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COMPARATIVE EVALUATION OF MINIMALLY INVASIVE 'TIBIAL TUBEROPLASTY' SURGICAL TECHNIQUE VERSUS CONVENTIONAL OPEN SURGERY FOR SCHATZKER II-III TIBIAL PLATEAU FRACTURES: DESIGN OF A MULTICENTRE, RANDOMISED, CONTROLLED AND BLINDED TRIAL (TUBERIMPACT STUDY)

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ABSTRACT

Introduction: Fractures of the tibial plateau are in constant progression. They affect an elderly population suffering from a number of comorbidities, but also a young population increasingly practicing high-risk sports.

The conventional open surgical technique used for tibial plateau fractures has several pitfalls: bone and skin devascularisation, increased risks of infection and functional rehabilitation difficulties.

Since 2011, Poitiers University Hospital is offering to its patients a new minimally invasive technique for the reduction and stabilization of tibial plateau fractures, named "tibial tuberoplasty". This technique involves expansion of the tibial plateau through inflation using a kyphoplasty balloon, filling of the fracture cavity with cement and percutaneous screw fixation.

We designed a study to evaluate the quality of fracture reduction offered by percutaneous tuberoplasty versus conventional open surgery for tibial plateau fracture and its impact on clinical outcome.

Methods and analysis: This is a multicentre randomized controlled trial comparing two surgical techniques in the treatment of tibial plateau fractures. 140 patients with a Schatzker II or III tibial plateau fracture will be recruited in France. They will be randomized either in tibial tuberoplasty arm or in conventional surgery arm. The primary outcome is the post-operative radiological step-off reduction blindly measured on CT-scan (within 48 hours post-op). Additional outcomes include other radiological endpoints, pain, functional abilities, quality of life assessment and health-economic endpoints. Outcomes assessment will be performed at baseline (before surgery), at Day 0 (surgery), at 2, 21, 45 days, 3, 6, 12 and 24 months post-surgery.

Ethics and dissemination: This study has been approved by the ethics committee Ile-De-France X and will be conducted in accordance with current Good Clinical Practice (GPC) guidelines, Declaration of Helsinki and standard operating procedures. The results will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial Registration Number: NCT03444779

Strengths and limitations of this study:

- This is a multicentre, randomized, controlled trial with a calculated number of subjects required to have 80% power to detect a 25% difference in postoperative radiological step-off reduction of tibial plateau fracture by tibial tuberoplasty versus conventional surgery.
- Primary endpoint blindly evaluated on CT-scan by an independent imaging core lab will provide robust and reliable data.
- Learning curve for tibial tuberoplasty technique could create a bias for endpoint evaluation. For this purpose each surgeon will participate in a tibial tuberoplasty workshop before the study.
- Unblinded patient's follow-up could introduce a bias for secondary endpoints evaluation.

INTRODUCTION

French Medico-Administrative Data (from PMSI) data show more than 10 000 proximal tibial fractures diagnosed in 2014 and 4055 lateral tibial plateau fractures operated in 2013 in France [1]. Half (50%) of these fractures are related to the lateral condyle and cause split/depression (Schatzker II) or pure depression (Schatzker III) [2]. This high rate results from the recent democratization of high-risk sports [3], as well as an aging population with increased risks of falling [4]. Aside from the resulting reduced physical activity, the social and professional impact of these fractures is undeniable and represents significant costs for the health care system. A recently published prospective case series reports 28 job losses out of 41 patients treated [5].

The clinical outcome of these patients depends mainly on the primary stability provided by the surgical treatment, after the greatest anatomical reduction possible. Indeed, *Giannoudis and al*. have demonstrated that under simple X-rays, the smaller the detected step-off, the better the outcome [6]. The aim is to allow for recovery of good joint mobility to promote rapid resumption of activity and to limit the onset of early osteoarthritis [7].

The conventional open surgical technique using a bone tamp for reduction and osteosynthesis of tibial plateau fractures has several pitfalls [3]: devascularization of the bone and skin, increased risks of infection and functional rehabilitation difficulties with delayed recovery of weight bearing. Moreover, this technique does not allow for the simultaneous diagnosis and treatment of other possible lesions, such as meniscal injuries in particular.

Since 2011, Poitiers University Hospital is offering to its patients a new minimally invasive technique for the reduction and stabilization of tibial plateau fractures, baptized “tibial tuberoplasty” [8].

The concept derives from the divergent use of vertebral kyphoplasty, initially dedicated to spinal injuries and transposed here to the tibial plateau. This technique involves expansion of the tibial plateau through inflation of a kyphoplasty balloon, filling of the created cavity with cement (PMMA or calcium phosphate) and percutaneous screw fixation. The clinical outcome of these patients depends mainly on the primary stability provided by the surgical treatment, after the greatest anatomical reduction possible “step-off” <5 mm, without axis shifting <5°.

We performed the first tibial tuberoplasties through a feasibility study on 36 cadaveric subjects and then transposed the technique to human. We identified major advantages such as minimal skin damage, possible treatment of posterior and multi-fragmented compressions (lifting in a single block by the balloon), reinforcement of the stability of the assembly using cement, possible use of combined arthroscopy [9] (for concomitant meniscal injuries treatment [10]).

This technique allows for optimization of the fracture reduction by elevating the posterior fragments with the inflatable bone tamp through an anterior approach. The reduction is made possible thanks to the specificity of the inflatable bone tamp which inflates and reduces the area of least resistance.

The aim of this innovative technique is focused on the anatomical reduction in order to restore the convexity of the tibial plateau [11] which is similar to the balloon convexity.

The results from the first 40 patients operated since 2011 are promising and show a proportion of 70% presenting less than 5 mm step-off reduction.

There is now a need for a larger-scaled multicentre randomized controlled trial to compare the efficacy of tibial tuberoplasty versus the gold standard treatment (conventional open surgery), not only in terms of radiological step-off reduction but also in terms of functional impact.

To bridge this gap, we designed a study to evaluate the quality of fracture reduction offered by percutaneous tuberoplasty versus conventional open surgery for tibial plateau fracture and its impact on clinical outcomes.

METHOD AND ANALYSIS

Study Population

The study population comprises two target populations with tibial plateau fracture:

- Young subjects with fractures mainly resulting from highway accidents and high-risk sports.
- Elderly population with fractures mainly caused by falls, in the context of osteoporosis.

The distinction between these populations will be included in the statistical analysis as a modifying factor, as the clinical expectations and medical and economic repercussions are different.

A patient must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for the study.

Inclusion criteria

The subjects are more than 18 years old; present a Schatzker type II or III tibial plateau fracture (compression with or without split) demonstrated on CT-scan and located in the lateral or medial condyle of tibia; have 10-day-old maximum fractures caused by trauma; understand and accept the constraints of the study; are beneficiaries or affiliated members of a Health Insurance plan; give written consent for the study after having received clear information.

Exclusion criteria

The subjects present fractures resulting from osteolysis; have open fractures; have fractures more than 10 days old; have concomitant fracture(s) or condition(s) during the trauma reducing the range of motion; were unable to walk before the injury; have a history of sepsis in the injured knee; have contraindications to anesthesia, contrast agent, medical devices or cement; have a history of hypersensitivity reactions to contrast media, bone filler or metal; present a degenerative joint disease (polyarthritis, etc.); require closer protection, i.e. minors, pregnant women, nursing mothers, subjects deprived of their freedom by a court or administrative decision, subjects admitted to a health or social welfare establishment, major subjects under legal protection, and finally patients in an emergency setting.

Sample size calculation and power calculations

The binary primary outcome is defined from the residual step-off measurement on non contrast CT-scan with a 5 mm cut-off criterion given by the literature. The results observed following treatment of this type of fracture by tibial tuberoplasty in the pilot study conducted at the Poitiers University Hospital describe a proportion of 70% presenting less than 5 mm step-off. A minimum of 25% difference between tuberoplasty and control (70% vs 45%) is expected. With 80% power and two-sided 5% alpha risk, the estimated number of patients is 68 per group. The total is rounded to 140 divided into two groups of 70 patients. The intended number of patients will be less than 50% of the total amount of tibial plateau fracture for each center.

Study design

This is a blinded prospective multicentre randomized controlled trial comparing 2 surgical techniques in the treatment of tibial plateau fractures. Patients will be randomized 1:1 to “tibial tuberosplasty” technique or conventional technique and followed-up for 24 months post-surgery. The enrollment period is planned to run for 12 months. The trial will be conducted at approximately 12 investigator sites in France. The study design is summarized in figure 1.

Interventions

Control group: The patients will be treated with an open technique: cutaneous incision with submeniscal arthrotomy under guidance of a fluoroscope. The reduction will be performed using a spatula, a bone tamp or open reduction internal fixation. The osteosynthesis and filling of the cavity will be performed by the same surgical access.
The conventional open surgery for reduction and fixation of tibial plateau fractures is described in the Campbell’ s operative orthopaedics textbook [12]. Any techniques derived from it with a minimized invasive approach and commonly used by investigator surgeons are considered as "Conventional open surgery".

Experimental group: The patients will be treated with the tibial tuberoplasty technique [8] under fluoroscopic guidance with or without arthroscopy. The reduction will be performed by an anterior approach using a kyphoplasty balloon (figures 2 [13] and 3). The combined osteosynthesis including cannulated screws and cementoplasty will both be performed by a percutaneous technique.

