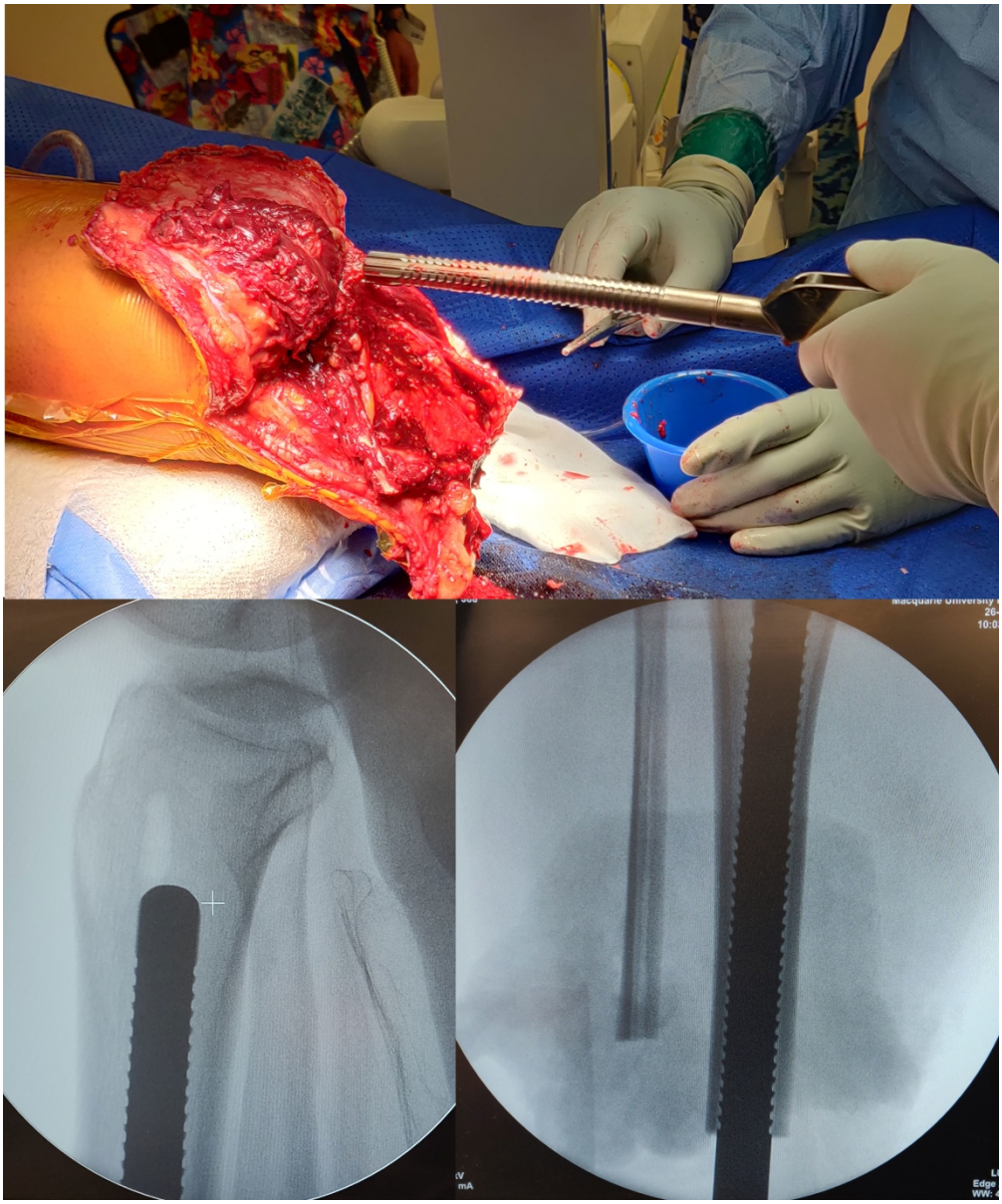

Figure 4: Broaching done under Image Intensifier guidance upto the desired size of implant for longer residuums

1365x1636mm (72 x 72 DPI)

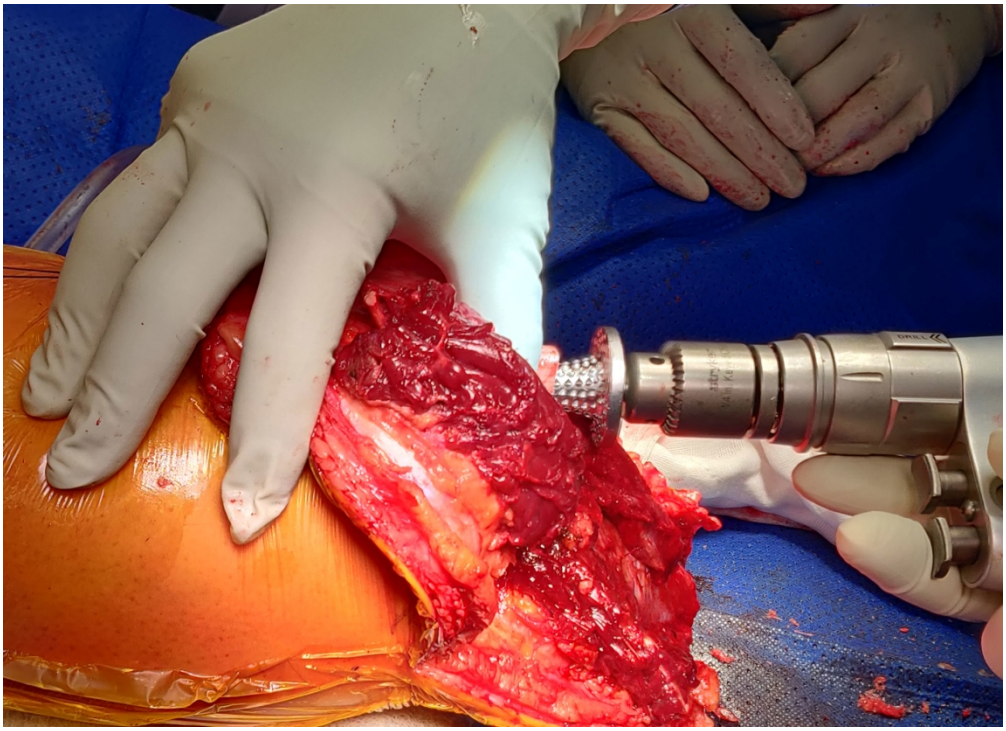

Figure 5: Face reaming done to smoothen the distal margins of the tibial stump

723x522mm (72 x 72 DPI)

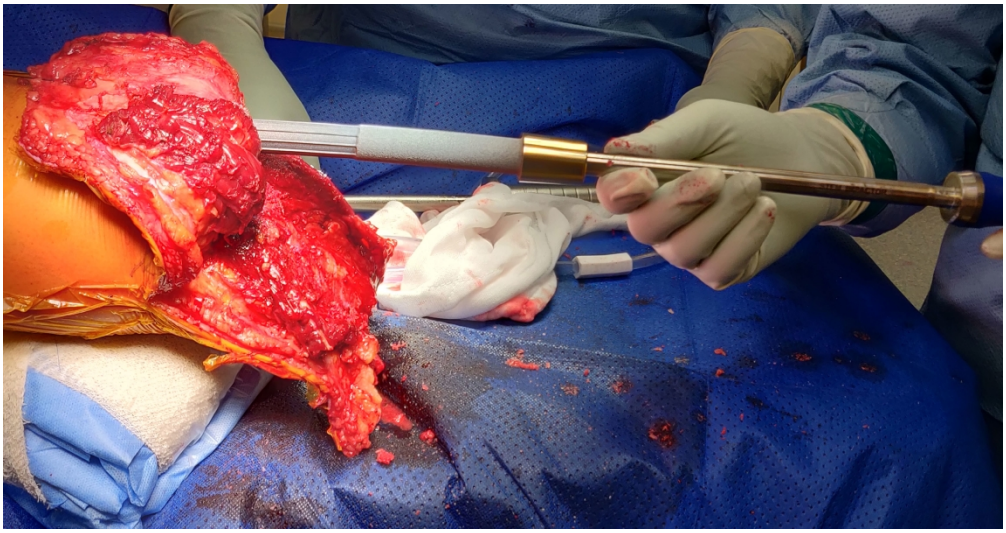

Figure 6: Final implantation of the definite intra-medullary component

1051x552mm (72 x 72 DPI)

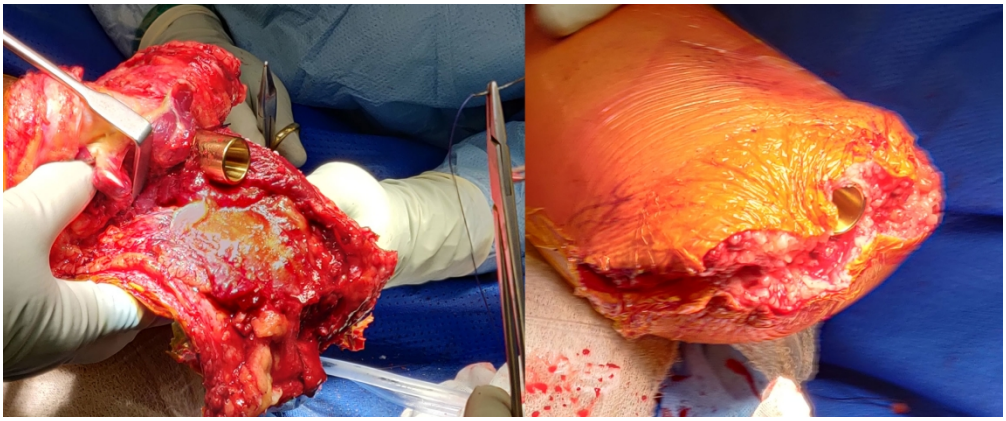

Figure 7: Closure of periosteum around the stump in a 'purse-string' fashion and the flaps around implant in 'fish-mouth' manner

867x357mm (72 x 72 DPI)

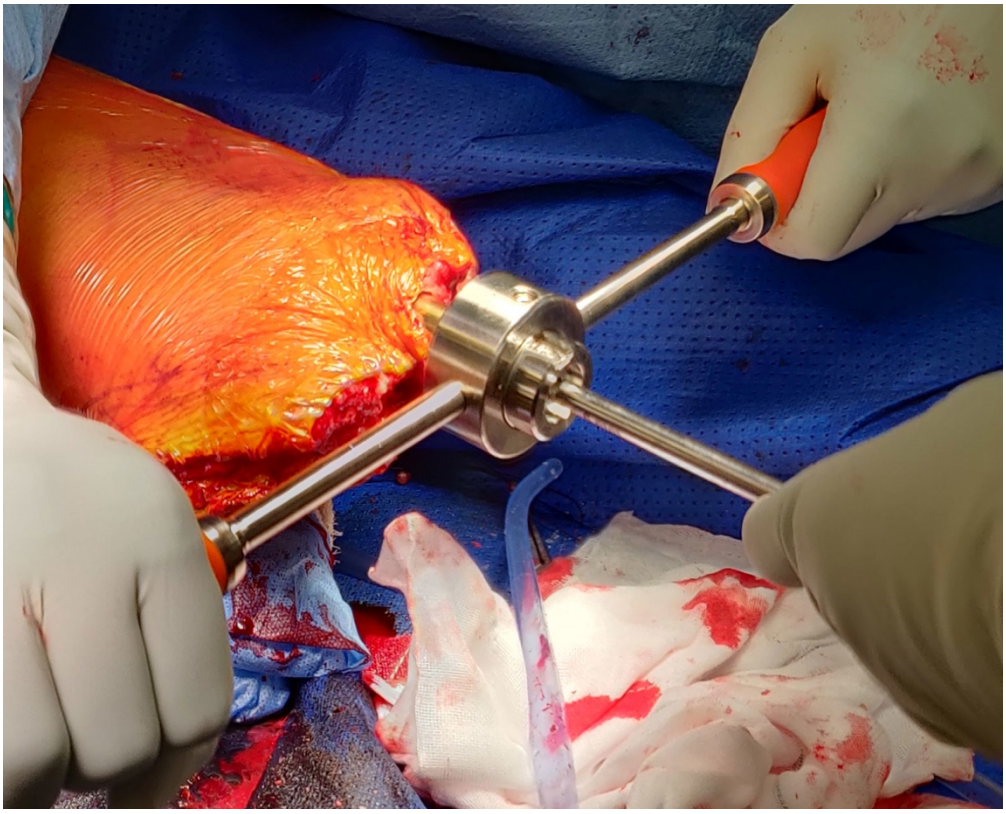

Figure 8: Attachment of extra-medullary components

552x444mm (72 x 72 DPI)

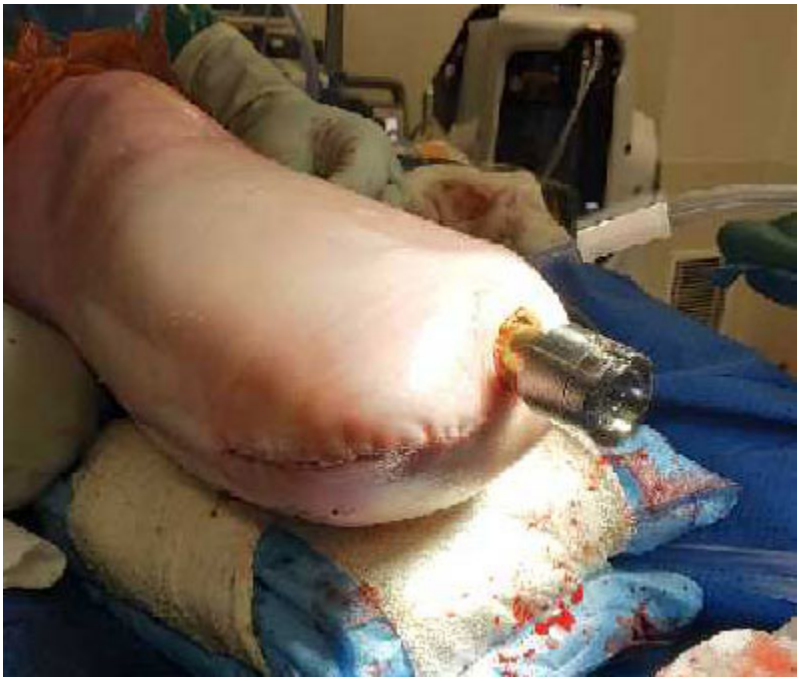

Figure 9: Final view of the closure of the stump

140x118mm (72 x 72 DPI)

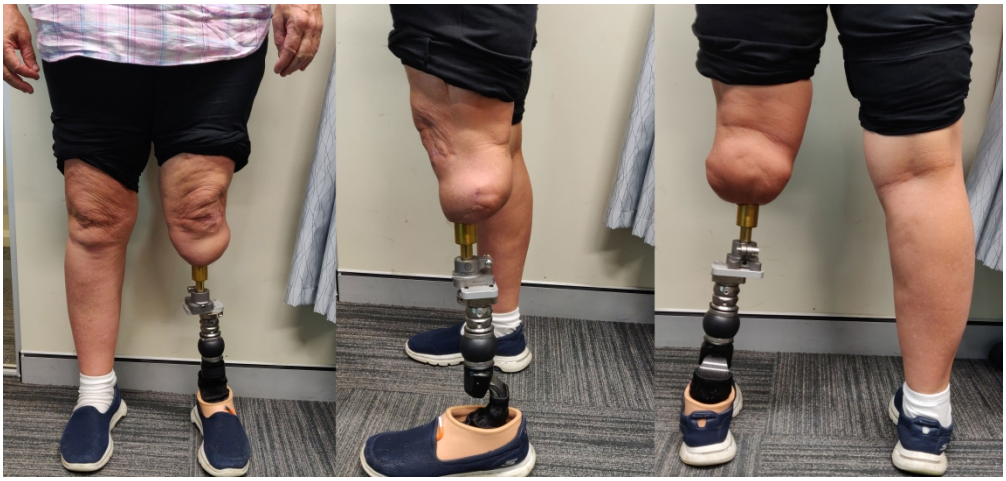

Figure 10: After fitting of prosthetic limb in a short residuum tibia

2417x1145mm (72 x 72 DPI)

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Osseointegrated Reconstruction and Rehabilitation of Transtibial Amputees: the Osseointegration Group of Australia surgical technique and protocol for a prospective cohort study

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Osseointegrated Reconstruction and Rehabilitation of Transtibial Amputees: the Osseointegration Group of Australia surgical technique and protocol for a prospective cohort study

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Abstract

Introduction

Lower extremity amputation uniformly impairs a person's vocational, social, and recreational capacity . Rehabilitation in Traditional Socket Prostheses (TSP) is associated with a spectrum of complications involving the socket-residuum interface which lead to reduced prosthetic use and quality of life. Osseointegration has recently emerged as a novel concept to overcome these complications by eliminating this interface and anchoring the prosthesis directly to bone. Though the complications of TSPs affect both transfemoral and transtibial amputees, Osseointegration has been predominantly performed in transfemoral ones assuming a greater benefit/risk ratio. However, as the safety of the procedure has been established, we intend to extend the concept to transtibial amputees and document the outcomes.

