

BMJ Open Comparison of autologous osteoperiosteal cylinder and osteochondral graft transplantation in the treatment of large cystic osteochondral lesions of the talus (OLTs): a protocol for a non-inferiority randomised controlled trial

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ABSTRACT

Introduction Large cystic osteochondral lesions of the talus (OLTs) have been shown to have inferior clinical outcomes after reparative techniques such as bone marrow stimulation. Autologous osteochondral transplantation has been viewed as an alternative choice for treating these lesions, but donor-site morbidity has limited its application. Excellent clinical outcomes have been shown in repairing these types of lesions with autologous osteoperiosteal grafts, and these outcomes are achieved at a low cost and without donor-site morbidity in the normal knee joint. This will be the first randomised controlled trial to compare the two surgical techniques, and recommendations for the treatment of patients with large cystic OLTs will be provided.

Methods and analysis A non-inferiority randomised controlled trial will be conducted. A total of 70 participants with clinically diagnosed large cystic OLTs will be randomly allocated to either the experimental group or the control group at a ratio of 1:1. The experimental group will be treated with autologous osteoperiosteal cylinder graft transplantation, while the control group will be treated with autologous osteochondral transplantation. The primary outcome measure will be the American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Score and the Short Form 12 (SF-12) questionnaire. Secondary outcome measures will include the secondary arthroscopy International Cartilage Repair Society score, the Magnetic Resonance Observation of Cartilage Repair Tissue score, the Tegner activity level score, the visual analogue scale, routine X-rays, CT and complications. These parameters will be evaluated preoperatively, as well as at 3, 6, 12, 24, 36 and 60 months postoperatively. In this trial, we hypothesised that both procedures offer good results for the treatment of patients with large cystic OLTs, and occurrence of donor-site morbidity in autologous osteoperiosteal cylinder graft transplantation group is less than that in autologous osteochondral transplantation group.

Ethics and dissemination The current study was approved by the board of research ethics of Peking

Strengths and limitations of this study

- This high-quality randomised controlled trial would have an important value in the scheduling and developing of treatment options for patients with large cystic osteochondral lesions of the talus.
- Randomisation will minimise the risk of selection bias.
- The key limitation of this trial is the lack of blinding of the participating surgeons and participants, which may result in potential bias.

University Third Hospital Medical Science Research Ethics Committee. The results of this study will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number NCT03347877.

INTRODUCTION

Background and rationale

Osteochondral lesions of the talus (OLTs), recognised as an increasingly common injury,^{1,2} occur in up to 73% of all ankle fractures, in 50% of ankle sprains and in 41% of ankles with lateral instability.³ These lesions involve the articular cartilage and/or subchondral bone and causes severe symptoms, such as pain, swelling, stiffness, weakness, a reduction in sports activity and quality of life, and osteoarthritis.⁴

The progression of subchondral cysts formation, associated with deep ankle pain, could cause the deterioration of clinical scores after a surgical procedure, as confirmed by Shimozono *et al.*⁵ The consensus statement for the treatment of OLT has been published in 2018.⁶

To date, it has been reported that bone marrow stimulation procedures, as a primary treatment strategy, have shown a reparative effect for OLTs without cysts or with small cysts.⁷ With the lack of healthy subchondral bone and the paucity of stem cells, the healing response after bone marrow stimulation for patients with large cystic OLTs is poor.⁸ Therefore, large cystic lesions require additional surgical options. The use of autologous chondrocyte implantation has been limited as a choice for treating such lesions because of its relatively high cost.⁹ According to recent animal studies, cell-free scaffolds are also efficacious in cartilage regeneration.¹⁰ Another clinical report has reported the clinical and radiological results of patients with OLTs who were treated by cell-free scaffold implantation in a single-step arthroscopic surgery. However, oversized bone cysts (>10mm of depth) were filled with autogenous cancellous iliac bone graft before implantation of the scaffold, but long-term changes such as degenerative arthritis were still controversial.¹¹ Although good results have been reported in previous studies with the use of fresh osteochondral allografts for large cystic OLTs, the process of obtaining fresh allografts and the risk of infection present challenges.^{12 13} Autologous osteochondral transplantation has been viewed as an alternative choice for treating these lesions, but the high proportion donor-site morbidity that ranged from 6.7% to 10.8% and the size of osteochondral grafts have limited the application of this technique.¹⁴ Thus, Hu *et al*¹⁵ have tried to repair large cystic OLTs with autologous osteoperiosteal grafts because of their low cost and the absence of donor-site morbidity in the normal knee joint; this procedure has shown favourable clinical outcomes and satisfactory incorporation of grafts into the adjacent tissue.