In both groups: Osteosynthesis is at surgeon’s discretion [14] (screws, plates, locking plates) [15]. The same applies to cavity filling (vacuity, demineralized bone matrix, PMMA, calcium phosphate cement…)[16][17]. Arthroscopy is allowed.

Study Objectives

The primary objective is to compare step-off anatomical reduction of tibial plateau fracture by tibial tuberoplasty versus conventional open surgery using CT-scan.
Secondary objectives are to analyze and compare in both groups the clinical parameters as the knee range of motion and time to resume partial / full weight-bearing; to compare the two groups in terms of pain reduction, functional impact and quality of life; to describe the pain management and the safety of the two surgical techniques; to analyze and compare in both groups the radiological parameters to evaluate the fracture healing, the absence of axis shifting (source of secondary osteoarthritis) and the maintenance of the step-off reduction on the long term follow-up; to compare simulated reduction (ANSYS software) versus reduction observed on the CT-Scan; to assess and compare the economic impact of the two surgical techniques; to analyze the pre and per-operative factors which could influence the outcomes of the tuberoplasty.

Study Endpoints

The primary endpoint is the post-operative radiological step-off reduction blindly measured by CT-scan (within 48 hours post-op) and assessed by an independent imaging core lab. The primary endpoint is defined as the proportion of patients showing an optimal reduction with less than 5 mm step-off. A software specially developed for medical image processing and segmentation will be used in this study to quantify the reduction in the most reliable and objective manner.

Clinical secondary endpoints are knee range of motion (degrees); Numeric Pain Rating Scale (NPRS); KOOS (Knee injury and Osteoarthritis Outcome Score) questionnaire; score on EQ-5D (Euro Quality of Life-5 Dimension Health) questionnaire; time to partial and full weight-bearing (in days); pain medication changes, non-drug pain treatment, adjuvant therapies; adverse events; factors which could influence the outcomes of the tuberoplasty (age, gender, nature of the trauma, work-related injury, initial step-off, balloon technique, maximal volume inflate in the balloon, filling-in nature and volume, osteosynthesis coupled, surgery duration, arthroscopy coupled).

Radiological secondary endpoints are tibial fracture healing CTcriteria as defined by Mustonen and al [18] (i.e. lack of non-union signs, cortical continuity, cancellous bone replacement); residual step-off (in mm), measured on the CT-scan at the level of the knee joint at M3; simulated residual step-off (ANSYS Software); femoro-tibial axes on Hip-Knee-Ankle X-rays (in degrees).

Health-economic secondary endpoints are health care utilization (HCU); employment status; incremental cost-utility ratio estimated from the perspective of the healthcare system, at 2 years, by comparing the difference in costs and Quality-Adjusted-Life-Years between tibial tuberoplasty and conventional open surgery for tibial plateau fractures.

Experimental design

The patients will be invited to participate in the study during a trauma care consultation. Once the informed consent form has been signed, the inclusion criteria have been checked and a CT-scan has been performed, the patients will be randomized through a central randomization list. Each included patient will be identified with a single patient number. The patients will be treated in the surgical theater within 10 days following the trauma, either by the minimally invasive technique or by conventional surgery. As tuberoplasty is a new surgical technique, the surgeons involved in this study will receive specific theoretical and practical training before to start the trial.

Follow-up with a non-contrast CT-scan will be performed 2 days and 3 months after the surgery to analyze the maintenance of the reduction. A blinded evaluation will be performed by an independent imaging core lab.

Patients will be assessed prior the randomization and the surgery (D0) and 2, 21, 45 days and 3, 6, 12 and 24 months after. An independent medical evaluator blinded for the surgical technique will assess the patient during the follow-up visits. Axis shifting will be checked at 3-month, 6-month, 12-month and 24-month follow-up visits by performing Hip-Knee-Ankle films.

The 2-year follow-up visit of the patients will be used to monitor the stability of the reduction over time, to check the safety of this new technique and to evaluate the occurrence of secondary early osteoarthritis.

The study flow-chart is summarized in Table 1.

Table 1: Study flow-chart

	Inclusion Visit	Surgery D_0	D_2 Visit	D_{21} Visit	D_{45} Visit	M_3 Visit	M_6 Visit	M_{12} Visit	M_{24} Visit
Patient information	X								
Informed Consent Form	X								
Demographics (i.e. age, gender)	X								
Medical history	X								
Inclusion and exclusion criteria	X								
Randomization	X								
Fracture reduction		X							
CT-scan	X		X			X			
Operative report			X						
Knee X-ray				X	X				
Hip-Knee-Ankle X-ray (Axis shifting)						X	X	X	X
Knee range of motion (degrees)				X	X	X	X	X	X
Numeric Pain Rating Scale (NPRS)	X		X	X	X	X	X	X	X
KOOS questionnaire	X			X	X	X	X	X	X
EQ5D-5L	X				X	X	X	X	X
Pain medication changes, non-drug pain treatment, adjuvant therapies	X	X	X	X	X	X	X	X	X
Health care utilization		X	X	X	X	X	X	X	X
Employment status	X			X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Procedures designed to minimize bias

Randomization method

Subjects who give informed consent and fulfill the inclusion and exclusion criteria will be randomized to be operated using the tibial tuberoplasty or using the open technique in a 1:1 ratio.

The permuted-block randomization list, stratified by center, will be prepared by a methodologist using a random selection program developed under SAS V9.4. The randomization numbers will be assigned in strict sequence, i.e., when a subject is confirmed as eligible for randomization, the next unassigned randomization number in sequence will be given. The randomization allocation will be concealed from the evaluators and subject, using a centralized automatic web-based data management system. Once assigned the randomization assignment for the subject cannot be changed. Early departure from the study for any reason whatsoever, will not give rise to replacement or reassignment of the rank of inclusion.

Blindness

The surgeons who participated in the study are not allowed to become evaluators. An independent medical evaluator blinded for the surgical technique will assess the patient during the follow-up visits. The peroperative dressing applied during the intervention will be replaced by uniform dressing after the 48-hours CT-scan to maintain the patient blinded. In order to keep the evaluator blinded, at every follow-up visit, the patient must wear opaque compression socks to hide the surgery scars.

For the primary endpoint assessment, a blinded CT-scan evaluation will be performed by an independent imaging core lab. To dissimulate the incision side and the technique from the radiologists, the surgeon will close the incisions with radio-transparent suture and not with a skin stapler.

Confidentiality, Data collection and Quality control

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be anonymized. Each patient will only be identified by his/her initials and inclusion number.

Clinical research assistants are available at each participating hospital to help investigators with running the study and data collection. Data will be collected through an eCRF.

A clinical research associate, mandated by the sponsor, will ensure that patient's rights and safety are respected, that inclusion and data collection are in line with the protocol and that the study is conducted in accordance with the Good Clinical Practice guidelines.

Data analysis

All analyses will be performed by a methodologist-biostatistician using the SAS statistical package version 9.4 (SAS Institute Cary, NC). The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion and exclusion criteria for each patient.

Descriptive analysis

The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The categorical variables will be presented in the form of numbers and percentages in each modality.

Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as those lost to follow-up will be described. Deviations from the protocol will be described and analyzed on a case-by-case basis.

Analysis pertaining to the primary criterion

The proportion of patients showing an optimal reduction with less than 5 mm residual step-off will be compared between the two groups at day 2 using Fisher's exact test at the two-sided $p<5\%$ significance level.

The different parameters that would be potentially predictive of an optimal reduction with less than 5 mm step-off (which include young vs elderly population) will be investigated by means of the Student's t-Test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by Fisher's exact test for qualitative variables.

The univariate analysis will be followed by multivariate logistic regression. The initial logistic model will include all variables associated with the dependent outcome ($p<0.20$) as well as relevant variables according to the literature (forced variables). The model will be simplified according to a step-by-step elimination procedure; only the variables associated with the dependent variable (threshold p-value: 5%) and the forced variables will be retained in the final model. Interactions will be tested in the final model. Goodness of fit will be assessed using the Hosmer-Lemeshow chi^2 test.

Analysis pertaining to the secondary criteria

The secondary criteria will be compared using Mann-Whitney U test for quantitative variables and Fisher's exact test for qualitative variables.

The incremenatal cost utility ratio is defined by the difference in average total cost divided by the average 2-year QALYS, the uncertainty of the results will be analyzed using a non-parametric bootstrap which provides multiple estimates of the ICER by randomly re-sampling the patient population 1,000 times. The results will be presented in a scatter plot of 1,000 ICERs on the cost-effectiveness plane and transformed into a cost-effectiveness acceptability curve based on the decision-makers' willingness to pay for an additional QALY.

Timing of analysis

A first analysis on primary and second outcomes is planned after the last day 2 CT-scan of the last patient included in the study. This analysis will provide data to prepare a publication. This analysis will not impact the last patient assessment mainly based on objective data.

DISCUSSION

Justification of study primary objective and primary endpoint

In the treatment of tibial plateau fracture, the complexity to transpose anatomical reduction to clinical outcome explains that surgical treatment efficacy could be assessed by three different types of criteria: 1/ an initial radiological evaluation documenting the anatomical reduction (step-off reduction); 2/ a clinical assessment reflecting the functional impact of the treatment (in terms of mobilization, pain, daily activity); 3/ a long-term follow-up analyzing the potential articular degeneration (based on radiological and clinical parameters).