Methods and analysis

This is protocol for a prospective cohort study, with patient enrollment started in 2014 and expected to be completed by 2022.The inclusion criteria are age over 18 years, unilateral, bilateral and mixed transtibial amputation and experiencing socket-related problems. All patients receive Osseointegrated implants, the type of which depend on the length of the residuum and quality of bone, which are press-fitted into the residual bone. Objective functional outcomes comprising 6-minute walk test, Timed Up-and-Go test and K level,subjective patient-reported-quality-of-life outcomes(SF-36, daily prosthetic wear hours, prosthetic wear satisfaction) and adverse events are recorded preoperatively and at post-operative follow-up intervals of 3, 6 , 12 months and yearly, and compared to the pre-operative values using appropriate statistical tests. Multivariable multilevel logistic regression will be performed with a focus to identify factors associated with outcomes and adverse events, specifically infection, periprosthetic fracture, implant fracture, and aseptic loosening

Ethics and dissemination

The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). The outcomes of this study will be disseminated by publications in peer-reviewed academic journals and scientific presentations at relevant orthopaedic conferences.

Strengths and Limitations of the study

- This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far.

- The findings of the study would assess whether osseointegration in transtibial amputees is feasible in terms of risks and benefits and also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations.
- The data may also help provide a foundation for estimating societal impact of transtibial osseointegration, particularly the true economic impact as compared to traditional socket prostheses by indirect means.
- It does not have a control group and therefore comparison of outcomes of transtibial osseointegration directly with traditional socket prostheses used by transtibial amputees is not possible.
- The study has a follow-up period of minimum 2 years, which does not allow the examination of longer term outcomes and risk of adverse events as well as long term survivorship

Introduction

Amputation of a lower extremity not only causes changes in the anatomy and function of the limb but also almost inevitably results in major impairments of the person's vocational, social and recreational abilities and overall quality of life.[1] The focus of management of extremity amputations has evolved over time due to advancement of medical technology from prevention of mortality to overcoming these impairments and improving quality of life.[2] For centuries, the conventional way of rehabilitating such individuals has been via traditional socket mounted prostheses (TSP),[3] and despite significant technological innovations to both socket materials and design, there has been very little change to the overall prosthetic-residuum interface from a moulded compression cone to modern suction-based socket suspension.[4]

The use of TSP is associated with a spectrum of complications arising mainly out of the socket-residuum-interface that causes reduction in prosthesis use, ability to mobilize and quality of life.[1, 5-7] These include skin problems such as infections, and skin breakdown due to chronic irritation and thermal injury,[8-11] mechanical problems such as suboptimal fit, pain and pistoning[12] and problems with proprioception that leads to loss of balance and falling.[13] Gait with a TSP has been found to be asymmetrical correlating with a weakness in the hip abductor muscles, which can explain the back pain and pain in other regions experienced by such users including ipsilateral and contralateral limb, buttocks, neck and shoulder.[14]Socket prostheses users account for their poor quality of life mostly to physical disability, pain and decreased energy levels.[5, 15]

In order to overcome these complications, a significantly different concept has emerged over the past two decades, which circumvents the socket-residuum-interface completely by anchoring the prosthesis directly to the bone, popularly known as Osseointegration.[16] It involves insertion of porous metal implant in the medullary cavity of the bone in a screw or press-fit technique, over which compact cortical bone grows without any intervening soft

tissue in a short course of time, integrating the implant structurally and functionally to the bone.[17]

This integration of nonvital component into living bone was first discovered serendipitously in 1950s in rabbit models[4] and has been well established in the field of dentistry for the treatment of edentulous jaws for many years with a 10-year survival of dental implants in mandibular bone of 95%.[18-21] Since its first introduction in 1990s in individuals with amputations, osseointegration has been predominantly used for the treatment of individuals with transfemoral amputation demonstrating multiple potential advantages such as improved walking ability, daily prosthetic use, reduced energy consumption, sitting comfort and osseoperception.[7, 22, 23] This results in improved mobility and quality of life for individuals with amputations.[1, 7, 22, 24]

Over the last few years multiple studies have been published investigating the safety of this procedure, especially in individuals with transfemoral amputations, as incorporating a metal implant into the bone, whilst having an open connection with the outside environment can give rise to substantial concerns regarding the risk of ascending infection and concomitant implant loosening or sepsis.[25-31] Multiple studies reported that despite frequent colonization around the skin-implant interface, the implant system caused few infections leading to disability or implant removal (average 4%).[25-31] Most encountered complications were soft tissue infections or redundancy of soft tissue possibly influenced by learning curve and iteration of surgical technique and implant design.[25, 29]

Osseointegration has been predominantly used in transfemoral amputees (TFA) as compared to transtibial amputees (TTA), due to apparently greater benefit-risk ratio with the TFA being perceived to have more socket related problems and poorer mobility as compared to TTAs and the extent of risks or complications of the new procedure largely unknown. [15, 32-34] Due to the same reasons, commercial availability of approved standard implants for TFA only promoted its use. Furthermore, it is much easier to press-fit or insert a screw fixation implant in to a cylindrical cortical bone such as a femur as opposed to the reverse pyramid shaped cancellous bone of the proximal tibia[26]. It is very challenging to press fit an implant into cancellous bone and achieve immediate stability. The same principles apply to a screw fixation device.

With the establishment of safety of this procedure in literature, there is enough justification now for its use in individuals with TTA. Firstly, the prevalence of transtibial amputations is much higher than transfemoral amputations.[35, 36] Of these individuals using socket prostheses, 40% experience at least one skin problem, with the percentage substantially higher in individuals with TTA (TTA: 45.8%, TFA: 20%; OR: 4.1). Secondly, there is increased percentage of stump pain reported in patients with TTA.[8, 37]. Thirdly, suboptimal socket fit occurs in both individuals with TTA and with TFA (TTA: 59%, TFA: 78%)[38] and dissatisfaction with socket prostheses does not differ when comparing for level of amputation, with only 43% being satisfied with the comfort of their prosthesis.[39-41] These problems are inherently

linked to intolerance of the prosthesis[12] and impact the ability of TTA to become independently mobile.[42]

Until recently, there is very little data assessing the protocol, techniques and results of Osseointegration in individuals with TTA. Only few papers with very small case series have been published with variable results.[26, 28, 43, 44]

Study objectives

The overall objective of this study is to assess the safety and efficacy of transtibial osseointegration procedure with at least 2 year follow-up and to compare the benefits and risks from pre-operative status and with the previously reported outcomes for transfemoral osseointegration. Specifically, this would involve:

1. Assessing the objective functional outcomes with the 6 Minute Walk Test (6MWT) [45], Timed Up and Go (TUG) [46] and K-levels[47], compared with preoperative data and with outcomes of TFA.
2. Assessing the subjective patient-reported quality-of-life outcomes with the Short Form Health Survey 36 (SF-36)[48], Stump Pain, Daily prosthetic wear hours and Prothetic wear satisfaction compared with preoperative data and with outcomes of TFA.
3. Examining the prevalence of adverse events, including infection, revision surgery, fractures, aseptic loosening and implant failures, and compare with the adverse events after TFA.

One of the primary objectives of this study is to identify the individual patient characteristics or factors that have a positive or negative influence in the outcomes mentioned above. This analysis in a regression model would help to identify the patients based on their characteristics who would be most or least benefitted with this novel procedure and who would be at a higher or lower risk of failure.

The other question that is study will identify is the rate of additional surgical interventions as well as to identify factors associated with further surgery, specifically for infection, periprosthetic fracture, implant fracture, and aseptic loosening

Methods and analysis

This is a prospective cohort study which is designed to assess the safety and efficacy of Transtibial Osseointegration procedure with a minimum of 2 years (range 2-8 years) follow-up.

Preliminary data and clinical experience has been obtained from an initial pilot study comprising 10 patients owing to absence of prior literature. Software G* Power was used to calculate an a priori sample size. Considering SF-36 physical component score as primary outcome measure, the pre-operative and 2 year post-operative scores were recorded. Comparing the means (37.62 and 44.83) and SDs (11.8 and 19.5) of these 2 groups respectively using Wilcoxon test, the effect size was calculated to be 0.36 and sample size was calculated to be 87 assuming α error to be 0.05 and in order to achieve a Power of 95

%. Considering a drop-out rate of 20%, a final sample size of 109 was decided upon. None of the patients of the pilot study have been included in this study due to absence of standard protocol.

The first patient enrolled in the study was in April 2014. Enrolment is ongoing at the time of publication of this paper, with 68 patients already enrolled and is expected to be completed by April 2022. The number of patients treated each year has shown a steep rising trend with about 26 patients enrolled in the study last year.

Patient selection

Eligibility criteria

The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). All participants gave their informed consent. Inclusion and Exclusion criteria along-with rationale are listed in Table 1.

Table 1: Inclusion and Exclusion Criteria with Reason

Inclusion Criteria	
Criteria	**Reason**
Age at least 18 years	Legal self-consent
Current unilateral, bilateral or mixed transtibial amputees with significant dissatisfaction regarding prosthesis fit or pain, mobility, or skin breakdown	Objective, identifiable deficit in current patient lifestyle
Patients with a full lower limb but with pain, deformity, or weakness distal to the mid-tibia who desired amputation for pain management or improved mobility following removal of the deformed or weak joint and muscles.	Objective, identifiable quality of life impairment that can be objectively improved by amputation, and patients likely would experience better rehabilitation with osseointegration than standard socket prosthesis.
Patients with recent amputations who wished to try osseointegration instead of a traditional socket prosthesis.	Honoring patient choice
Patient with sufficient resources and willingness to pursue surgery, post-operative rehabilitation, and prosthesis procurement.	Rehabilitation and prosthesis fitting are all required for appropriate, safe improvement following osseointegration surgery.
Exclusion Criteria	
Criteria	**Reason**
Active infection any location	Unacceptably high and modifiable infection risk
Active malignancy or ongoing/planned treatment for malignancy at any location	High risk for infection, impaired biology for osseointegration, impaired patient stamina for rehabilitation

Skeletal immaturity	Unknown risk given the current knowledge of osseointegration outcomes and biological impact
Amputee with no mobility, socket, or skin problems	No expected immediate, and uncertain eventual, benefit from additional surgical intervention
Patients with psychiatric concern identified during pre-operative consultation with psychiatrist	Minimize risk of performing surgery for a patient whose expressed deficits are psychiatric-based instead of musculoskeletal-based, and thus unlikely to improve with surgery.
Patients considered too medically ill, too muscularly weak, or insufficiently dedicated to improve following osseointegration	Avoid harming patients with surgery that may be either unlikely to benefit them or possibly pose a health risk.
Insufficient remaining tibia length to accept an implant	Avoid performing surgery for a patient who would be unlikely to achieve successful bone ingrowth to the implant
Uncontrolled diabetes mellitus	Avoid unnecessary, modifiable risk for infection
Females currently or intending to become pregnant within the year following surgery	Unnecessary risk to fetus due to potential for falls or other unforeseen adverse events

Patient recruitment

Setting and Patient Screening

Our surgical practice is located in a private university hospital in a major urban city with full, modern medical capabilities. Local patient referral can occur via the usual routes for our practice: from the general practitioner or by self-referral. Non-local patients within the country and international patients can also contact our office, as is typical already, and are encouraged to provide information for pre-evaluation. All patients being referred for, or requesting, osseointegration are required to complete an online Patient Screening Form. Those patients fitting our Inclusion and Exclusion criteria are invited for in-person consultation. Patients who sustain acute traumatic injuries for which amputation is recommended can request osseointegration as primary management, either acutely or following the resolution of their acute injury.

Patient Enrolment

All patients who complete the online Patient Screening Form and fit the inclusion/exclusion criteria are evaluated in the multidisciplinary Limb Reconstruction Clinic. The typical medical team includes at least three orthopaedic surgeons with extensive limb reconstruction experience. Also in attendance are a prosthetist and physiotherapist, to ensure the patient's complaints are not suitably improved by prosthesis adjustment or therapy. Patients are also evaluated by our psychiatrist to ensure absence of psychiatric conditions that can affect

post-operative rehabilitation. For patients who have neuropathic pain or a history of narcotic or other pain-related medication use or abuse, a pain medicine consultation is required. All patients who elect for osseointegration are informed their care is provided at the best clinical judgment, but that they will be enrolled as part of a prospective and longitudinal study which aims to investigate the indications, evaluation of patients, surgical technique, rehabilitation strategies, management of adverse events, and long term outcomes of osseointegration patients. There is no arbitrary treatment based on assignment into a treatment category. Implant selection and exact surgical technique is expressly tailored to each patient.

The time between patient enrolment and surgery will vary. Patients who have a traumatic injury and have inpatient consultation may have osseointegration the next day. Healthy patients with streamlined financial coverage and who are able to attain psychiatric evaluation quickly could have surgery within a week of consultation. For patients who do not have appropriate insurance coverage, there is a waiting period for the most appropriate coverage level of one year; and during that waiting time would be recommended to participate in pre-habilitation exercises and have other perioperative optimization performed.

Potential Selection Bias

We believe the relatively broad Inclusion and Exclusion criteria allow a very broad cohort of patients who we believe are medically and cognitively safe for osseointegration to be treated. One possible bias, if any, will be low income patients. Osseointegration is a very expensive surgery and thus is not covered by the standard government insurance for our country. It is covered by more premium insurance plans. Thus we counsel patients to enroll in these top level insurance plans so that not only will the surgery itself be provided but any additional surgery for an adverse event will be covered, so long as they maintain their coverage. Patients who choose to pay out of pocket are also permitted to do so, but are extensively counselled that additional surgery for infection, fracture, or soft tissue management may be required, sometimes without time to plan ahead. Based on our country's population, we expect the vast majority of patients will be of Caucasian descent; we do not make any inclusion or exclusion decisions based on patient nationality, ethnic background or religion.

Study intervention

Preoperative management

All the patients are assessed with AP and lateral plain radiographs of the residuum to assess the bone quality and presence of any anomaly. Long leg standing radiographs are performed to assess the mechanical alignment of the lower limbs and to rule out pathologies in the contralateral limb. DEXA scans of the proximal femora and the spine to assess the bone mineral density which would help determine the speed of post-operative rehabilitation. Furthermore, CT scans of the residual bone are performed to plan for the type of implant and required size..