Randomised controlled trials (RCTs) have the advantage of controlling for all possible variables because of the random sequence generation, without which confounding factors and bias may be more problematic. High-quality RCTs are often deemed to be the gold standard for investigating the consequences of an intervention. To our knowledge, no randomised controlled study of the clinical outcomes for autologous osteoperiosteal cylinder graft transplantation versus autologous osteochondral transplantation for the treatment of large cystic OLTs has been performed.

Research objectives

The aim of this RCT is to determinate whether autologous osteoperiosteal cylinder graft transplantation, compared with autologous osteochondral transplantation, has non-inferior clinical and radiographic outcomes and is superior in reducing donor-site morbidity of the normal knee joint in the treatment of large cystic OLTs.

METHODS AND DESIGN

Study design and settings

The present study will be a single-centre, prospective, non-inferiority RCT identifying whether autologous osteoperiosteal cylinder graft transplantation, compared with

autologous osteochondral transplantation, has an equivalent main therapeutic effect with fewer complications in the treatment of large cystic OLTs. The entire trial will be conducted at Peking University Third Hospital. All participants will be asked to sign an informed consent form. This trial has been registered at the US National Institutes of Health Clinical Trials Registry, a WHO compliant public domain trials register. A chart outlining the trial design is shown in [figure 1](#).

Patient and public involvement

The development of the research question and outcome measures will be informed by patients' priorities, experiences and preferences in the outpatient clinic during each follow-up. Based on our current studies on the treatment of large cystic OLTs, the inclusion criteria for patients in this study were designed. Patients will not be involved in the recruitment and conduct of the study. The results will be disseminated to study participants by phone call. The burden of the intervention will be assessed by the patients and our findings.

Participants

The patients who are referred to the outpatient clinic of the Peking University Third Hospital, complaining of chronic ankle pain and swelling, will undergo the initial clinical examination and MRI. Patients who are diagnosed with large cystic OLTs and who meet the inclusion criteria will be informed about the project and the possibility of participating. Additional inclusion and exclusion criteria are shown as follows:

Inclusion criteria

- ▶ Aged 18–60 years old, male or female.
- ▶ Chronic pain in the ankle, confirmed to be cystic OLTs by ankle joint MRI, with cyst diameters of larger than 8 mm as measured by CT.
- ▶ A lack of response to at least 3 months of conservative treatment (rest, oral administration of medication, external application of medication, physical therapy or intra-articular hyaluronic acid injections).
- ▶ Willingness to voluntarily participate in the clinical trial and sign informed consent.

Exclusion criteria

- ▶ Participating in other clinical trials.
- ▶ Obvious structural malalignment (varus or valgus deformity of the ankle of more than 5° degrees).
- ▶ Grade III ankle collateral ligament injury¹⁶ or obvious instability of the ankle joint that requires a ligament repair procedure.
- ▶ Moderate and severe osteoarthritis,^{17 18} traumatic arthritis or kissing lesions.
- ▶ Systemic diseases, such as diabetes, rheumatoid arthritis and gouty arthritis.
- ▶ Joint fibrosis, ankylosis or other significant deficiency of ROM.
- ▶ Previous failed surgery for OLTs.
- ▶ Patient medically not fit for surgery or MRI.