Giannoudis and al. have demonstrated that under simple X-rays, the smaller the detected step off, the better the outcome [6]. We therefore decided to consider and compare the radiological step-off reduction as the primary objective of this study since the quality of the fracture initial reduction appears to be the determinant factor of clinical outcome.

In this context, it remains surprising that, on the one hand, the pre-operative use of CT-scan is considered as a decisive tool to classify the tibial fracture type and to choose the treatment [19], on the other hand, the majority of surgeons use standard post-op X-ray and no CT-scan to evaluate the fracture reduction.

In addition, it has been mentioned in the literature that a less than 5 mm step-off on CT-scan is not detectable on simple X-ray [20] (figure 4).

We can thus wonder if standard X-ray alone is the best radiological option to evaluate the radiological anatomical reduction precisely. This could represent a significant limitation for clinicians in comparing surgical techniques [20] and create some major difficulties in choosing the best option to treat these patients.

We decided to use CT-Scan to analyze the postoperative radiological step-off reduction. Giving the fact that the lack of any visible step-off would reflect an optimal reduction on standard X-ray and that CT-Scan would be able to detect in this situation a 5 mm residual step-off, our primary endpoint is defined as the proportion of patients showing an

optimal reduction with less than 5 mm residual step-off. This criterion will be measured by CT-scan and assessed by an independent imaging core lab.

We will perform the CT-Scan 48 hours after the surgery in order to reduce the bias by avoiding loss of contact with the patients; keeping the operated patient blinded from the operative technique; assessing the potential failure of osteosynthesis or osteonecrosis; checking the compliance or noncompliance of the operator instructions.

Limitations

We identify two factors which could bias endpoint evaluations: 1/ regarding intervention, even if surgeons will be trained on tibial tuberoplasty before their participation, we cannot guarantee that all surgeons will have the same level of control of this technique. In addition, medial or lateral tibial plateau fractures are accepted in this protocol and osteosynthesis and cavity filling are free. These three elements may influence tibial plateau fracture reduction and its impact on clinical outcomes. 2/ regarding blindness, it can be ensured for primary endpoint as evaluation will be done by an independent imaging core lab. However, for secondary endpoints, investigators could be aware of the technique due the patient's interview after 48h, or due to site organization.

Expected benefits

For the patients randomized in the "tibial tuberoplasty " arm, the expected benefits over the short and medium term are:

- earlier knee range of motion recovery, less stiffness. Knee range of motion is the direct reflection of functional capacity. For example, 83 degrees allow for going up stairs, 90 degrees allow for going down stairs and 93 degrees allows for getting up from a chair.
- improvement of quality of life and functional impact.
- reduction of the time without weight-bearing.
- reduction of acute and chronic pain.
- reduction of the risk of surgical revision and infection of the surgical site [21].
- reduction of complications in conjunction with confinement to bed (particularly in elderly persons).
- treatment of any associated meniscal or ligament injuries during the same surgery, which affect the functional prognosis over the shorter term.
- early resumption of activities.
- reduction of comorbidities connected with the use of iliac crest grafts.
- aesthetic benefits due to the size of the incisions.

The medical-economic benefits expected over the short and medium term are overall reductions of the cost of treatment of these patients taking into consideration the following factors: earlier resumption of social and professional activities; reduction of the time in hospital (absence of minimally invasive Redon drain no longer limits discharge to D3); reduction of painkiller consumption and physical therapy.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Poitiers University Hospital, Research and Innovation Department.

This clinical trial has been categorized as a Class 2 human research study, with minimal constraints and risks, according to the French Jardé law. So, study protocol (V4 - 17 July 2018), information notice and informed consent form have been approved by the french ethics committee Ile-De-France X and sent for information to the French National Agency for Medicines and Health Products Safety. Any substantial modification to study documents must obtain approval of ethics committee before its implementation. The study will be conducted in accordance with current International Conference on Harmonisation (ICH) Good Clinical Practice (GPC) guidelines, Declaration of Helsinki and standard operating procedures. Design, conduct and analysis will adhere to the CONSORT statement.

Dissemination policy

Poitiers University Hospital is the owner of the data. The data cannot be used or disclosed to a third party without its prior submission.

The results of the study will be released to the participating physicians, referring physicians and medical community no later than 1 year after the completion of the trial, through presentation at scientific conferences and publication in peer-reviewed journals

STUDY STATUS

The recruitment is planned to start in October 2018 and is expected to be completed in October 2019. It is anticipated that primary endpoint findings will be available at the beginning of 2020.

The 12 participating sites are, all in France: University Hospital of Poitiers, University Hospital of Pitié-Salpétrière, University Hospital of Bordeaux, University Hospital of Versailles, University Hospital of Amiens, University Hospital of Nantes, University Hospital of Ambroise Paré, University Hospital of Tours, University Hospital of Rennes, University Hospital of Angers, University Hospital of Brest and University Hospital of Rouen.

COMPETING INTERESTS STATEMENT

TV has received consultancy honoraria from Medtronic and Depuy-Synthes. PR is a consultant for Medtronic. He also received honoraria for medical training and research grants from Medtronic. IDZ has received grants from ministry of health. All other co-authors (OM, CB, MR, GH, AG, LEG, PI and FK): none declared

FUNDING STATEMENT

This study received in 2018 funding from the French public health services 'Direction Générale de l'Offre de Soins (DGOS)' through a National Hospital Clinical Research Program. As recommended by the DGOS, Medtronic will provide kyphoplasty kits needed to conduct the study.

AUTHOR CONTRIBUTIONS

TV, LEG, AG, FK and PR contributed to the development of tibial tuberoplasty. TV is the national coordinator of this study, supported by OM, MR and CB. PI helped to design the trial and provided expertise on statistics and

methodology. IDZ provided expertise on heatlh-economic aspects and GH on image processing and analysis for primary endpoint evaluation.

TV, OM, MR and PR designed the trial and drafted the manuscript. CB drafted the manuscript. AG, GH, PI, IDZ, FK and LEG revised the manuscript.

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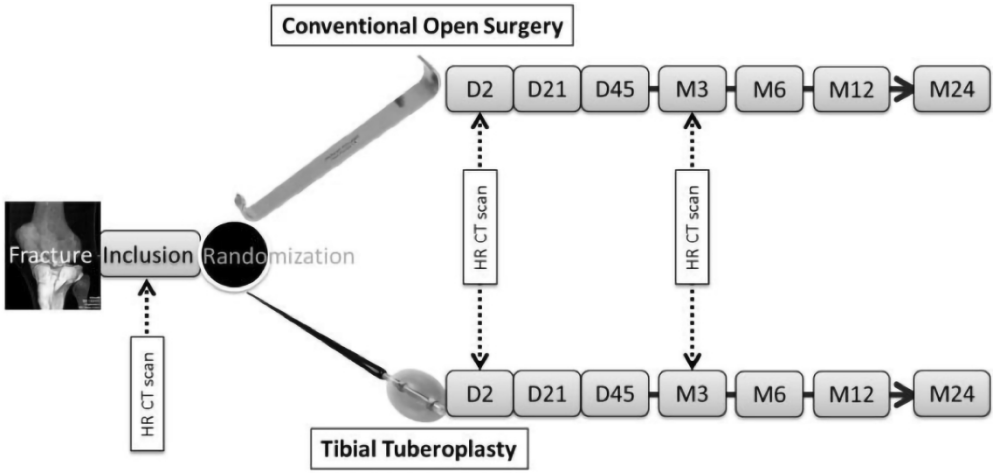

Figure 1: Study design

77x37mm (600 x 600 DPI)

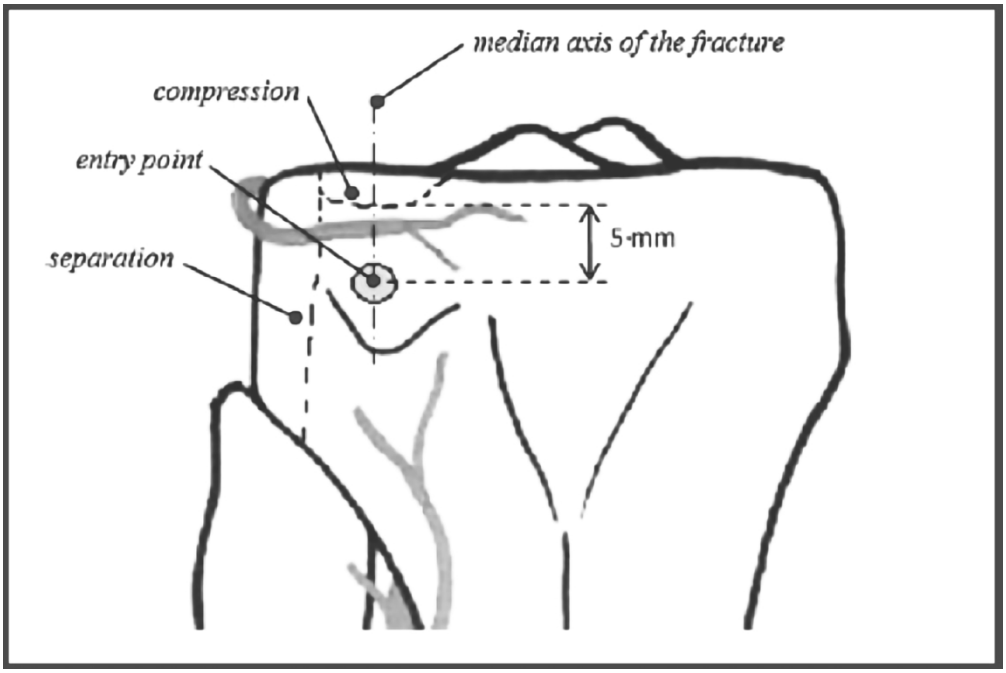

Figure 2: Tuberoplasty entry point (adapted from Hannouche et al., 2006)