Osseointegration Implant

The Transtibial Osseointegration implant used by us for, was designed by senior author (MAM) into mainly two types. For longer residuums with sufficient cortical bone, a standard titanium implant which was machine manufactured of 160mm length with plasma spraying on the surface was used (Figure 1). Alternatively, for short residuums with metaphyseal bone a custom-made short stem titanium implant with coarser surface structure was either machine manufactured or 3D printed. The surface of the implant is composed of a macroporous mesh-like structure allowing for bone ingrowth. Some implants contain longitudinal flanges for additional rotational stability. All implants are connected to a dual cone adapter with Morse-taper ends connecting the implant with the external prosthesis. The surface of the dual cone adapter is highly polished and coated with titanium-niobium oxide, an alloy known to have bacterial repellant properties[4], which also facilitates the excursion of the soft tissues and skin over it avoiding adhesions. A safety mechanism is built into the dual cone, with a safety pin that breaks to reduce the chance of periprosthetic fractures or implant breakage.

Surgical Technique

All patients receive an osseointegrated implant in a single-stage surgery. At the level of the distal stump, a horizontal elliptical incision is made, the amount of soft tissue and muscle tissue is minimalized and all nerves are sharply severed and vessels are ligated or cauterized until hemostasis is achieved. The saphenous, tibial and common peroneal nerves are re-innervated to surrounding muscle branches if symptoms of nerve pain or excessive phantom pain existed pre-operatively (Figure 2). Alternatively, the re-innervation of tibial and common peroneal nerves can be performed via a separate lateral distal thigh incision and posterior dissection.

Care is taken to preserve the periosteum at all times. If the distal end of the tibia needs to be re-cut, the periosteum is elevated and re-sutured to the end of the bone after using an oscillating saw for the distal tibia osteotomy. The fibula is usually cut 2-3 cm shorter than the tibia using the saw.

The intramedullary canal is prepared depending on the length of the residuum. If the amputation is at the diaphysial level with good cortical bone distally then reaming up to 0.5 mm larger than the definite implant anticipated to be used after cortical chatter is heard (Figure 3) followed by sequential broaching up to the size of the desired implant (Figure 4). If the tibial stump is at the metaphyseal level with poor quality bone then no reaming is done and only impaction broaching is performed usually stopping at 2 mm smaller than the definite size of the implant. Both reaming and broaching is performed under image intensifier guidance to ensure accurate positioning in the centre of the tibia on the AP and lateral planes. Finally, the distal edge of the tibia is smoothened with use of a face-reamer (Figure 5).

Final implantation of the osseointegration intramedullary component is done using press-fit technique up to the subchondral bone of the proximal tibia (Figure 6). To stabilize the implant in shorter residual stumps, multiple locking screws were initially used, before it was abandoned due to increased risk of loosening and no added benefits.

Closure is initiated by suturing the fascia to the periosteum all around at the distal end of the tibial stump in a 'purse-string' fashion. This has not been described previously for tibias and is unique to our group. The anterior and posterior soft tissue sleeves are refashioned to remove subcutaneous fat. A flap is created-preferably anterior, to cover the end of the stump and to begin closure in layers. A sharp corer is used to make a stoma in the flap to communicate to the exact diameter of the implant, before progressing to close the rest of the wound in layers. Alternatively, the anterior and posterior flaps are closed around the implant in a 'fish-mouth' fashion (Figure 7). After this step, the dual cone component of the osseointegration device is inserted and secured with an internal locking screw, followed by fixing the taper sleeve and bushing to the dual cone using an external screw, all the time securing the implant to prevent rotation using a special device (Figure 8 and 9).

Postoperative Rehabilitation

The rehabilitation for transtibial osseointegration is carried out in phases and described in details in Figure 10 and 11.The adherence to the rehabilitation protocol is recorded in the database by the physiotherapist. Following the fitting of a prosthetic limb (Figure 12), patients are encouraged to weight-bear daily on their prosthesis using two crutches for six weeks and then one crutch on the opposite side for a further six weeks and then unaided thereafter

Outcome

Data sampling

Data sampling is done at baseline pre-operatively and post-operatively at 3, 6 and 12 months and yearly follow-ups thereafter. It is done by dedicated research assistants who are unaware of the details of patients' demographic characteristics, surgical and implant details and previous scores to reduce the risk of any bias. Clinical information from surgery and follow-ups are added to the database by the operating or reviewing surgeon. Data that is sampled including the time points of measurement are tabulated in Table 2.

Table 2: Data Sampling Table showing the parameters sampled and time points of measurement

Parameter Sampled	Details	Time point of measurement
Name		T0
Date of Birth		T0
Address		T0

Phone number/Email		T0
Gender		T0
Height		T0
Weight		T0
Military	Yes/No	T0
Athlete	Yes/No	T0
Race		T0
Education Level		T0
Employment status before OI surgery		T0
Type of occupation before OI surgery		T0
Age at 1st Surgery		T0
Date of 1st Surgery		T0
Any Further surgeries	Yes/No. Dates of further surgeries if Yes	When it occurs
Side		T0
Bilateral	Yes/No	T0
Mixed	Yes/No	T0
Same Day Amputation and OI	Yes/No	T0/TS
Cause of Amputation	Each cause assigned a number	T0
Date of amputation		T0
Co-Morbidities	Each cause assigned a number	T0
Psychiatric evaluation before surgery	Yes/No	T0
Depression	Yes/No	T0
Alcohol >3/day	Yes/No	T0
TMR at index surgery	Yes/No	T0
Reasons for Osseointegration	Fit Problems/ Skin Problems/ Painful prosthesis/Prosthetic Mobility Dissatisfaction/ Other Pain/ Other causes. Each cause assigned a number	T0
Implant Details	Implant Brand, Type, Manufacture method, Collared/Flared, Width, Length	TS
Retention of Hardware	None/Cable/Screw/Both	
Implant Removal		When it occurs
Reason for removal		When it occurs
Years to Fail		When it occurs
Re-implant date		When it occurs
Further surgeries details	Washouts/Neurectomy/Refashioning/ Periprosthetic Fractures/Other Surgeries details	When it occurs
Antibiotics administration	Intravenous/ Oral. Details	When it occurs
Other Adverse events		When it occurs
Length of Residuum		T0
Length after OI		TS
Pre-Op Weight Bearing status		T0
Pre-Op K Level		T0
Pre-Op Walking Aid		T0
Pre-Op 6 Minute Walk Test		T0
Pre-Op Timed Up-and-Go Test		T0
Pre-Op SF-36 (PCS)		T0

Pre-Op SF-36 (MCS)		T0
Pre-op Subjective	Functional Level and Problems. "How would you summarise your level of function with your current prosthesis?"	T0
Pre-Op Stump Pain (VAS)		T0
Daily Prosthetic Wear Hours		T0
Prosthetic Wear Satisfaction		T0
Adherence to Rehabilitation Protocol	Yes/No	TR
Post-Op Weight Bearing status		T1, T2, T3, T4…
Post-Op K Level		T1, T2, T3, T4…
Post-Op Walking Aid		T1, T2, T3, T4…
Post-Op 6 Minute Walk Test		T1, T2, T3, T4…
Post-Op Timed Up-and-Go Test		T1, T2, T3, T4…
Post-Op SF-36 (PCS)		T1, T2, T3, T4…
Post-Op SF-36 (MCS)		T1, T2, T3, T4…
Post-op Subjective	Functional Level and Problems. "How would you summarise your level of function with your current prosthesis?"	T1, T2, T3, T4…
Post-Op Stump Pain (VAS)		T1, T2, T3, T4…
Daily Prosthetic Wear Hours		T1, T2, T3, T4…
Prosthetic Wear Satisfaction		T1, T2, T3, T4…
T0: Pre-operative, TS: At Surgery, TR: During Rehabilitation, T1: 3 months, T2: 6 months, T3: 1 year, T4: 2 years and so on		

Adverse events

Adverse events are reported which includes infection that require administration of intravenous or oral antibiotics or surgical intervention, periprosthetic fracture, implant breakage, aseptic loosening, need for revision surgery or additional amputation and death. Severity of infections are assessed and graded into Al Muderis et al. classification system.[25].

Data analysis

The primary questions this study aim to identify are 1. the individual patient characteristics or factors that have a positive or negative influence in the outcomes measured or in other words who would be most or least benefitted with this novel procedure and who would be at a higher or lower risk of failure? and 2. what are the rates of additional intervention for patients undergoing transtibial osseointegration, and for what reasons? This project will also aim to collect data which can allow investigation of diverse questions regarding transtibial osseointegration as further insight develops.

Multivariable logistic regression will be performed with a focus to identify factors associated with further surgery, specifically for infection, periprosthetic fracture, implant fracture, and aseptic loosening. Additionally, factors associated with Daily prosthesis wear hours, Prosthetic wear satisfaction, SF-36 and mobility (6MWT, TUG, K level) will be evaluated.

Separate regression models will be developed for short and long residuum TTOIs as well. A p value of 0.05 will be the cutoff of significance. The p value for each regression identifying significant predictors of dependent variable outcome will be reported, as will the coefficients of relative influence of each variable.

The pre- versus post-operative continuous value data will be presented as mean and standard deviation and compared with Student's T-test or analysis of variance (ANOVA) if the data is normally distributed. Should the data not be normally distributed the median and interquartile ranges will be reported and comparison made using Wilcoxon test.

For comparison of qualitative variables such as gender, laterality, or reason for amputation, frequency comparison will be performed using Chi-squared test or Fisher's Exact test, depending on the actual occurrence of each variable. P=0.05 will be considered statistically significant.

Reducing risk of bias

In addition to reducing the risk of selection bias as described above, bias relating to surgeon expertise and protocol adherence is eliminated since all operations will be performed by a single primary surgeon. Bias related to data collection will be minimized by employing dedicated research assistants who will be unaware about details of patient demographic characteristics, surgical and implant details and previous recorded scores. Further, the results of functional outcome measures (6MWT, TUG, K-levels) depend on the patients' actual performance, while the results of subjective outcome measures are completely patient reported from surveys. In addition, the assessors will not be involved in data analysis.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and Dissemination

All patients included in this study will sign a consent form that provides sufficient information about the study for patients to make an informed decision about their participation. Outcomes of the current study will be disseminated by publications in peer-reviewed academic journals and presentations at relevant orthopaedic conferences.

Discussion

This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far. The findings of the study would assess whether osseointegration in transtibial amputees is feasible in terms of risks and benefits

and also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations. As evidenced by literature, transtibial amputees using TSP suffer from same difficulties involving skin breakdown[8], suboptimal fit[49] and pain[4] as do the transfemoral ones, which ultimately affect their prosthetic use, mobility and overall quality of life. As the dramatically different concept of osseointegration proved life-changing in management of transfemoral amputees with established safety, it is only logical to extend the science to transtibial amputees and document the outcomes.

The challenges posed by TSP were overcome by direct anchorage of the implant to the bone that enabled physiological weight bearing[17], increased flexibility and range of motion[50], sitting comfort[51], mechanoreception-based sensory feedback (osseoperception)[23], improved donning and doffing[24], better mobility[7] and improved prosthetic use[24], body image[49] and quality of life[24]. The safety of the implant was established in subsequent studies in terms of stability and risk of infection.[25]

Although largely unreported in literature so far, the further application of osseointegration to transtibial amputees has been done in pilot project by our group to suitable patients as well as some other surgeons worldwide. Prospective outcomes at 12 months of five patients with peripheral vascular disease who underwent transtibial osseointegration was published recently by Al Muderis et al.[43] Results showed that all the patients enrolled in the study were able to mobilize unaided at final follow-up. There was notable improvement of objective functional measures of 6MWT and TUG as well as subjective functional measures, while only two superficial infections were noted which resolved with conservative treatment and no implant loosening or other adverse event documented. However, two previous studies from Germany[26, 28] reporting on nine individuals with transtibial amputations treated with their custom cobalt chrome implants reported an explantation rate of 43% and rates of both septic and aseptic loosening of 22% each, though patient eligibility, rehabilitation and follow-up is unclear.

Recently, another study comprising of a small number of nine transtibial patients having a follow-up of only 12 months has been reported from The Netherlands.[44] The cohort was a mixed one with majority (31 patients) being transfemoral patients. Comparison of outcomes between transtibial and transfemoral osseointegrated patients revealed higher overall baseline values in transtibial patients except walking distance in daily life and prosthetic comfort. Improvement in the outcome measures was also greater in transtibial patients (except hip abductor strength and prosthesis wearing time), and at final follow-up lesser transtibial patients experienced stump pain as compared to transfemoral patients (transfemoral: 20/31 (65%), transtibial: 2/9 (22%)). Major adverse events related to implants was recorded as 8% which included both groups and included three dual-cone breakages and four bone fractures (due to fall), which were all managed successfully. However, a lower uneventful course was noted in transtibial patients (44%) compared to

transfemoral ones (61%). The authors concluded that transtibial osseointegration was both efficacious and safe at 12 months follow-up

Thus, the proposed study would comprise the largest cohort of Transtibial amputees undergoing Osseointegration with a substantial follow-up time. The clinical outcomes, adverse events, and their associations noted in this study would help considerably to set the standard of care in transtibial amputee patients and provide directions of further research in terms of implant design, surgical technique, rehabilitation or management of complications.

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Figure Captions

Figure 1: The Standard Implant for longer residuums. The parts include: 1, proximal cap screw. 2, Intramedullary body. 3, internal safety screw. 4, dual cone transcutaneous abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector.

Figure 2: Targeted re-innervation of nerves (posterior tibial nerve highlighted) to surrounding muscular branches

Figure 3: Reaming was done for longer residuums to 0.5 mm more than the diameter of implant expected to be used

Figure 4: Broaching done under Image Intensifier guidance upto the desired size of implant for longer residuums

Figure 5: Face reaming done to smoothen the distal margins of the tibial stump

Figure 6: Final implantation of the definite intra-medullary component

Figure 7: Closure of periosteum around the stump in a 'purse-string' fashion and the flaps around implant in 'fish-mouth' manner.

Figure 8: Attachment of extra-medullary components

Figure 9: Final view of the closure of the stump

Figure 10: Transtibial Osseointegration Rehabilitation Protocol

Figure 11: Transtibial Osseointegration Physiotherapy Protocol

Figure 12: After fitting of prosthetic limb in a short residuum tibia

AUTHORS' CONTRIBUTIONS

R Haque: Study design; patient care and surgical team; manuscript preparation.
S Al-Jawazneh: Data collection; patient care and surgical team
J Hoellwarth: Data collection; patient care and surgical team
M A Akhtar: Data collection; patient care and surgical team
K Doshi: Data collection; patient care and surgical team
Y Tan: Data collection, statistical evaluation
W. Lu: Data collection; manuscript preparation.
C Roberts: Patient care; data collection; manuscript preparation.
M Al Muderis: Study design; patient care and surgical procedure; manuscript preparation.

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Bridget Dean: For formulating Transtibial Rehabilitation and Physiotherapy Protocol

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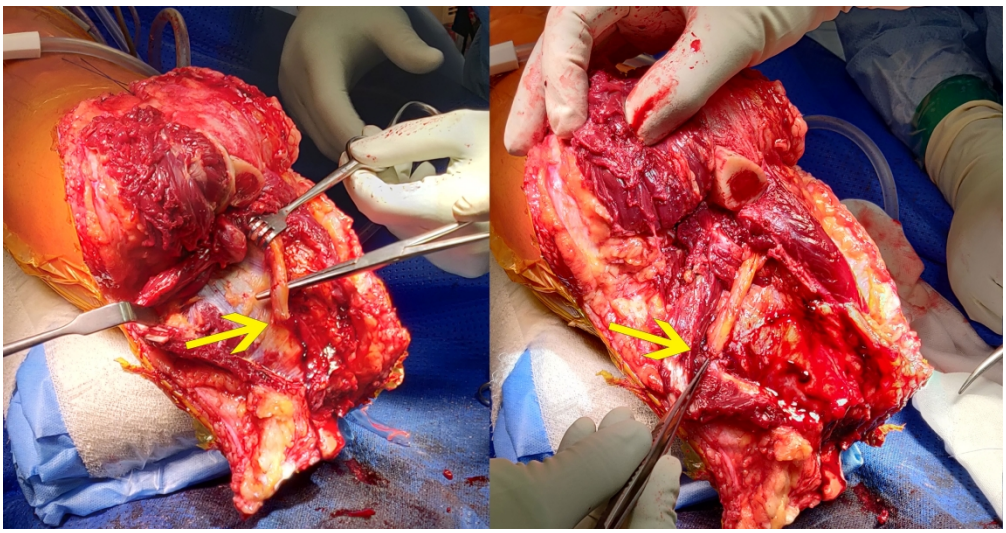
COMPETING INTERESTS STATEMENT

M. Al Muderis receives royalties for design contributions for the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a; Milan, Italy) implant system. All other authors listed in this study declare no competing interests.

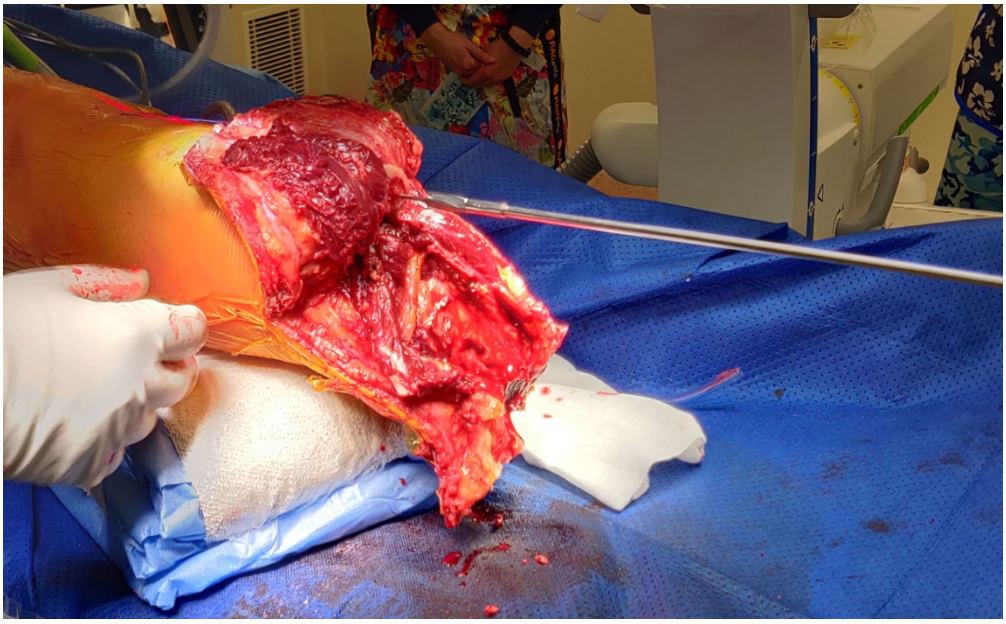
The Standard Implant for longer residuums. The parts include: 1, proximal cap screw. 2, Intramedullary body. 3, internal safety screw. 4, dual cone transcutaneous abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector.

21x49mm (300 x 300 DPI)



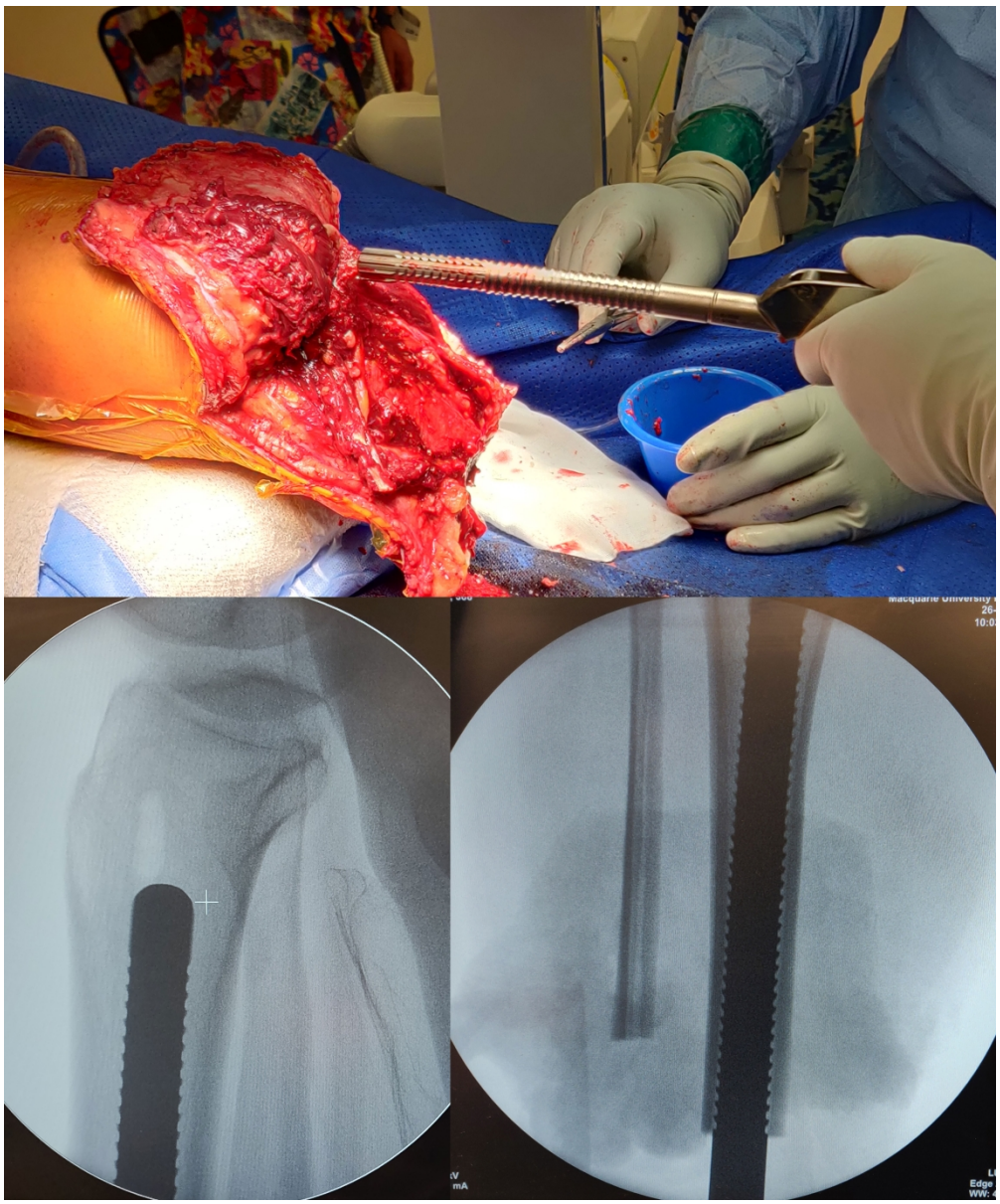
Targeted re-innervation of nerves (posterior tibial nerve highlighted) to surrounding muscular branches

327x171mm (300 x 300 DPI)



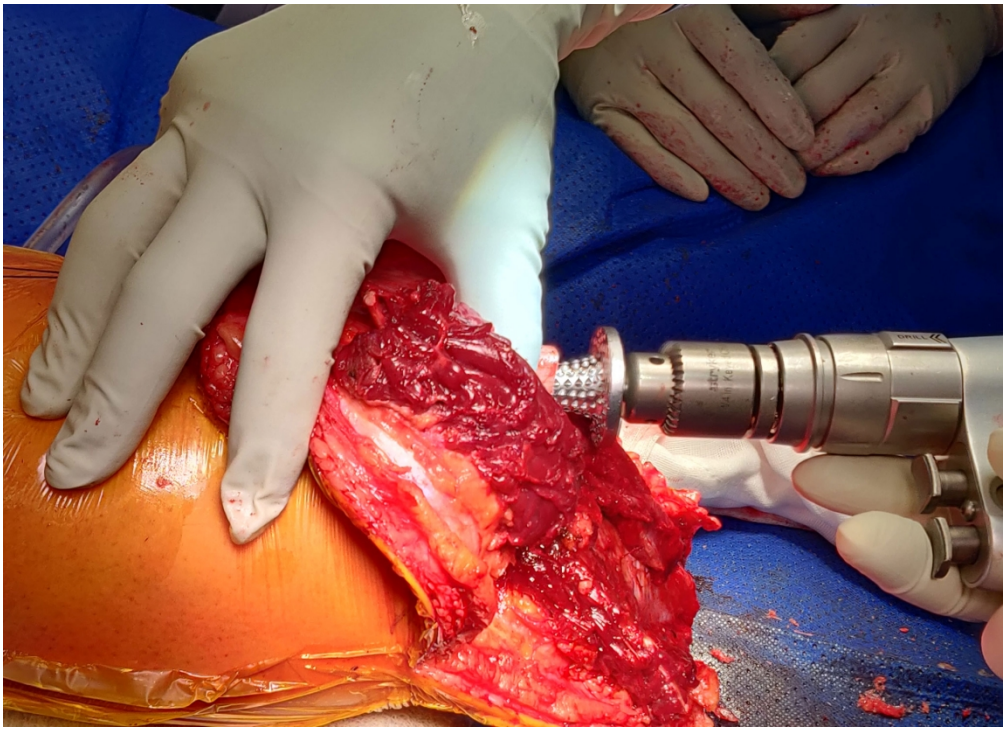
Reaming was done for longer residuums to 0.5 mm more than the diameter of implant expected to be used

195x119mm (300 x 300 DPI)



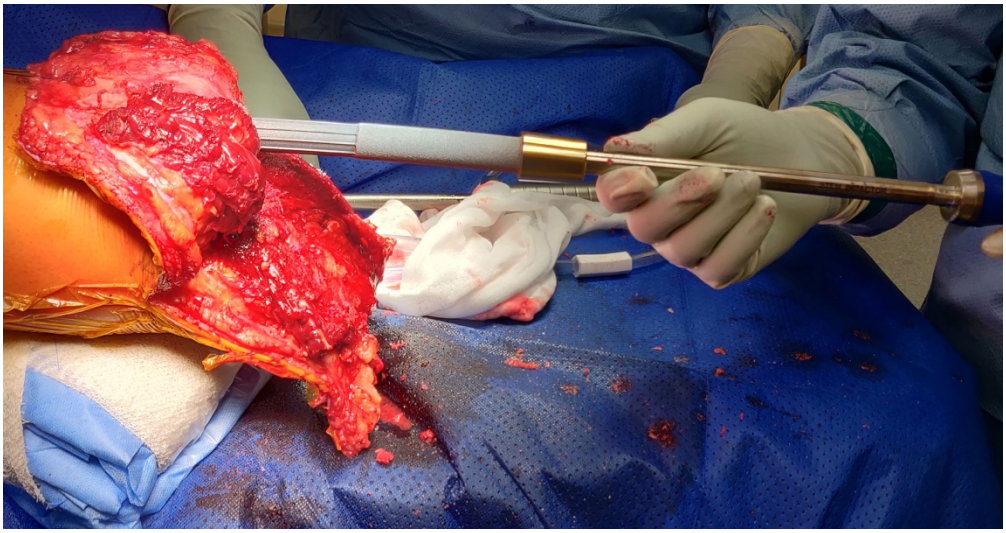
Broaching done under Image Intensifier guidance upto the desired size of implant for longer residuums

325x390mm (300 x 300 DPI)



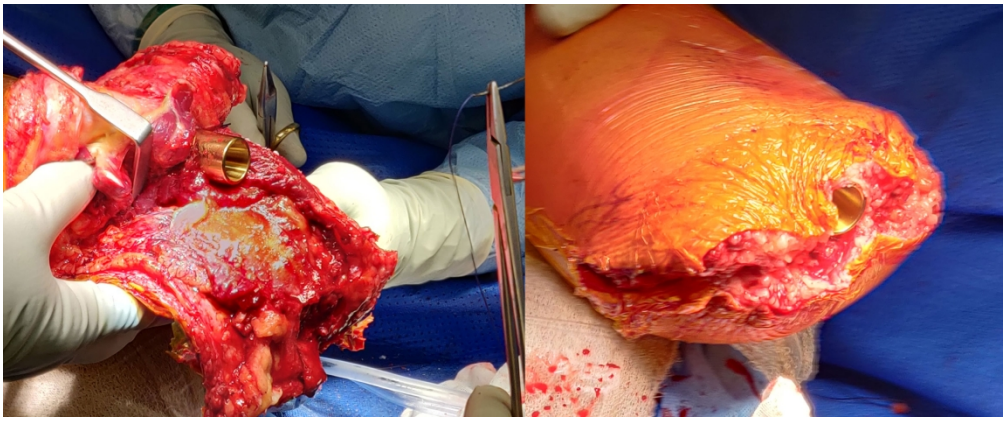
Face reaming done to smoothen the distal margins of the tibial stump

173x125mm (300 x 300 DPI)



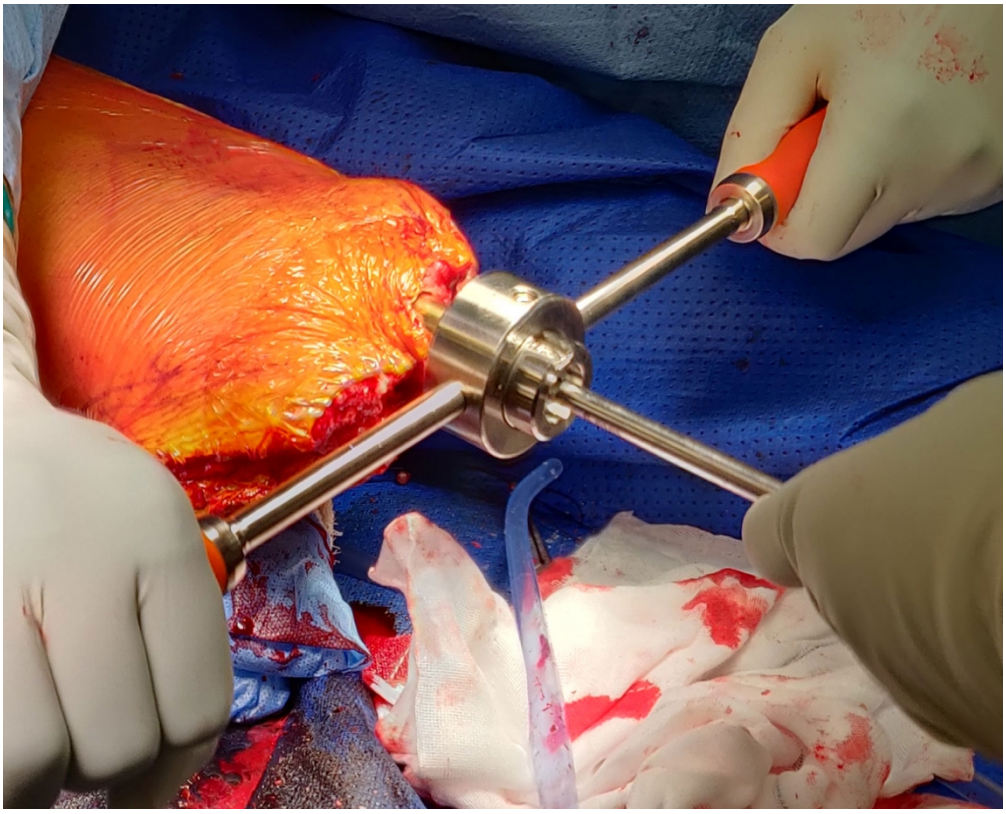
Final implantation of the definite intra-medullary component

252x132mm (300 x 300 DPI)