82x54mm (600 x 600 DPI)

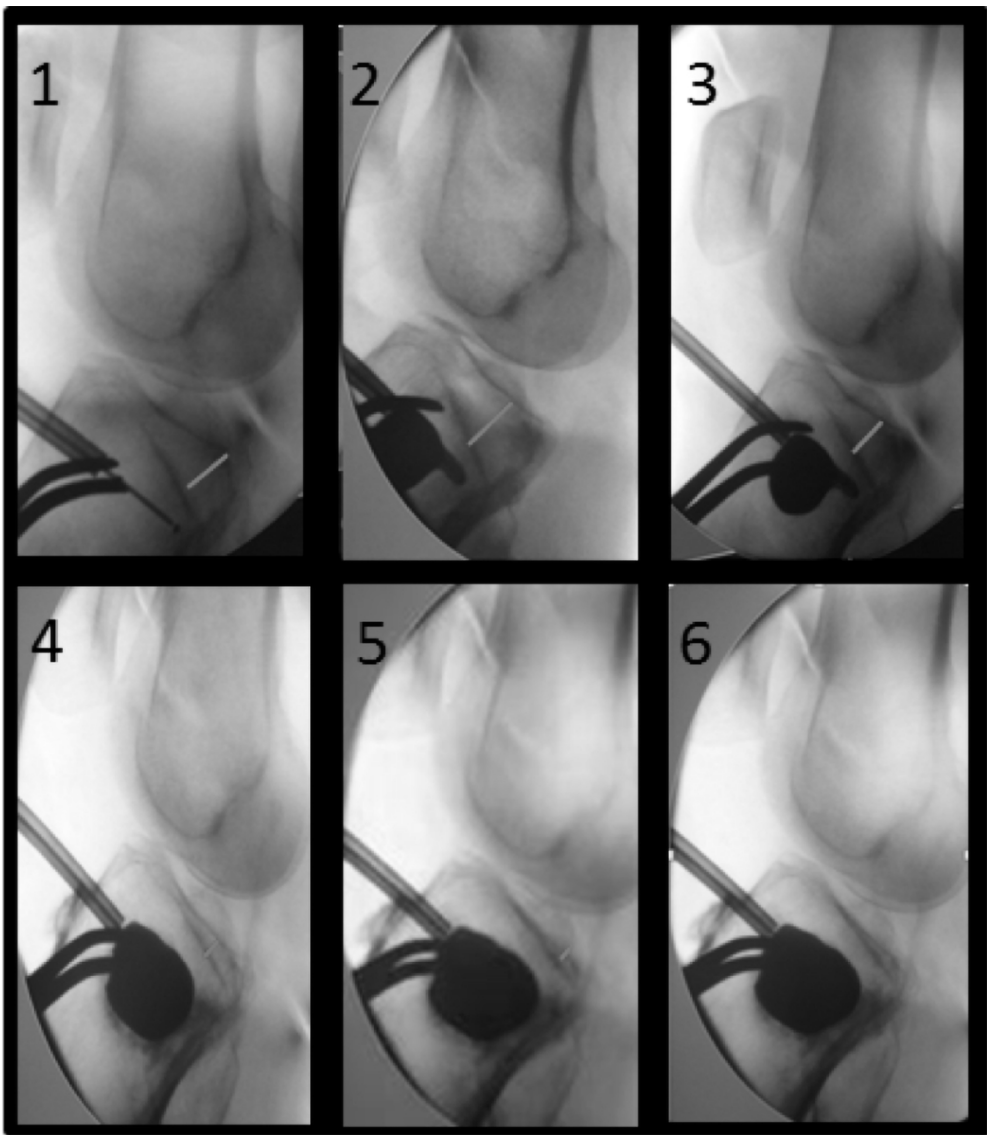

Figure 3: Fluoroscopy of tibial plateau fracture reduction by Tuberoplasty (from Vendeuvre et al., 2013)

151x170mm (300 x 300 DPI)

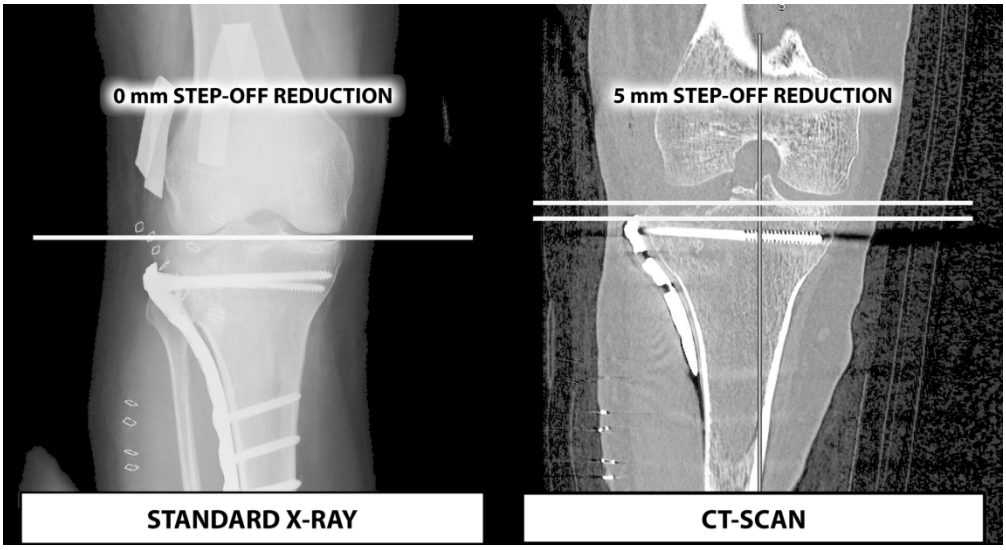

Figure 4: A radiological comparison between standard X-Ray and CT-scan (adapted from Haller et al., 2015)

170x92mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	11
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 11, 12
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 6

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A (surgeon unblinded and can decide to adapt his surgery if necessary)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	-
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	7

generation		any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A (surgeon unblinded)
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data	8

		management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg,	11

		investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11-12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	-
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised	11

		surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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COMPARATIVE EVALUATION OF MINIMALLY INVASIVE 'TIBIAL TUBEROPLASTY' SURGICAL TECHNIQUE VERSUS CONVENTIONAL OPEN SURGERY FOR SCHATZKER II-III TIBIAL PLATEAU FRACTURES: DESIGN OF A MULTICENTRE, RANDOMISED, CONTROLLED AND BLINDED TRIAL (TUBERIMPACT STUDY)

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Keywords:	tibial plateau fracture, balloon reduction, randomized controlled trial, minimally-invasive surgery

COMPARATIVE EVALUATION OF MINIMALLY INVASIVE 'TIBIAL TUBEROPLASTY' SURGICAL TECHNIQUE VERSUS CONVENTIONAL OPEN SURGERY FOR SCHATZKER II-III TIBIAL PLATEAU FRACTURES: DESIGN OF A MULTICENTRE, RANDOMISED, CONTROLLED AND BLINDED TRIAL (TUBERIMPACT STUDY)

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Tibial plateau fracture, balloon reduction, minimally invasive surgery, randomized controlled trial

ABSTRACT

Introduction: Fractures of the tibial plateau are in constant progression. They affect an elderly population suffering from a number of comorbidities, but also a young population increasingly practicing high-risk sports.

The conventional open surgical technique used for tibial plateau fractures has several pitfalls: bone and skin devascularisation, increased risks of infection and functional rehabilitation difficulties.

Since 2011, Poitiers University Hospital is offering to its patients a new minimally invasive technique for the reduction and stabilization of tibial plateau fractures, named "tibial tuberoplasty". This technique involves expansion of the tibial plateau through inflation using a kyphoplasty balloon, filling of the fracture cavity with cement and percutaneous screw fixation.

We designed a study to evaluate the quality of fracture reduction offered by percutaneous tuberoplasty versus conventional open surgery for tibial plateau fracture and its impact on clinical outcome.

Methods and analysis: This is a multicentre randomized controlled trial comparing two surgical techniques in the treatment of tibial plateau fractures. 140 patients with a Schatzker II or III tibial plateau fracture will be recruited in France. They will be randomized either in tibial tuberoplasty arm or in conventional surgery arm. The primary outcome is the post-operative radiological step-off reduction blindly measured on CT-scan (within 48 hours post-op). Additional outcomes include other radiological endpoints, pain, functional abilities, quality of life assessment and health-economic endpoints. Outcomes assessment will be performed at baseline (before surgery), at Day 0 (surgery), at 2, 21, 45 days, 3, 6, 12 and 24 months post-surgery.