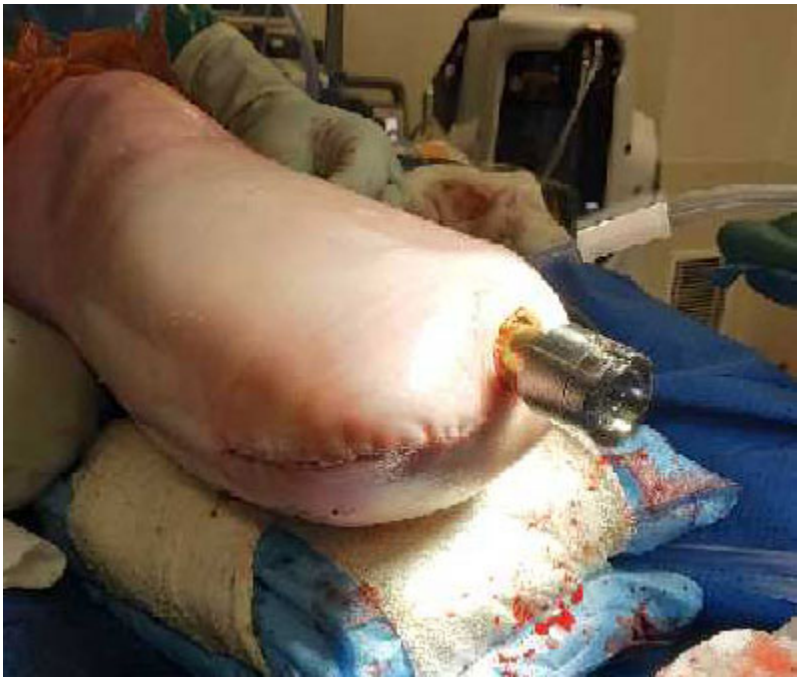
Closure of periosteum around the stump in a ‘purse-string’ fashion and the flaps around implant in ‘fish-mouth’ manner

208x85mm (300 x 300 DPI)



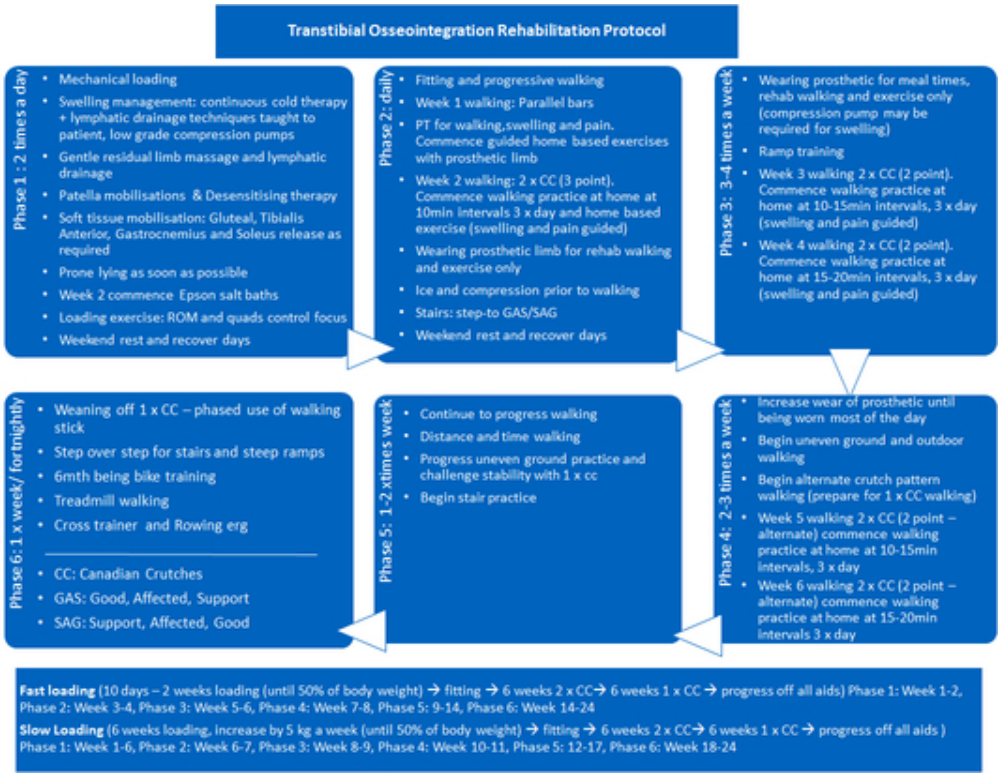
Attachment of extra-medullary components

132x106mm (300 x 300 DPI)



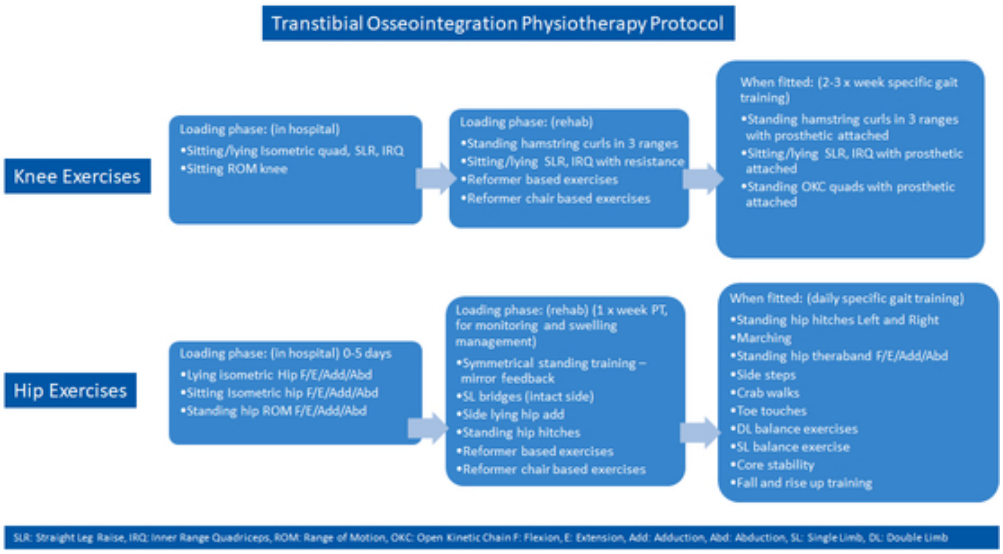
Final view of the closure of the stump

33x28mm (300 x 300 DPI)



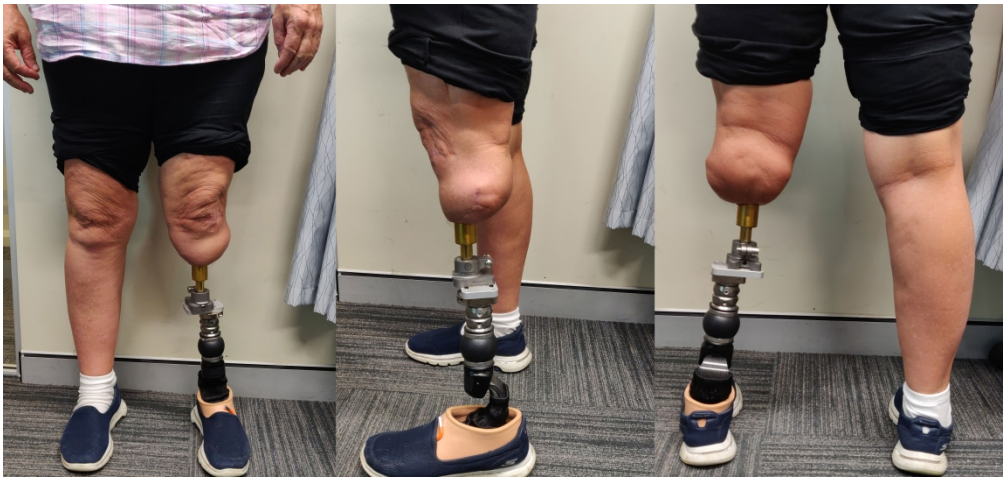
Transtibial Osseointegration Rehabilitation Protocol

45x34mm (300 x 300 DPI)



Transtibial Osseointegration Physiotherapy Protocol

47x25mm (300 x 300 DPI)



After fitting of prosthetic limb in a short residuum tibia

580x274mm (300 x 300 DPI)

BMJ Open

Osseointegrated Reconstruction and Rehabilitation of Transtibial Amputees: the Osseointegration Group of Australia surgical technique and protocol for a prospective cohort study

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Osseointegrated Reconstruction and Rehabilitation of Transtibial Amputees: the Osseointegration Group of Australia surgical technique and protocol for a prospective cohort study

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Keywords: Osseointegration; Lower limb amputees; Transtibial

Abstract

Introduction

Lower extremity amputation uniformly impairs a person's vocational, social, and recreational capacity . Rehabilitation in Traditional Socket Prostheses (TSP) is associated with a spectrum of complications involving the socket-residuum interface which lead to reduced prosthetic use and quality of life. Osseointegration has recently emerged as a novel concept to overcome these complications by eliminating this interface and anchoring the prosthesis directly to bone. Though the complications of TSPs affect both transfemoral and transtibial amputees, Osseointegration has been predominantly performed in transfemoral ones assuming a greater benefit/risk ratio. However, as the safety of the procedure has been established, we intend to extend the concept to transtibial amputees and document the outcomes.

Methods and analysis

This is protocol for a prospective cohort study, with patient enrollment started in 2014 and expected to be completed by 2022.The inclusion criteria are age over 18 years, unilateral, bilateral and mixed transtibial amputation and experiencing socket-related problems. All patients receive Osseointegrated implants, the type of which depend on the length of the residuum and quality of bone, which are press-fitted into the residual bone. Objective functional outcomes comprising 6-minute walk test, Timed Up-and-Go test and K level,subjective patient-reported-quality-of-life outcomes(SF-36, daily prosthetic wear hours, prosthetic wear satisfaction) and adverse events are recorded preoperatively and at post-operative follow-up intervals of 3, 6 , 12 months and yearly, and compared to the pre-operative values using appropriate statistical tests. Multivariable multilevel logistic regression will be performed with a focus to identify factors associated with outcomes and adverse events, specifically infection, periprosthetic fracture, implant fracture, and aseptic loosening

Ethics and dissemination

The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). The outcomes of this study will be disseminated by publications in peer-reviewed academic journals and scientific presentations at relevant orthopaedic conferences.

Strengths and Limitations of the study

- This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far.

- The findings of the study would assess whether osseointegration in transtibial amputees is feasible in terms of risks and benefits and also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations.
- The data may also help provide a foundation for estimating societal impact of transtibial osseointegration, particularly the true economic impact as compared to traditional socket prostheses by indirect means.
- It does not have a control group and therefore comparison of outcomes of transtibial osseointegration directly with traditional socket prostheses used by transtibial amputees is not possible.
- The study has a follow-up period of minimum 2 years, which does not allow the examination of longer term outcomes and risk of adverse events as well as long term survivorship

Introduction

Amputation of a lower extremity not only causes changes in the anatomy and function of the limb but also almost inevitably results in major impairments of the person's vocational, social and recreational abilities and overall quality of life.[1] The focus of management of extremity amputations has evolved over time due to advancement of medical technology from prevention of mortality to overcoming these impairments and improving quality of life.[2] For centuries, the conventional way of rehabilitating such individuals has been via traditional socket mounted prostheses (TSP),[3] and despite significant technological innovations to both socket materials and design, there has been very little change to the overall prosthetic-residuum interface from a moulded compression cone to modern suction-based socket suspension.[4]

The use of TSP is associated with a spectrum of complications arising mainly out of the socket-residuum-interface that causes reduction in prosthesis use, ability to mobilize and quality of life.[1, 5-7] These include skin problems such as infections, and skin breakdown due to chronic irritation and thermal injury,[8-11] mechanical problems such as suboptimal fit, pain and pistoning[12] and problems with proprioception that leads to loss of balance and falling.[13] Gait with a TSP has been found to be asymmetrical correlating with a weakness in the hip abductor muscles, which can explain the back pain and pain in other regions experienced by such users including ipsilateral and contralateral limb, buttocks, neck and shoulder.[14]Socket prostheses users account for their poor quality of life mostly to physical disability, pain and decreased energy levels.[5, 15]

In order to overcome these complications, a significantly different concept has emerged over the past two decades, which circumvents the socket-residuum-interface completely by anchoring the prosthesis directly to the bone, popularly known as Osseointegration.[16] It involves insertion of porous metal implant in the medullary cavity of the bone in a screw or press-fit technique, over which compact cortical bone grows without any intervening soft

tissue in a short course of time, integrating the implant structurally and functionally to the bone.[17]

This integration of nonvital component into living bone was first discovered serendipitously in 1950s in rabbit models[4] and has been well established in the field of dentistry for the treatment of edentulous jaws for many years with a 10-year survival of dental implants in mandibular bone of 95%.[18-21] Since its first introduction in 1990s in individuals with amputations, osseointegration has been predominantly used for the treatment of individuals with transfemoral amputation demonstrating multiple potential advantages such as improved walking ability, daily prosthetic use, reduced energy consumption, sitting comfort and osseoperception.[7, 22, 23] This results in improved mobility and quality of life for individuals with amputations.[1, 7, 22, 24]

Over the last few years multiple studies have been published investigating the safety of this procedure, especially in individuals with transfemoral amputations, as incorporating a metal implant into the bone, whilst having an open connection with the outside environment can give rise to substantial concerns regarding the risk of ascending infection and concomitant implant loosening or sepsis.[25-31] Multiple studies reported that despite frequent colonization around the skin-implant interface, the implant system caused few infections leading to disability or implant removal (average 4%).[25-31] Most encountered complications were soft tissue infections or redundancy of soft tissue possibly influenced by learning curve and iteration of surgical technique and implant design.[25, 29]

Osseointegration has been predominantly used in transfemoral amputees (TFA) as compared to transtibial amputees (TTA), due to apparently greater benefit-risk ratio with the TFA being perceived to have more socket related problems and poorer mobility as compared to TTAs and the extent of risks or complications of the new procedure largely unknown. [15, 32-34] Due to the same reasons, commercial availability of approved standard implants for TFA only promoted its use. Furthermore, it is much easier to press-fit or insert a screw fixation implant in to a cylindrical cortical bone such as a femur as opposed to the reverse pyramid shaped cancellous bone of the proximal tibia[26]. It is very challenging to press fit an implant into cancellous bone and achieve immediate stability. The same principles apply to a screw fixation device.

With the establishment of safety of this procedure in literature, there is enough justification now for its use in individuals with TTA. Firstly, the prevalence of transtibial amputations is much higher than transfemoral amputations.[35, 36] Of these individuals using socket prostheses, 40% experience at least one skin problem, with the percentage substantially higher in individuals with TTA (TTA: 45.8%, TFA: 20%; OR: 4.1). Secondly, there is increased percentage of stump pain reported in patients with TTA.[8, 37]. Thirdly, suboptimal socket fit occurs in both individuals with TTA and with TFA (TTA: 59%, TFA: 78%)[38] and dissatisfaction with socket prostheses does not differ when comparing for level of amputation, with only 43% being satisfied with the comfort of their prosthesis.[39-41] These problems are inherently

linked to intolerance of the prosthesis[12] and impact the ability of TTA to become independently mobile.[42]

Until recently, there is very little data assessing the protocol, techniques and results of Osseointegration in individuals with TTA. Only few papers with very small case series have been published with variable results.[26, 28, 43, 44]

Study objectives

The overall objective of this study is to assess the safety and efficacy of transtibial osseointegration procedure with at least 2 year follow-up and to compare the benefits and risks from pre-operative status and with the previously reported outcomes for transfemoral osseointegration. Specifically, this would involve:

1. Assessing the objective functional outcomes with the 6 Minute Walk Test (6MWT) [45], Timed Up and Go (TUG) [46] and K-levels[47], compared with preoperative data and with outcomes of TFA.
2. Assessing the subjective patient-reported quality-of-life outcomes with the Short Form Health Survey 36 (SF-36)[48], Stump Pain, Daily prosthetic wear hours and Prothetic wear satisfaction compared with preoperative data and with outcomes of TFA.
3. Examining the prevalence of adverse events, including infection, revision surgery, fractures, aseptic loosening and implant failures, and compare with the adverse events after TFA.