Ethics and dissemination: This study has been approved by the ethics committee Ile-De-France X and will be conducted in accordance with current Good Clinical Practice (GPC) guidelines, Declaration of Helsinki and standard operating procedures. The results will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial Registration Number: NCT03444779

Strengths and limitations of this study:

- This is a multicentre, randomized, controlled trial with a calculated number of subjects required to have 80% power to detect a 25% difference in postoperative radiological step-off reduction of tibial plateau fracture by tibial tuberoplasty versus conventional surgery.
- Primary endpoint blindly evaluated on CT-scan by an independent imaging core lab will provide robust and reliable data.
- Learning curve for tibial tuberoplasty technique could create a bias for endpoint evaluation. For this purpose each surgeon will participate in a tibial tuberoplasty workshop before the study.
- Unblinded patient's follow-up could introduce a bias for secondary endpoints evaluation.

INTRODUCTION

French Medico-Administrative Data (from PMSI) data show more than 10 000 proximal tibial fractures diagnosed in 2014 and 4055 lateral tibial plateau fractures operated in 2013 in France [1]. Half (50%) of these fractures are related to the lateral condyle and cause split/depression (Schatzker II) or pure depression (Schatzker III) [2]. This high rate results from the recent democratization of high-risk sports [3], as well as an aging population with increased risks of falling [4]. Aside from the resulting reduced physical activity, the social and professional impact of these fractures is undeniable and represents significant costs for the health care system. A recently published prospective case series reports 28 job losses out of 41 patients treated [5].

The clinical outcome of these patients depends mainly on the primary stability provided by the surgical treatment, after the greatest anatomical reduction possible. Indeed, *Giannoudis and al*. have demonstrated that under simple X-rays, the smaller the detected step-off, the better the outcome [6]. The aim is to allow for recovery of good joint mobility to promote rapid resumption of activity and to limit the onset of early osteoarthritis [7].

The conventional open surgical technique using a bone tamp for reduction and osteosynthesis of tibial plateau fractures has several pitfalls [3]: devascularization of the bone and skin, increased risks of infection and functional rehabilitation difficulties with delayed recovery of weight bearing. Moreover, this technique does not allow for the simultaneous diagnosis and treatment of other possible lesions, such as meniscal injuries in particular.

Since 2011, Poitiers University Hospital is offering to its patients a new minimally invasive technique for the reduction and stabilization of tibial plateau fractures, baptized “tibial tuberoplasty” [8].

The concept derives from the divergent use of vertebral kyphoplasty, initially dedicated to spinal injuries and transposed here to the tibial plateau. This technique involves expansion of the tibial plateau through inflation of a kyphoplasty balloon, filling of the created cavity with cement (PMMA or calcium phosphate) and percutaneous screw fixation. A review of literature regarding this technique is summarized in Table 1. The clinical outcome of these patients depends mainly on the primary stability provided by the surgical treatment, after the greatest anatomical reduction possible “step-off” <5 mm, without axis shifting <5°.

Table 1 : Tuberoplasty/Tibioplasty literature review

	Details	Conclusion
Pizanis, et al 2012 [9]	Technique description + clinical and radiologic results in 5 cases, Schatzker II/III	This new technique may be a useful tool to facilitate the reduction of select depressed tibial fractures in the future
Vendeuvre, et al 2013 [8]	Description of tibial tuberoplasty with an anterior entry point	This new minimally invasive tuberoplasty technique is a good alternative to the conventional technique using a bone tamp in the treatment of tibial plateau fractures
Panzica, et al 2014 [10]	Cadaveric and biomechanical study, 30 test series in synthetic bones	The depth was the decisive factor in the reduction of the fracture and not the diameter
Craiovan, et al 2014 [11]	Video article describing surgical technique	Results are promising, but long-term results are still lacking
Ziogas, et al 2015 [12]	Case Report, Schatzker III, minimal approach which included percutaneous reduction of the fracture under arthroscopy and fluoroscopy guidance + CPC	Arthroscopy assisted balloon osteoplasty seems to be a safe and effective method for the treatment of depressed tibia plateau fractures
Mayr, et al 2015 [13]	Cadeveric study, 8 matched pairs of human tibia, Schatzker III, reduction performed using a	Loss of reduction can be minimised by using locking plate fixation after balloon reduction

	balloon inflation system, followed by cement augmentation	and cement augmentation
Ollivier, et al 2016 [14]	Prospective study, 20 patients, Schatzker II/III , tuberoplasty (optimal entry point) + CPC	The use of balloon-guided inflation tibioplasty with injection of a resorbable bone substitute is safe, and results in a high rate of anatomic reduction and good clinical outcomes
Doria, et al 2017 [15]	Randomized Controlled Trial, 30 patients, Schatzker II/III, tibioplasty versus traditional reduction technique	Tibioplasty technique provides anatomical reduction of the fracture in a gentle and progressive manner and mechanical stability allowing early rehabilitation and more fast weight-bearing
Wang, et al 2018 [16]	Randomized Controlled Trial, 80 patients, Schatzker II / III and IV, arthroscopic-assisted balloon tibioplasty versus Open Reduction Internal Fixation	Study protocol, results expected in 2021
Vendeuvre, et al 2018 [17]	Cadaveric and biomechanical study, 12 human tibia, contribution of minimally invasive bone augmentation to primary stabilization of the osteosynthesis of Schatzker type II tibial plateau fractures: Balloon vs bone tamp	The minimally invasive balloon technique has fewer negative effects than the use of bone tamp on the osseous stock, thereby enabling better primary structural strength of the fracture

We performed the first tibial tuberoplasties through a feasibility study on 36 cadaveric subjects and then transposed the technique to human. We identified major advantages such as minimal skin damage, possible treatment of posterior and multi-fragmented compressions (lifting in a single block by the balloon), reinforcement of the stability of the assembly using cement, possible use of combined arthroscopy [18] (for concomitant meniscal injuries treatment [19]).

This technique allows for optimization of the fracture reduction by elevating the posterior fragments with the inflatable bone tamp through an anterior approach. The reduction is made possible thanks to the specificity of the inflatable bone tamp which inflates and reduces the area of least resistance.

The aim of this innovative technique is focused on the anatomical reduction in order to restore the convexity of the tibial plateau [20] which is similar to the balloon convexity.

The results from the first 40 patients operated since 2011 are promising and show a proportion of 70% presenting less than 5 mm step-off reduction.

There is now a need for a larger-scaled multicentre randomized controlled trial to compare the efficacy of tibial tuberoplasty versus the gold standard treatment (conventional open surgery), not only in terms of radiological step-off reduction but also in terms of functional impact.

To bridge this gap, we designed a study to evaluate the quality of fracture reduction offered by percutaneous tuberoplasty versus conventional open surgery for tibial plateau fracture and its impact on clinical outcomes.

METHOD AND ANALYSIS

Study Population

The study population comprises two target populations with tibial plateau fracture:

- Young subjects with fractures mainly resulting from highway accidents and high-risk sports.

- Elderly population with fractures mainly caused by falls, in the context of osteoporosis.

A patient must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for the study.

Inclusion criteria

The subjects are more than 18 years old; present a Schatzker type II or III tibial plateau fracture (compression with or without split) demonstrated on CT-scan and located in the lateral or medial condyle of tibia; have 10-day-old maximum fractures caused by trauma; understand and accept the constraints of the study; are beneficiaries or affiliated members of a Health Insurance plan; give written consent for the study after having received clear information.

Exclusion criteria

The subjects present fractures resulting from osteolysis; have open fractures; have fractures more than 10 days old; have concomitant fracture(s) or condition(s) during the trauma reducing the range of motion; were unable to walk before the injury; have a history of sepsis in the injured knee; have contraindications to anesthesia, contrast agent, medical devices or cement; have a history of hypersensitivity reactions to contrast media, bone filler or metal; present a degenerative joint disease (polyarthritis, etc.); require closer protection, i.e. minors, pregnant women, nursing mothers, subjects deprived of their freedom by a court or administrative decision, subjects admitted to a health or social welfare establishment, major subjects under legal protection, and finally patients in an emergency setting.

Sample size calculation and power calculations

The binary primary outcome is defined from the residual step-off measurement on non contrast CT-scan with a 5 mm cut-off criterion given by the literature. The results observed following treatment of this type of fracture by tibial tuberoplasty in the pilot study conducted at the Poitiers University Hospital describe a proportion of 70% presenting less than 5 mm step-off. A minimum of 25% difference between tuberoplasty and control (70% vs 45%) is expected. With 80% power and two-sided 5% alpha risk, the estimated number of patients is 68 per group. The total is rounded to 140 divided into two groups of 70 patients. The intended number of patients will be less than 50% of the total amount of tibial plateau fracture for each center.

Study design

This is a blinded prospective multicentre randomized controlled trial comparing 2 surgical techniques in the treatment of tibial plateau fractures. Patients will be randomized 1:1 to “tibial tuberosplasty” technique or conventional technique and followed-up for 24 months post-surgery. The enrollment period is planned to run for 12 months. The trial will be conducted at approximately 12 investigator sites in France. The study design is summarized in figure 1.

Interventions

Control group: The patients will be treated with a conventional surgery. The reduction will be performed using a spatula, a bone tamp or open reduction internal fixation. The osteosynthesis and filling of the cavity will be performed by the same surgical access.

The conventional open surgery for reduction and fixation of tibial plateau fractures is described in the Campbell' s operative orthopaedics textbook [21]. Any techniques derived from it with a minimized invasive approach and commonly used by investigator surgeons are considered as "Conventional open surgery".

Experimental group: The patients will be treated with the tibial tuberoplasty technique [8] under fluoroscopic guidance with or without arthroscopy. The reduction will be performed by an anterior approach using a kyphoplasty balloon (figures 2 [22] and 3). The combined osteosynthesis including cannulated screws and cementoplasty will both be performed by a percutaneous technique.

In both groups: Osteosynthesis is at surgeon's discretion [23] (screws, plates, locking plates) [24]. The same applies to cavity filling (vacuity, demineralized bone matrix, PMMA, calcium phosphate cement…)[25][26]. Arthroscopy is allowed.

Study Objectives

The primary objective is to compare step-off anatomical reduction of tibial plateau fracture by tibial tuberoplasty versus conventional open surgery using CT-scan.

Secondary objectives are to analyze and compare in both groups the clinical parameters as the knee range of motion and time to resume partial / full weight-bearing; to compare the two groups in terms of pain reduction, functional impact and quality of life; to describe the pain management and the safety of the two surgical techniques; to analyze and compare in both groups the radiological parameters to evaluate the fracture healing, the absence of axis shifting (source of secondary osteoarthritis) and the maintenance of the step-off reduction on the long term follow-up; to compare simulated reduction (ANSYS software) versus reduction observed on the CT-Scan; to assess and compare the economic impact of the two surgical techniques; to analyze the pre and per-operative factors which could influence the outcomes of the tuberoplasty.

Study Endpoints

The primary endpoint is the post-operative radiological step-off reduction blindly measured by CT-scan (within 48 hours post-op) and assessed by an independent imaging core lab. The primary endpoint is defined as the proportion of patients showing an optimal reduction with less than 5 mm step-off. A software specially developed for medical image processing and segmentation will be used in this study to quantify the reduction in the most reliable and objective manner. The measurement error is unfortunately well known as a bias in all radiological studies. According to Kim et al [27], spacial resolution described thanks to 3D Multi-Planar Resolution mode is 0,3 mm. In order to optimize this measurement, it is important to consider scanner calibration using a phantom, 3D reconstruction in

order to be in the strict plan of tibial plateau and CT-scan assessment thanks to a consensus between 2 specialized radiologists.

Clinical secondary endpoints are knee range of motion (degrees); Numeric Pain Rating Scale (NPRS); KOOS (Knee injury and Osteoarthritis Outcome Score) questionnaire; score on EQ-5D (Euro Quality of Life-5 Dimension Health) questionnaire; time to partial and full weight-bearing (in days); pain medication changes, non-drug pain treatment, adjuvant therapies; adverse events; factors which could influence the outcomes of the tuberoplasty (age, gender, nature of the trauma, work-related injury, initial step-off, balloon technique, maximal volume inflate in the balloon, filling-in nature and volume, osteosynthesis coupled, surgery duration, arthroscopy coupled).

Radiological secondary endpoints are tibial fracture healing CTcriteria as defined by Mustonen and al [28] (i.e. lack of non-union signs, cortical continuity, cancellous bone replacement); residual step-off (in mm), measured on the CT-scan at the level of the knee joint at M3; simulated residual step-off (ANSYS Software); femoro-tibial axes on Hip-Knee-Ankle X-rays (in degrees).

Health-economic secondary endpoints are health care utilization (HCU); employment status; incremental cost-utility ratio estimated from the perspective of the healthcare system, at 2 years, by comparing the difference in costs and Quality-Adjusted-Life-Years between tibial tuberoplasty and conventional open surgery for tibial plateau fractures.

Experimental design

The patients will be invited to participate in the study during a trauma care consultation. Once the informed consent form has been signed, the inclusion criteria have been checked and a CT-scan has been performed, the patients will be randomized through a central randomization list. Each included patient will be identified with a single patient number. The patients will be treated in the surgical theater within 10 days following the trauma, either by the minimally invasive technique or by conventional surgery. As tuberoplasty is a new surgical technique, the surgeons involved in this study will receive specific theoretical and practical training before to start the trial.

Follow-up with a non-contrast CT-scan will be performed 2 days and 3 months after the surgery to analyze the maintenance of the reduction. A blinded evaluation will be performed by an independent imaging core lab.

Patients will be assessed prior the randomization and the surgery (D0) and 2, 21, 45 days and 3, 6, 12 and 24 months after. An independent medical evaluator blinded for the surgical technique will assess the patient during the follow-up visits. Axis shifting will be checked at 3-month, 6-month, 12-month and 24-month follow-up visits by performing Hip-Knee-Ankle films.

The 2-year follow-up visit of the patients will be used to monitor the stability of the reduction over time, to check the safety of this new technique and to evaluate the occurrence of secondary early osteoarthritis.

The study flow-chart is summarized in Table 2.

Table 2: Study flow-chart

	Inclusion Visit	**Surgery D_0**	**D_2 Visit**	**D_{21} Visit**	**D_{45} Visit**	**M_3 Visit**	**M_6 Visit**	**M_{12} Visit**	**M_{24} Visit**
Patient information	X								
Informed Consent Form	X								
Demographics (i.e. age, gender)	X								

Medical history	X								
Inclusion and exclusion criteria	X								
Randomization	X								
Fracture reduction		X							
CT-scan	X		X			X			
Operative report			X						
Knee X-ray				X	X				
Hip-Knee-Ankle X-ray (Axis shifting)						X	X	X	X
Knee range of motion (degrees)				X	X	X	X	X	X
Numeric Pain Rating Scale (NPRS)	X		X	X	X	X	X	X	X
KOOS questionnaire	X			X	X	X	X	X	X
EQ5D-5L	X				X	X	X	X	X
Pain medication changes, non-drug pain treatment, adjuvant therapies	X	X	X	X	X	X	X	X	X
Health care utilization		X	X	X	X	X	X	X	X
Employment status	X			X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Procedures designed to minimize bias

Randomization method

Subjects who give informed consent and fulfill the inclusion and exclusion criteria will be randomized to be operated using the tibial tuberoplasty or using the open technique in a 1:1 ratio.

The permuted-block randomization list, stratified by center, will be prepared by a methodologist using a random selection program developed under SAS V9.4. The randomization numbers will be assigned in strict sequence, i.e., when a subject is confirmed as eligible for randomization, the next unassigned randomization number in sequence will be given. The randomization allocation will be concealed from the evaluators and subject, using a centralized automatic web-based data management system. Once assigned the randomization assignment for the subject cannot be changed. Early departure from the study for any reason whatsoever, will not give rise to replacement or reassignment of the rank of inclusion.

Blindness

The surgeons who participated in the study are not allowed to become evaluators. An independent medical evaluator blinded for the surgical technique will assess the patient during the follow-up visits. The peroperative dressing applied during the intervention will be replaced by uniform dressing after the 48-hours CT-scan to maintain the patient blinded. In order to keep the evaluator blinded, at every follow-up visit, the patient must wear opaque compression socks to hide the surgery scars.

For the primary endpoint assessment, a blinded CT-scan evaluation will be performed by an independent imaging core lab. To dissimulate the incision side and the technique from the radiologists, the surgeon will close the incisions with radio-transparent suture and not with a skin stapler. For reminder, osteosynthesis and filling are totally at surgeon discretion, whatever the randomization group.

Confidentiality, Data collection and Quality control

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be anonymized. Each patient will only be identified by his/her initials and inclusion number.

Clinical research assistants are available at each participating hospital to help investigators with running the study and data collection. Data will be collected through an eCRF.

A clinical research associate, mandated by the sponsor, will ensure that patient's rights and safety are respected, that inclusion and data collection are in line with the protocol and that the study is conducted in accordance with the Good Clinical Practice guidelines.

Data analysis

All analyses will be performed by a methodologist-biostatistician using the SAS statistical package version 9.4 (SAS Institute Cary, NC). The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion and exclusion criteria for each patient. Unblinding will be performed after the blind review.

Two types of population are expected in this study. These populations will be included in the statistical analysis as a modifying factor, as the clinical expectations, medical and economic repercussions are different. According to Rothman [29], effect modification refers to a change in magnitude of an effect measure according to the value of some third variable which is called an effect modifier.

Dealing with a suspected effect modifier requires to stratify the analysis, not necessarily to stratify the randomization plan.

Stratified analysis will provide a pooled estimate of treatment effect (as usual) as well as stratum-specific estimates. Homogeneity between age strata will be tested from the interaction between age stratum and treatment from bivariate logistic regression.

Descriptive analysis

The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The categorical variables will be presented in the form of numbers and percentages in each modality.

Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as those lost to follow-up will be described. Deviations from the protocol will be described and analyzed on a case-by-case basis.

Analysis pertaining to the primary criterion

The proportion of patients showing an optimal reduction with less than 5 mm residual step-off will be compared between the two groups at day 2 using Fisher's exact test at the two-sided $p<5\%$ significance level.