One of the primary objectives of this study is to identify the individual patient characteristics or factors that have a positive or negative influence in the outcomes mentioned above. This analysis in a regression model would help to identify the patients based on their characteristics who would be most or least benefitted with this novel procedure and who would be at a higher or lower risk of failure.

The other objective is to identify the rate of additional surgical interventions as well as to identify factors associated with further surgery, specifically for infection, periprosthetic fracture, implant fracture, and aseptic loosening.

Methods and analysis

This is a prospective cohort study which is designed to assess the safety and efficacy of Transtibial Osseointegration procedure with a minimum of 2 years (range 2-8 years) follow-up.

Preliminary data and clinical experience has been obtained from an initial pilot study comprising 10 patients owing to absence of prior literature. Software G* Power was used to calculate an a priori sample size. Considering SF-36 physical component score as primary outcome measure, the pre-operative and 2 year post-operative scores were recorded. Comparing the means (37.62 and 44.83) and SDs (11.8 and 19.5) of these 2 groups respectively using Wilcoxon test, the effect size was calculated to be 0.36 and sample size was calculated to be 87 assuming α error to be 0.05 and in order to achieve a Power of 95

%. Considering a drop-out rate of 20%, a final sample size of 109 was decided upon. None of the patients of the pilot study have been included in this study due to absence of standard protocol.

The first patient enrolled in the study was in April 2014. Enrolment is ongoing at the time of publication of this paper, with 68 patients already enrolled and is expected to be completed by April 2022. The number of patients treated each year has shown a steep rising trend with about 26 patients enrolled in the study last year.

Patient selection

Eligibility criteria

The Ethics approval for the study has been received from the University of Notre Dame, Sydney, Australia (014153S). All participants gave their informed consent. Inclusion and Exclusion criteria along-with rationale are listed in Table 1.

Table 1: Inclusion and Exclusion Criteria with Reason

Inclusion Criteria	
Criteria	**Reason**
Age at least 18 years	Legal self-consent
Current unilateral, bilateral or mixed transtibial amputees with significant dissatisfaction regarding prosthesis fit or pain, mobility, or skin breakdown	Objective, identifiable deficit in current patient lifestyle
Patients with a full lower limb but with pain, deformity, or weakness distal to the mid-tibia who desired amputation for pain management or improved mobility following removal of the deformed or weak joint and muscles.	Objective, identifiable quality of life impairment that can be objectively improved by amputation, and patients likely would experience better rehabilitation with osseointegration than standard socket prosthesis.
Patients with amputations who wished to try osseointegration instead of a traditional socket prosthesis.	Honoring patient choice after an ethical, shared and sound decision making process
Patient with sufficient resources and willingness to pursue surgery, post-operative rehabilitation, and prosthesis procurement.	Rehabilitation and prosthesis fitting are all required for appropriate, safe improvement following osseointegration surgery.
Exclusion Criteria	
Criteria	**Reason**
Active infection any location	Unacceptably high and modifiable infection risk
Active malignancy or ongoing/planned treatment for malignancy at any location	High risk for infection, impaired biology for osseointegration, impaired patient stamina for rehabilitation

Skeletal immaturity	Unknown risk given the current knowledge of osseointegration outcomes and biological impact
Patients with psychiatric concern identified during pre-operative consultation with psychiatrist	Minimize risk of performing surgery for a patient whose expressed deficits are psychiatric-based instead of musculoskeletal-based, and thus unlikely to improve with surgery.
Patients considered too medically ill, too muscularly weak, or insufficiently dedicated to improve following osseointegration	Avoid harming patients with surgery that may be either unlikely to benefit them or possibly pose a health risk.
Insufficient remaining tibia length to accept an implant	Avoid performing surgery for a patient who would be unlikely to achieve successful bone ingrowth to the implant
Uncontrolled diabetes mellitus	Avoid unnecessary, modifiable risk for infection
Females currently or intending to become pregnant within the year following surgery	Unnecessary risk to fetus due to potential for falls or other unforeseen adverse events

Patient recruitment

Setting and Patient Screening

Our surgical practice is located in a private university hospital in a major urban city with full, modern medical capabilities. Local patient referral can occur via the usual routes for our practice: from the general practitioner or by self-referral. Non-local patients within the country and international patients can also contact our office, as is typical already, and are encouraged to provide information for pre-evaluation. All patients being referred for, or requesting, osseointegration are required to complete an online Patient Screening Form. Those patients fitting our Inclusion and Exclusion criteria are invited for in-person consultation. Patients who sustain acute traumatic injuries for which amputation is recommended can request osseointegration as primary management, either acutely or following the resolution of their acute injury.

Patient Enrolment

All patients who complete the online Patient Screening Form and fit the inclusion/exclusion criteria are evaluated in the multidisciplinary Limb Reconstruction Clinic. The typical medical team includes at least three orthopaedic surgeons with extensive limb reconstruction experience. Also in attendance are a prosthetist and physiotherapist, to ensure the patient's complaints are not suitably improved by prosthesis adjustment or therapy. Patients are also evaluated by our psychiatrist to ensure absence of psychiatric conditions that can affect post-operative rehabilitation. For patients who have neuropathic pain or a history of narcotic or other pain-related medication use or abuse, a pain medicine consultation is required. All patients are counselled extensively by the team which includes a dynamic

assessment and discussion of the benefits (mobility, quality of life, etc) as well as the risks (infection, fracture, further surgery including full removal or further amputation, etc) of osseointegration. The patients are fully explained about the relative novelty of this surgery and that the immediate and long term risk/benefit profile is still not very well defined so that an ethical, sound and shared decision making process is achieved. All patients who elect for osseointegration are informed their care is provided at the best clinical judgment, but that they will be enrolled as part of a prospective and longitudinal study as described. There is no arbitrary treatment based on assignment into a treatment category. Implant selection and exact surgical technique is expressly tailored to each patient.

The time between patient enrolment and surgery will vary. Patients who have a traumatic injury and have inpatient consultation may have osseointegration the next day. Healthy patients with streamlined financial coverage and who are able to attain psychiatric evaluation quickly could have surgery within a week of consultation. For patients who do not have appropriate insurance coverage, there is a waiting period for the most appropriate coverage level of one year, and during that waiting time would be recommended to participate in pre-habilitation exercises and have other perioperative optimization performed.

Potential Selection Bias

One of the limitations of this study is possibility of selection bias to exclude low income patients. Osseointegration is an expensive surgery and thus is not covered by the standard government insurance for our country. It is covered by more premium insurance plans. Thus we counsel patients to enrol in these top level insurance plans so that not only will the surgery itself be provided but any additional surgery for an adverse event will be covered, so long as they maintain their coverage. Due to this limitation the results of the study may not be generalizable to all countries and all populations.

Study intervention

Preoperative management

All the patients are assessed with AP and lateral plain radiographs of the residuum to assess the bone quality and presence of any anomaly. Long leg standing radiographs are performed to assess the mechanical alignment of the lower limbs and to rule out pathologies in the contralateral limb. DEXA scans of the proximal femora and the spine to assess the bone mineral density which would help determine the speed of post-operative rehabilitation. Furthermore, CT scans of the residual bone are performed to plan for the type of implant and required size..

Osseointegration Implant

The Transtibial Osseointegration implant used by us for, was designed by senior author (MAM) into mainly two types. For longer residuums with sufficient cortical bone, a standard titanium implant which was machine manufactured of 160mm length with plasma spraying on the surface was used (Figure 1). Alternatively, for short residuums with metaphyseal

bone a custom-made short stem titanium implant with coarser surface structure was either machine manufactured or 3D printed. The surface of the implant is composed of a macroporous mesh-like structure allowing for bone ingrowth. Some implants contain longitudinal flanges for additional rotational stability. All implants are connected to a dual cone adapter with Morse-taper ends connecting the implant with the external prosthesis. The surface of the dual cone adapter is highly polished and coated with titanium-niobium oxide, an alloy known to have bacterial repellant properties[4], which also facilitates the excursion of the soft tissues and skin over it avoiding adhesions. A safety mechanism is built into the dual cone, with a safety pin that breaks to reduce the chance of periprosthetic fractures or implant breakage.

Surgical Technique

All patients receive an osseointegrated implant in a single-stage surgery. At the level of the distal stump, a horizontal elliptical incision is made, the amount of soft tissue and muscle tissue is minimalized and all nerves are sharply severed and vessels are ligated or cauterized until hemostasis is achieved. The saphenous, tibial and common peroneal nerves are re-innervated to surrounding muscle branches if symptoms of nerve pain or excessive phantom pain existed pre-operatively (Figure 2). Alternatively, the re-innervation of tibial and common peroneal nerves can be performed via a separate lateral distal thigh incision and posterior dissection.

Care is taken to preserve the periosteum at all times. If the distal end of the tibia needs to be re-cut, the periosteum is elevated and re-sutured to the end of the bone after using an oscillating saw for the distal tibia osteotomy. The fibula is usually cut 2-3 cm shorter than the tibia using the saw.

The intramedullary canal is prepared depending on the length of the residuum. If the amputation is at the diaphysial level with good cortical bone distally then reaming up to 0.5 mm larger than the definite implant anticipated to be used after cortical chatter is heard (Figure 3) followed by sequential broaching up to the size of the desired implant (Figure 4). If the tibial stump is at the metaphyseal level with poor quality bone then no reaming is done and only impaction broaching is performed usually stopping at 2 mm smaller than the definite size of the implant. Both reaming and broaching is performed under image intensifier guidance to ensure accurate positioning in the centre of the tibia on the AP and lateral planes. Finally, the distal edge of the tibia is smoothened with use of a face-reamer (Figure 5).

Final implantation of the osseointegration intramedullary component is done using press-fit technique up to the subchondral bone of the proximal tibia (Figure 6). To stabilize the implant in shorter residual stumps, multiple locking screws were initially used, before it was abandoned due to increased risk of loosening and no added benefits.

Closure is initiated by suturing the fascia to the periosteum all around at the distal end of the tibial stump in a ‘purse-string’ fashion. This has not been described previously for tibias

and is unique to our group. The anterior and posterior soft tissue sleeves are refashioned to remove subcutaneous fat. A flap is created-preferably anterior, to cover the end of the stump and to begin closure in layers. A sharp corer is used to make a stoma in the flap to communicate to the exact diameter of the implant, before progressing to close the rest of the wound in layers. Alternatively, the anterior and posterior flaps are closed around the implant in a 'fish-mouth' fashion (Figure 7). After this step, the dual cone component of the osseointegration device is inserted and secured with an internal locking screw, followed by fixing the taper sleeve and bushing to the dual cone using an external screw, all the time securing the implant to prevent rotation using a special device (Figure 8 and 9).

Postoperative Rehabilitation

The rehabilitation for transtibial osseointegration is carried out in phases and described in details in Figure 10 and 11.The adherence to the rehabilitation protocol is recorded in the database by the physiotherapist. Following the fitting of a prosthetic limb (Figure 12), patients are encouraged to weight-bear daily on their prosthesis using two crutches for six weeks and then one crutch on the opposite side for a further six weeks and then unaided thereafter

Outcome

Data sampling

Data sampling is done at baseline pre-operatively and post-operatively at 3, 6 and 12 months and yearly follow-ups thereafter. It is done by dedicated research assistants who are unaware of the details of patients' demographic characteristics, surgical and implant details and previous scores to reduce the risk of any bias. Clinical information from surgery and follow-ups are added to the database by the operating or reviewing surgeon. Data that is sampled including the time points of measurement are tabulated in Table 2.

Table 2: Data Sampling Table showing the parameters sampled and time points of measurement

Parameter Sampled	Details	Time point of measurement
Name		T0
Date of Birth		T0
Address		T0
Phone number/Email		T0
Gender		T0
Height		T0
Weight		T0
Military	Yes/No	T0
Athlete	Yes/No	T0
Race		T0
Education Level		T0

Employment status before OI surgery		T0
Type of occupation before OI surgery		T0
Age at 1st Surgery		T0
Date of 1st Surgery		T0
Any Further surgeries	Yes/No. Dates of further surgeries if Yes	When it occurs
Side		T0
Bilateral	Yes/No	T0
Mixed	Yes/No	T0
Same Day Amputation and OI	Yes/No	T0/TS
Cause of Amputation	Each cause assigned a number	T0
Date of amputation		T0
Co-Morbidities	Each cause assigned a number	T0
Psychiatric evaluation before surgery	Yes/No	T0
Depression	Yes/No	T0
Alcohol >3/day	Yes/No	T0
TMR at index surgery	Yes/No	T0
Reasons for Osseointegration	Fit Problems/ Skin Problems/ Painful prosthesis/Prosthetic Mobility Dissatisfaction/ Other Pain/ Other causes. Each cause assigned a number	T0
Implant Details	Implant Brand, Type, Manufacture method, Collared/Flared, Width, Length	TS
Retention of Hardware	None/Cable/Screw/Both	
Implant Removal		When it occurs
Reason for removal		When it occurs
Years to Fail		When it occurs
Re-implant date		When it occurs
Further surgeries details	Washouts/Neurectomy/Refashioning/ Periprosthetic Fractures/Other Surgeries details	When it occurs
Antibiotics administration	Intravenous/ Oral. Details	When it occurs
Other Adverse events		When it occurs
Length of Residuum		T0
Length after OI		TS
Pre-Op Weight Bearing status		T0
Pre-Op K Level		T0
Pre-Op Walking Aid		T0
Pre-Op 6 Minute Walk Test		T0
Pre-Op Timed Up-and-Go Test		T0
Pre-Op SF-36 (PCS)		T0
Pre-Op SF-36 (MCS)		T0
Pre-op Subjective	Functional Level and Problems. “How would you summarise your level of function with your current prosthesis?”	T0
Pre-Op Stump Pain (VAS)		T0
Daily Prosthetic Wear Hours		T0
Prosthetic Wear Satisfaction		T0

Adherence to Rehabilitation Protocol	Yes/No	TR
Post-Op Weight Bearing status		T1, T2, T3, T4…
Post-Op K Level		T1, T2, T3, T4…
Post-Op Walking Aid		T1, T2, T3, T4…
Post-Op 6 Minute Walk Test		T1, T2, T3, T4…
Post-Op Timed Up-and-Go Test		T1, T2, T3, T4…
Post-Op SF-36 (PCS)		T1, T2, T3, T4…
Post-Op SF-36 (MCS)		T1, T2, T3, T4…
Post-op Subjective	Functional Level and Problems. "How would you summarise your level of function with your current prosthesis?"	T1, T2, T3, T4…
Post-Op Stump Pain (VAS)		T1, T2, T3, T4…
Daily Prosthetic Wear Hours		T1, T2, T3, T4…
Prosthetic Wear Satisfaction		T1, T2, T3, T4…
T0: Pre-operative, TS: At Surgery, TR: During Rehabilitation, T1: 3 months, T2: 6 months, T3: 1 year, T4: 2 years and so on		

Adverse events

Adverse events are reported which includes infection that require administration of intravenous or oral antibiotics or surgical intervention, periprosthetic fracture, implant breakage, aseptic loosening, need for revision surgery or additional amputation and death. Severity of infections are assessed and graded into Al Muderis et al. classification system.[25].

Data analysis

The primary questions this study aim to identify are 1. the individual patient characteristics or factors that have a positive or negative influence in the outcomes measured or in other words who would be most or least benefitted with this novel procedure and who would be at a higher or lower risk of failure? and 2. what are the rates of additional intervention for patients undergoing transtibial osseointegration, and for what reasons? This project will also aim to collect data which can allow investigation of diverse questions regarding transtibial osseointegration as further insight develops.