The different parameters that would be potentially predictive of an optimal reduction with less than 5 mm step-off (which include young vs elderly population) will be investigated by means of the Student's t-Test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by Fisher's exact test for qualitative variables.

The univariate analysis will be followed by multivariate logistic regression. The initial logistic model will include all variables associated with the dependent outcome ($p<0.20$) as well as relevant variables according to the literature (forced variables). The model will be simplified according to a step-by-step elimination procedure; only the variables associated with the dependent variable (threshold p-value: 5%) and the forced variables will be retained in the final model. Interactions will be tested in the final model. Goodness of fit will be assessed using the Hosmer-Lemeshow chi^2 test.

Analysis pertaining to the secondary criteria

The secondary criteria will be compared using Mann-Whitney U test for quantitative variables and Fisher's exact test for qualitative variables.

The incremenatal cost utility ratio is defined by the difference in average total cost divided by the average 2-year QALYS, the uncertainty of the results will be analyzed using a non-parametric bootstrap which provides multiple estimates of the ICER by randomly re-sampling the patient population 1,000 times. The results will be presented in a scatter plot of 1,000 ICERs on the cost-effectiveness plane and transformed into a cost-effectiveness acceptability curve based on the decision-makers' willingness to pay for an additional QALY.

Timing of analysis

A first analysis on primary and second outcomes is planned after the last day 2 CT-scan of the last patient included in the study. This analysis will provide data to prepare a publication. A final analysis is planned after the last patient last visit.

Patient and Public Involvement

Patients or public were not involved in study design, recruitment or conduct. Study results will be disseminated to study participants via a thank you letter which will received at the end of the study.

DISCUSSION

Justification of study primary objective and primary endpoint

In the treatment of tibial plateau fracture, the complexity to transpose anatomical reduction to clinical outcome explains that surgical treatment efficacy could be assessed by three different types of criteria: 1/ an initial radiological evaluation documenting the anatomical reduction (step-off reduction); 2/ a clinical assessment reflecting the functional impact of the treatment (in terms of mobilization, pain, daily activity); 3/ a long-term follow-up analyzing the potential articular degeneration (based on radiological and clinical parameters).

Giannoudis and al. have demonstrated that under simple X-rays, the smaller the detected step off, the better the outcome [6]. We therefore decided to consider and compare the radiological step-off reduction as the primary objective of this study since the quality of the fracture initial reduction appears to be the determinant factor of clinical outcome.

In this context, it remains surprising that, on the one hand, the pre-operative use of CT-scan is considered as a decisive tool to classify the tibial fracture type and to choose the treatment [30], on the other hand, the majority of surgeons use standard post-op X-ray and no CT-scan to evaluate the fracture reduction.

In addition, it has been mentioned in the literature that a less than 5 mm step-off on CT-scan is not detectable on simple X-ray [31] (figure 4).

We can thus wonder if standard X-ray alone is the best radiological option to evaluate the radiological anatomical reduction precisely. This could represent a significant limitation for clinicians in comparing surgical techniques [31] and create some major difficulties in choosing the best option to treat these patients.

We decided to use CT-Scan to analyze the postoperative radiological step-off reduction. Giving the fact that the lack of any visible step-off would reflect an optimal reduction on standard X-ray and that CT-Scan would be able to detect in this situation a 5 mm residual step-off, our primary endpoint is defined as the proportion of patients showing an optimal reduction with less than 5 mm residual step-off. This criterion will be measured by CT-scan and assessed by an independent imaging core lab.

We will perform the CT-Scan 48 hours after the surgery in order to reduce the bias by avoiding loss of contact with the patients; keeping the operated patient blinded from the operative technique; assessing the potential failure of osteosynthesis or osteonecrosis; checking the compliance or noncompliance of the operator instructions.

Limitations

We identify two factors which could bias endpoint evaluations: 1/ regarding intervention, even if surgeons will be trained on tibial tuberoplasty before their participation, we cannot guarantee that all surgeons will have the same level of control of this technique. In addition, medial or lateral tibial plateau fractures are accepted in this protocol and osteosynthesis and cavity filling are free. These three elements may influence tibial plateau fracture reduction and its impact on clinical outcomes. 2/ regarding blindness, it can be ensured for primary endpoint as evaluation will be done by an independent imaging core lab. However, for secondary endpoints, investigators could be aware of the technique due the patient's interview after 48h, or due to site organization.

Expected benefits

For the patients randomized in the "tibial tuberoplasty " arm, the expected benefits over the short and medium term are:

- earlier knee range of motion recovery, less stiffness. Knee range of motion is the direct reflection of functional capacity. For example, 83 degrees allow for going up stairs, 90 degrees allow for going down stairs and 93 degrees allows for getting up from a chair.
- improvement of quality of life and functional impact.
- reduction of the time without weight-bearing.

- reduction of acute and chronic pain.
- reduction of the risk of surgical revision and infection of the surgical site [32].
- reduction of complications in conjunction with confinement to bed (particularly in elderly persons).
- treatment of any associated meniscal or ligament injuries during the same surgery, which affect the functional prognosis over the shorter term.
- early resumption of activities.
- reduction of comorbidities connected with the use of iliac crest grafts.
- aesthetic benefits due to the size of the incisions.

The medical-economic benefits expected over the short and medium term are overall reductions of the cost of treatment of these patients taking into consideration the following factors: earlier resumption of social and professional activities; reduction of the time in hospital (absence of minimally invasive Redon drain no longer limits discharge to D3); reduction of painkiller consumption and physical therapy.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Poitiers University Hospital, Research and Innovation Department.

This clinical trial has been categorized as a Class 2 human research study, with minimal constraints and risks, according to the French Jardé law. So, study protocol (V4 - 17 July 2018), information notice and informed consent form have been approved by the french ethics committee Ile-De-France X and sent for information to the French National Agency for Medicines and Health Products Safety (ref protocole 24-2018 or 2018-A01027-48). Any substantial modification to study documents must obtain approval of ethics committee before its implementation. The study will be conducted in accordance with current International Conference on Harmonisation (ICH) Good Clinical Practice (GPC) guidelines, Declaration of Helsinki and standard operating procedures. Design, conduct and analysis will adhere to the CONSORT statement.

Dissemination policy

Poitiers University Hospital is the owner of the data. The data cannot be used or disclosed to a third party without its prior submission.

The results of the study will be released to the participating physicians, referring physicians and medical community no later than 1 year after the completion of the trial, through presentation at scientific conferences and publication in peer-reviewed journals

STUDY STATUS

The recruitment is planned to start in October 2018 and is expected to be completed in October 2019. It is anticipated that primary endpoint findings will be available at the beginning of 2020.

The 12 participating sites are, all in France: University Hospital of Poitiers, University Hospital of Pitié-Salpétrière, University Hospital of Bordeaux, University Hospital of Versailles, University Hospital of Amiens, University Hospital

of Nantes, University Hospital of Ambroise Paré, University Hospital of Tours, University Hospital of Rennes, University Hospital of Angers, University Hospital of Brest and University Hospital of Rouen.

COMPETING INTERESTS STATEMENT

TV has received consultancy honoraria from Medtronic and Depuy-Synthes. PR is a consultant for Medtronic. He also received honoraria for medical training and research grants from Medtronic. IDZ has received grants from ministry of health. All other co-authors (OM, CB, MR, GH, AG, LEG, PI and FK): none declared

FUNDING STATEMENT

This study received in 2018 funding from the French public health services 'Direction Générale de l'Offre de Soins (DGOS)' through a National Hospital Clinical Research Program. As recommended by the DGOS, Medtronic will provide kyphoplasty kits needed to conduct the study.

AUTHOR CONTRIBUTIONS

TV, LEG, AG, FK and PR contributed to the development of tibial tuberoplasty. TV is the national coordinator of this study, supported by OM, MR and CB. PI helped to design the trial and provided expertise on statistics and methodology. IDZ provided expertise on heatlh-economic aspects and GH on image processing and analysis for primary endpoint evaluation.

TV, OM, MR and PR designed the trial and drafted the manuscript. CB drafted the manuscript. AG, GH, PI, IDZ, FK and LEG revised the manuscript.

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FIGURE LEGENDS

Figure 1: Study design

Figure 2: Tuberoplasty entry point (adapted from Hannouche et al., 2006)

Figure 3: Fluoroscopy of tibial plateau fracture reduction by Tuberoplasty (from Vendeuvre et al., 2013)

Figure 4: A radiological comparison between standard X-Ray and CT-scan (adapted from Haller et al., 2015)

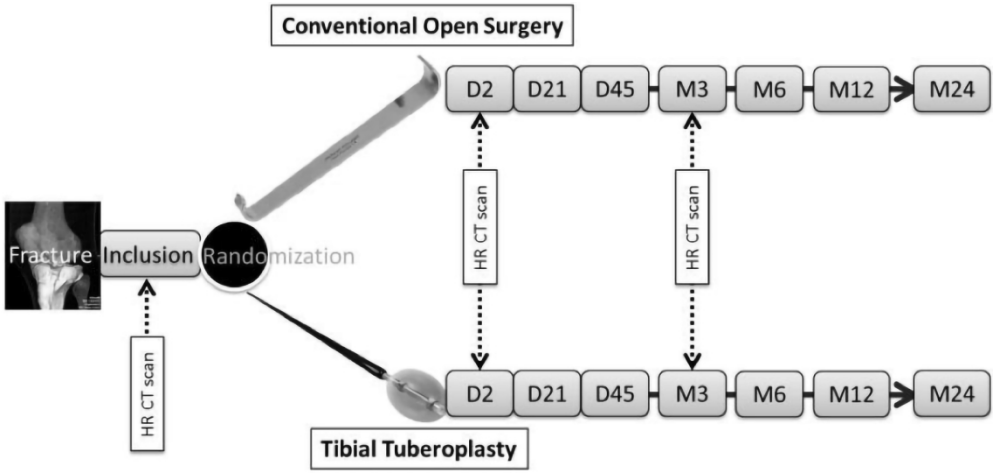

Figure 1: Study design

77x37mm (600 x 600 DPI)

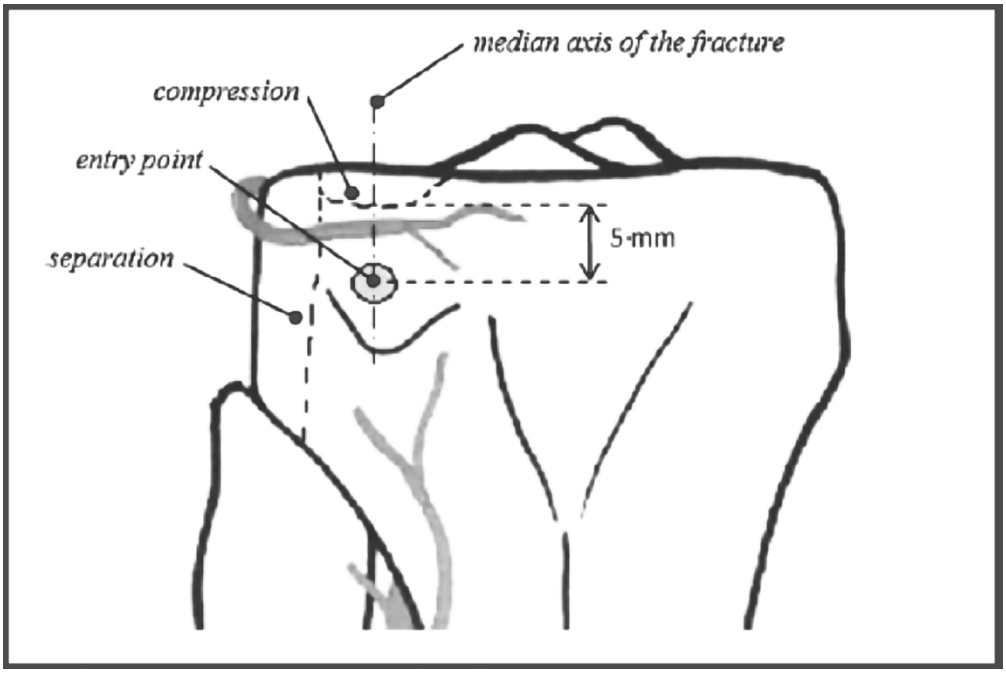

Figure 2: Tuberoplasty entry point (adapted from Hannouche et al., 2006)

82x54mm (600 x 600 DPI)

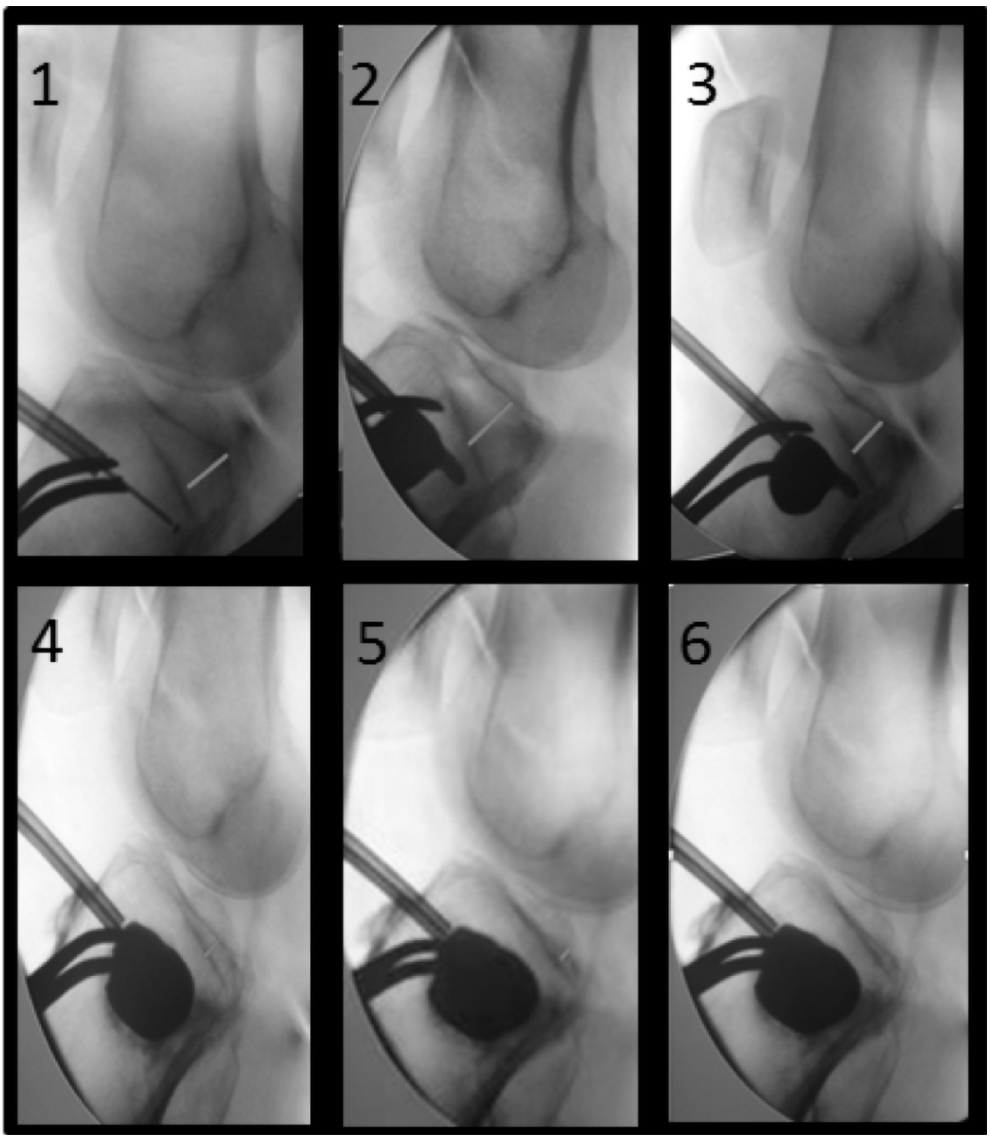

Figure 3: Fluoroscopy of tibial plateau fracture reduction by Tuberoplasty (from Vendeuvre et al., 2013)

151x170mm (300 x 300 DPI)

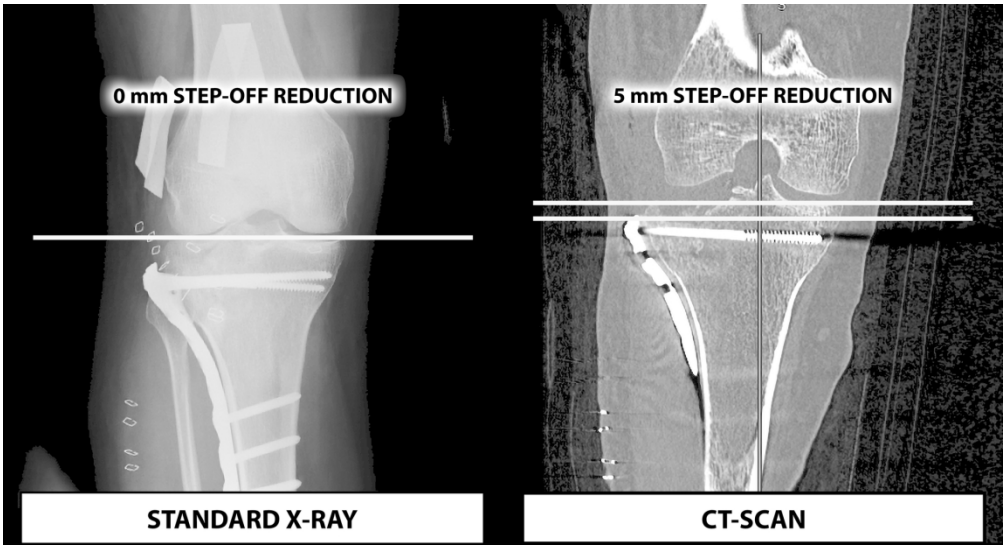

Figure 4: A radiological comparison between standard X-Ray and CT-scan (adapted from Haller et al., 2015)

170x92mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	11
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 11, 12
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 6

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A (surgeon unblinded and can decide to adapt his surgery if necessary)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	-
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	7

generation		any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A (surgeon unblinded)
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data	8

		management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg,	11

		investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11-12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	-
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised	11

		surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A