The influence of various factors such as patient gender, age, and cause of amputation on dependent variables relating to potential risks (infection, fracture, further surgery, etc) or benefit (mobility, QOL outcomes, etc) will be assessed. Multivariable logistic regression will be performed with a focus to identify factors associated with further surgery, specifically for infection, periprosthetic fracture, implant fracture, and aseptic loosening. Additionally, factors associated with Daily prosthesis wear hours, Prosthetic wear satisfaction, SF-36 and mobility (6MWT, TUG, K level) will be evaluated. Separate regression models will be developed for short and long residuum TTOIs as well. A p value of ≤ 0.05 will be considered as significant. The p value for each regression identifying significant predictors of dependent variable outcome will be reported, as will the coefficients of relative influence of each variable.

The pre- versus post-operative continuous value data will be presented as mean and standard deviation and compared with Student's T-test or analysis of variance (ANOVA) if the data is normally distributed. Post-hoc analyses related to longitudinal data analysis at T0, T1, T2, etc will also be performed. Should the data not be normally distributed the median and interquartile ranges will be reported and comparison made using Wilcoxon test.

Reducing risk of bias

In addition to reducing the risk of selection bias as described above, bias relating to surgeon expertise and protocol adherence is eliminated since all operations will be performed by a single primary surgeon. Bias related to data collection will be minimized by employing dedicated research assistants who will be unaware about details of patient demographic characteristics, surgical and implant details and previous recorded scores. Further, the results of functional outcome measures (6MWT, TUG, K-levels) depend on the patients' actual performance, while the results of subjective outcome measures are completely patient reported from surveys. In addition, the assessors will not be involved in data analysis.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and Dissemination

All patients included in this study will sign a consent form that provides sufficient information about the study for patients to make an informed decision about their participation. Outcomes of the current study will be disseminated by publications in peer-reviewed academic journals and presentations at relevant orthopaedic conferences.

Discussion

This study will be the first major one to focus on transtibial osseointegration only and will have the largest cohort reported in literature so far. The findings of the study would assess whether osseointegration in transtibial amputees is feasible in terms of risks and benefits and also make an important contribution to the otherwise limited literature regarding outcomes of osseointegration in lower extremity amputations. As evidenced by literature, transtibial amputees using TSP suffer from same difficulties involving skin breakdown[8], suboptimal fit[49] and pain[4] as do the transfemoral ones, which ultimately affect their prosthetic use, mobility and overall quality of life. As the dramatically different concept of osseointegration proved life-changing in management of transfemoral amputees with established safety, it is only logical to extend the science to transtibial amputees and document the outcomes.

The challenges posed by TSP were overcome by direct anchorage of the implant to the bone that enabled physiological weight bearing[17], increased flexibility and range of motion[50], sitting comfort[51], mechanoreception-based sensory feedback (osseoperception)[23], improved donning and doffing[24], better mobility[7] and improved prosthetic use[24], body image[49] and quality of life[24]. The safety of the implant was established in subsequent studies in terms of stability and risk of infection.[25]

Although largely unreported in literature so far, the further application of osseointegration to transtibial amputees has been done in pilot project by our group to suitable patients as well as some other surgeons worldwide. Prospective outcomes at 12 months of five patients with peripheral vascular disease who underwent transtibial osseointegration was published recently by Al Muderis et al.[43] Results showed that all the patients enrolled in the study were able to mobilize unaided at final follow-up. There was notable improvement of objective functional measures of 6MWT and TUG as well as subjective functional measures, while only two superficial infections were noted which resolved with conservative treatment and no implant loosening or other adverse event documented. However, two previous studies from Germany[26, 28] reporting on nine individuals with transtibial amputations treated with their custom cobalt chrome implants reported an explantation rate of 43% and rates of both septic and aseptic loosening of 22% each, though patient eligibility, rehabilitation and follow-up is unclear.

Recently, another study comprising of a small number of nine transtibial patients having a follow-up of only 12 months has been reported from The Netherlands.[44] The cohort was a mixed one with majority (31 patients) being transfemoral patients. Comparison of outcomes between transtibial and transfemoral osseointegrated patients revealed higher overall baseline values in transtibial patients except walking distance in daily life and prosthetic comfort. Improvement in the outcome measures was also greater in transtibial patients (except hip abductor strength and prosthesis wearing time), and at final follow-up lesser transtibial patients experienced stump pain as compared to transfemoral patients (transfemoral: 20/31 (65%), transtibial: 2/9 (22%)). Major adverse events related to implants was recorded as 8% which included both groups and included three dual-cone breakages and four bone fractures (due to fall), which were all managed successfully. However, a lower uneventful course was noted in transtibial patients (44%) compared to transfemoral ones (61%). The authors concluded that transtibial osseointegration was both efficacious and safe at 12 months follow-up

Thus, the proposed study would comprise the largest cohort of Transtibial amputees undergoing Osseointegration with a substantial follow-up time. The clinical outcomes, adverse events, and their associations noted in this study would help considerably to set the standard of care in transtibial amputee patients and provide directions of further research in terms of implant design, surgical technique, rehabilitation or management of complications.

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Figure Captions

Figure 1: The Standard Implant for longer residuums. The parts include: 1, proximal cap screw. 2, Intramedullary body. 3, internal safety screw. 4, dual cone transcutaneous abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector.

Figure 2: Targeted re-innervation of nerves (posterior tibial nerve highlighted) to surrounding muscular branches

Figure 3: Reaming was done for longer residuums to 0.5 mm more than the diameter of implant expected to be used

Figure 4: Broaching done under Image Intensifier guidance upto the desired size of implant for longer residuums

Figure 5: Face reaming done to smoothen the distal margins of the tibial stump

Figure 6: Final implantation of the definite intra-medullary component

Figure 7: Closure of periosteum around the stump in a 'purse-string' fashion and the flaps around implant in 'fish-mouth' manner.

Figure 8: Attachment of extra-medullary components

Figure 9: Final view of the closure of the stump

Figure 10: Transtibial Osseointegration Rehabilitation Protocol

Figure 11: Transtibial Osseointegration Physiotherapy Protocol

Figure 12: After fitting of prosthetic limb in a short residuum tibia

AUTHORS' CONTRIBUTIONS

R Haque: Study design; patient care and surgical team; manuscript preparation.
S Al-Jawazneh: Data collection; patient care and surgical team
J Hoellwarth: Data collection; patient care and surgical team
M A Akhtar: Data collection; patient care and surgical team
K Doshi: Data collection; patient care and surgical team
Y Tan: Data collection, statistical evaluation
W. Lu: Data collection; manuscript preparation.
C Roberts: Patient care; data collection; manuscript preparation.
M Al Muderis: Study design; patient care and surgical procedure; manuscript preparation.

Acknowledgement
Bridget Dean: For formulating Transtibial Rehabilitation and Physiotherapy Protocol

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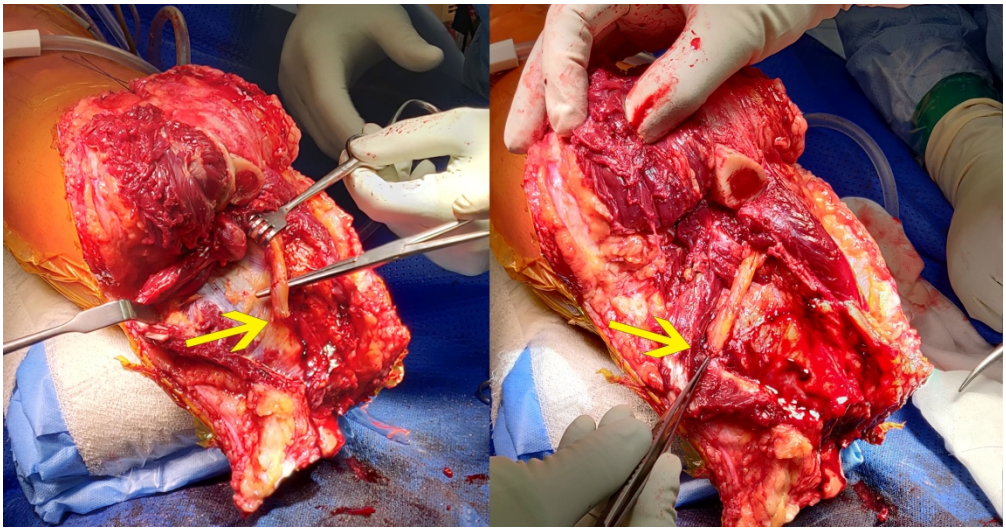
COMPETING INTERESTS STATEMENT

M. Al Muderis receives royalties for design contributions for the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a; Milan, Italy) implant system. All other authors listed in this study declare no competing interests.

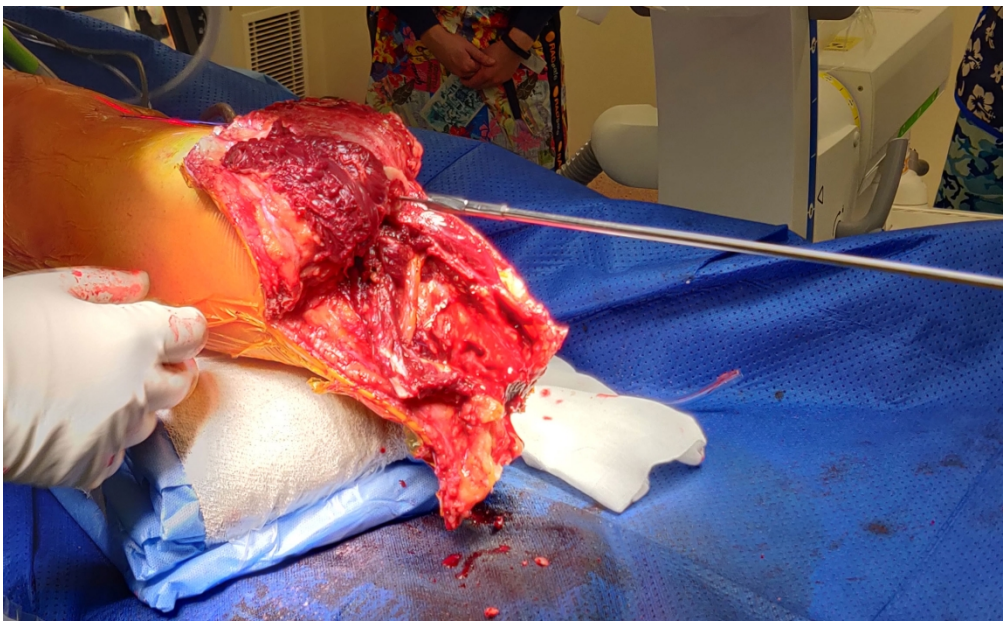
The Standard Implant for longer residuums. The parts include: 1, proximal cap screw. 2, Intramedullary body. 3, internal safety screw. 4, dual cone transcutaneous abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector.

21x49mm (600 x 600 DPI)



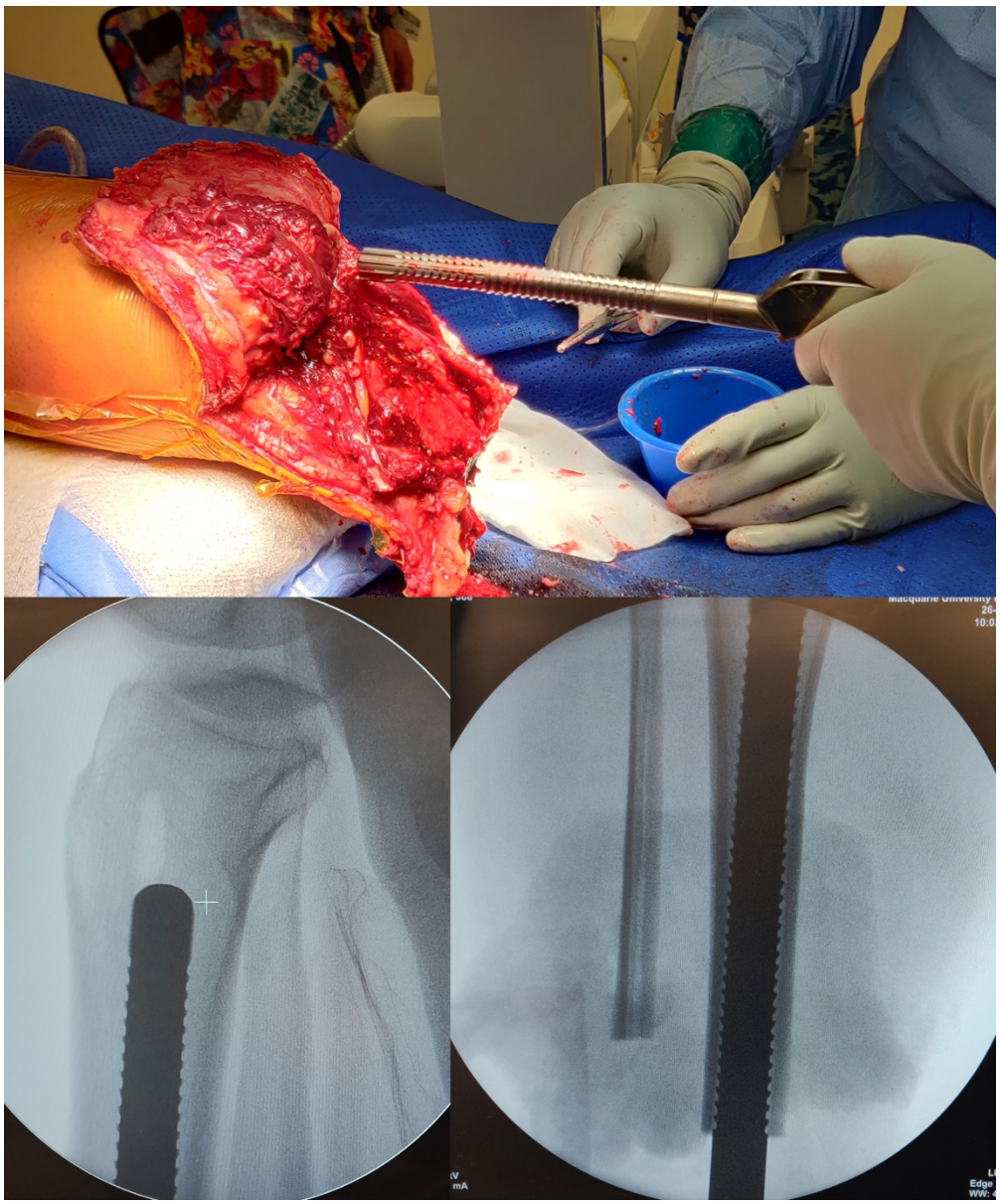
Targeted re-innervation of nerves (posterior tibial nerve highlighted) to surrounding muscular branches

327x171mm (300 x 300 DPI)



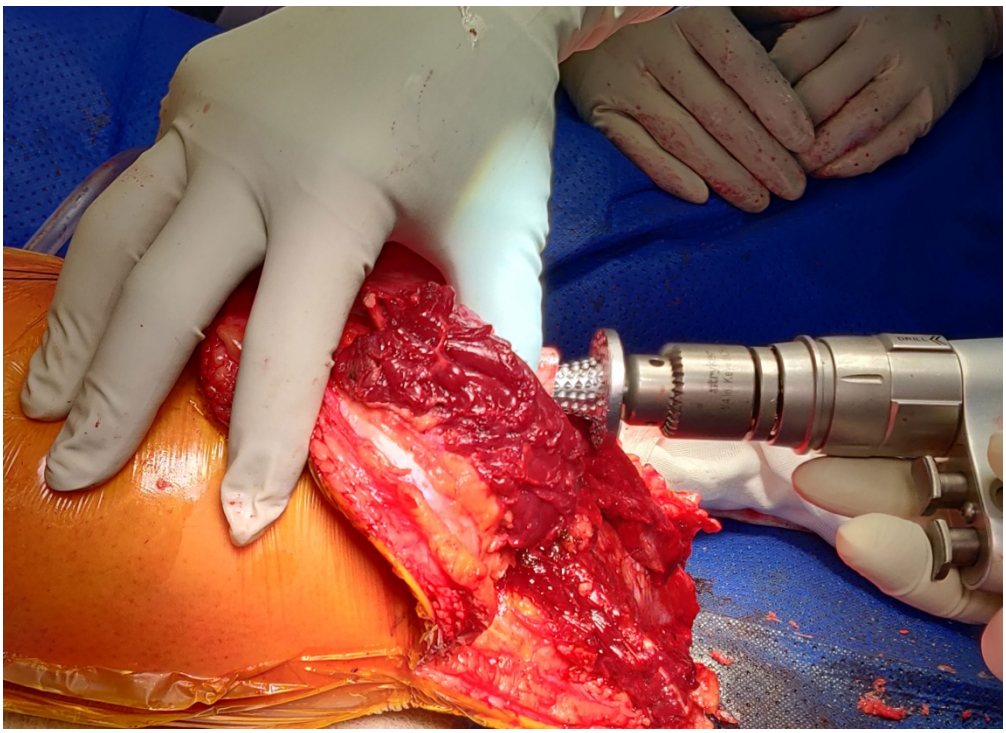
Reaming was done for longer residuums to 0.5 mm more than the diameter of implant expected to be used

195x119mm (300 x 300 DPI)



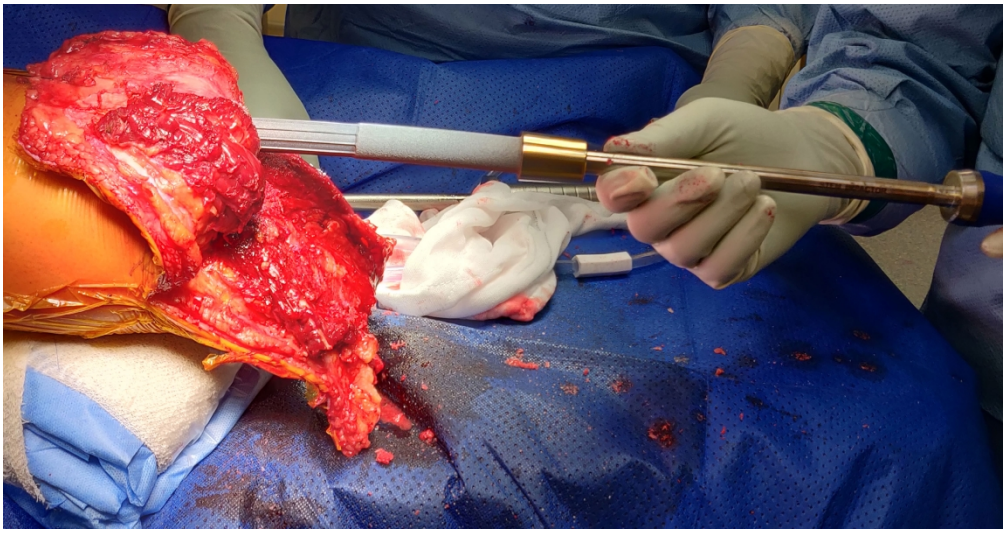
Broaching done under Image Intensifier guidance upto the desired size of implant for longer residuums

325x390mm (300 x 300 DPI)



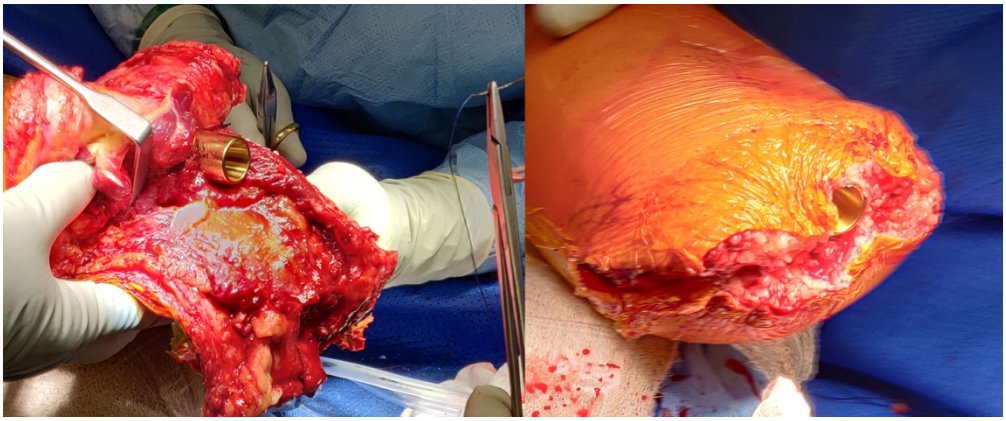
Face reaming done to smoothen the distal margins of the tibial stump

173x125mm (300 x 300 DPI)



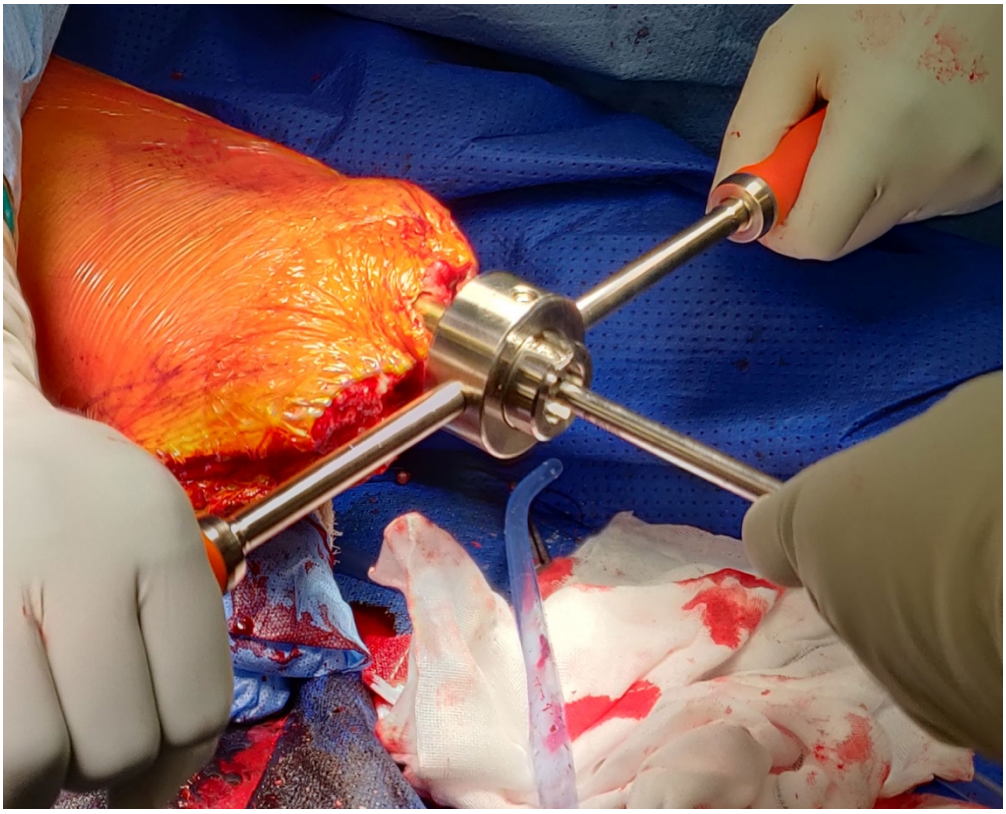
Final implantation of the definite intra-medullary component

252x132mm (300 x 300 DPI)



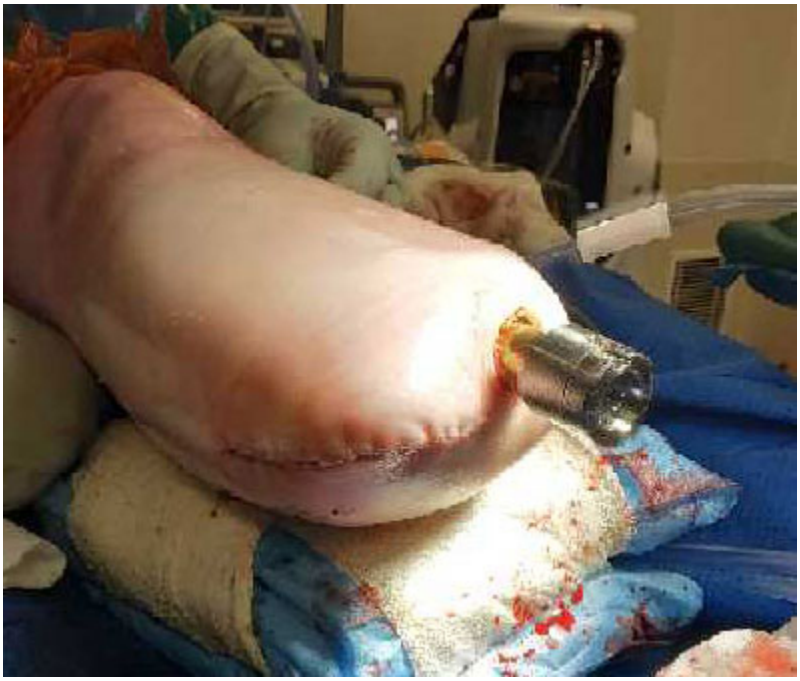
Closure of periosteum around the stump in a ‘purse-string’ fashion and the flaps around implant in ‘fish-mouth’ manner

208x85mm (300 x 300 DPI)



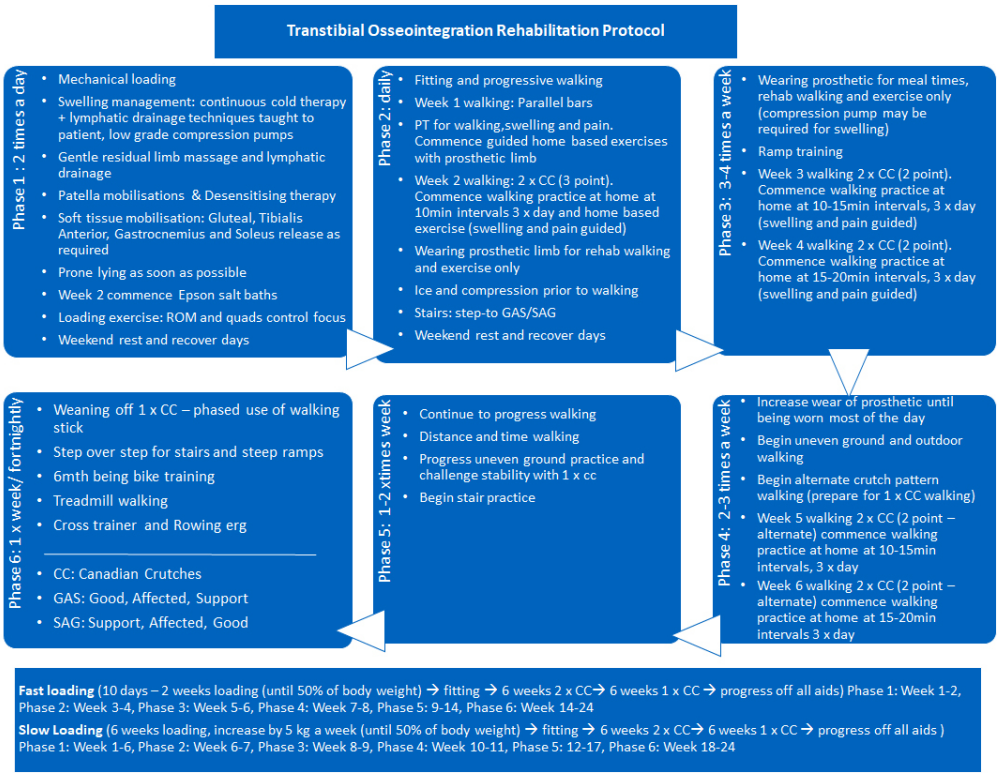
Attachment of extra-medullary components

132x106mm (300 x 300 DPI)



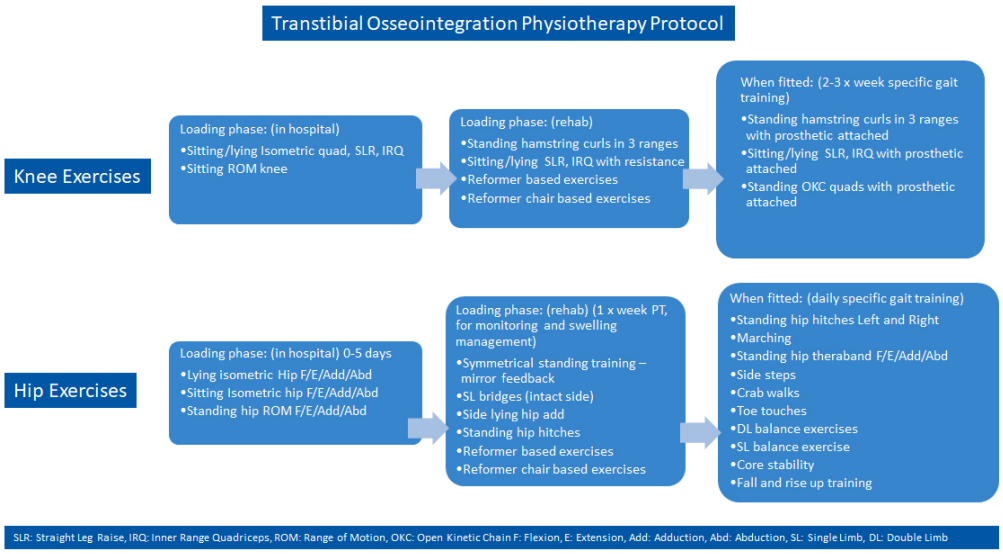
Final view of the closure of the stump

33x28mm (300 x 300 DPI)



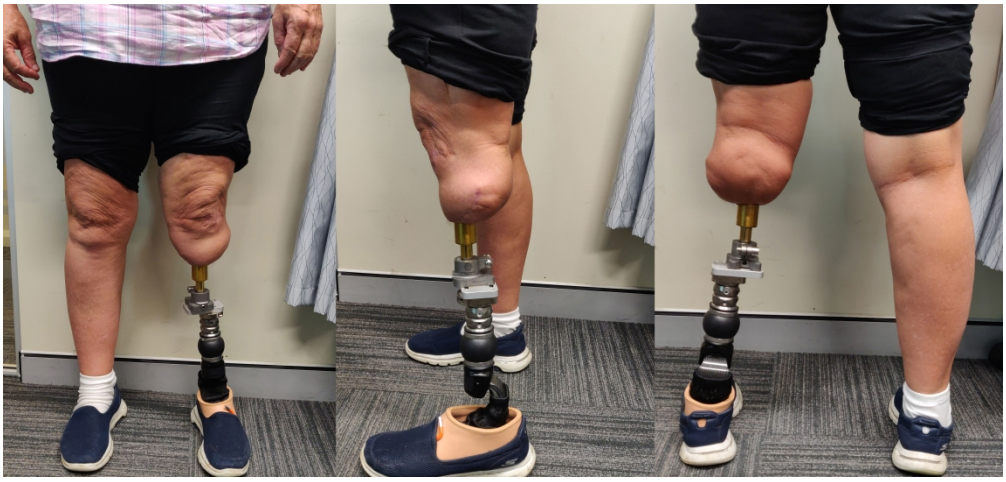
Transtibial Osseointegration Rehabilitation Protocol

45x34mm (600 x 600 DPI)



Transtibial Osseointegration Physiotherapy Protocol

47x25mm (600 x 600 DPI)



After fitting of prosthetic limb in a short residuum tibia

580x274mm (300 x 300 DPI)