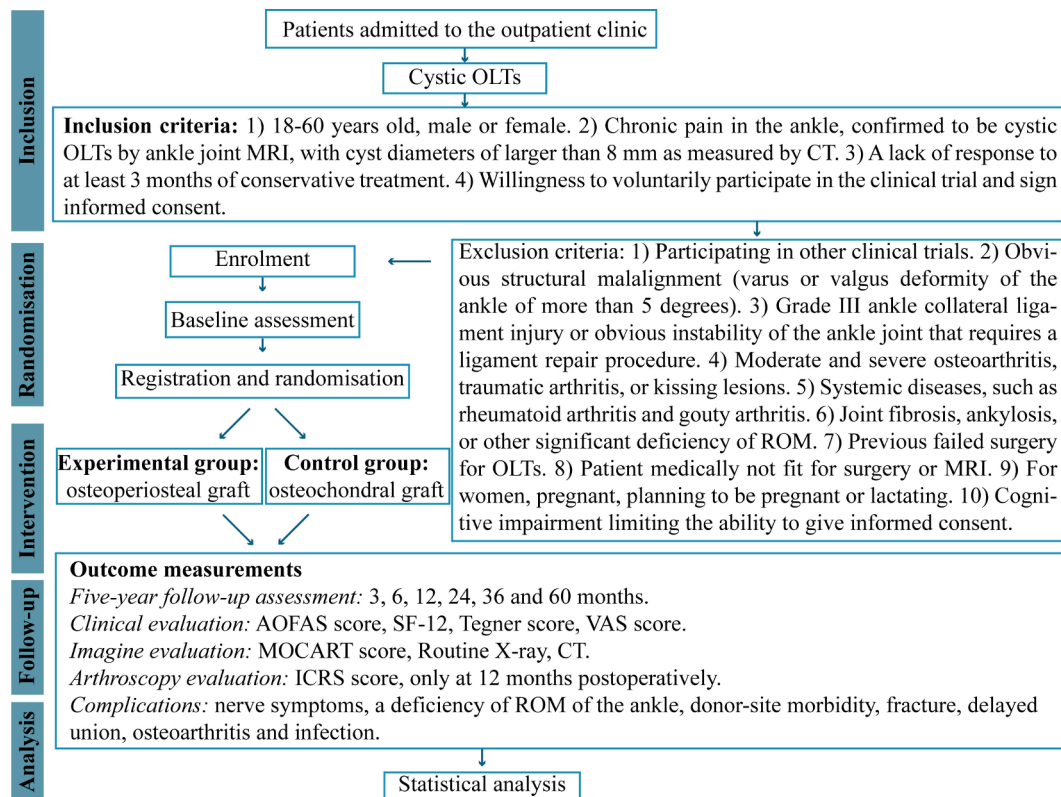


Figure 1 Trial workflow. AOFAS, American Orthopaedic Foot & Ankle Society; ICRS, International Cartilage Repair Society; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; OLTs, osteochondral lesions of the talus; ROM, range of motion; SF-12, Short Form 12 questionnaire; Tegner, Tegner activity level; VAS, visual analogue scale.

- ▶ For women, pregnant, planning to be pregnant or lactating.
- ▶ Cognitive impairment limiting the ability to give informed consent.

Randomisation and blinding

Based on a permuted block randomisation scheme, participants will be equally randomised to either the experimental group or the control group. To ensure the proper management of the randomisation procedure, the sequence numbers will be marked on opaque envelopes, and the operative group allocation will be sealed inside. To be numbered sequentially, all envelopes will be delivered according to patients' sequence numbers, and the surgeon will be informed of the random numbers and operative group allocations by telephone.

Blinding is not feasible in this surgical trial because of differences in surgical wounds; thus, neither the surgeons nor participants will be blinded to the treatment allocation. Independent statisticians performing statistical analysis and assessors evaluating clinical and radiographic outcomes will be blinded to operative group allocations.

Surgical intervention

While under general or spinal anaesthesia, all patients will be placed in a supine position, and a pneumatic tourniquet will be applied to the ipsilateral thigh. With distraction and plantar flexion, a 4.5 mm 30° angled arthroscope will be inserted into the joint, and visualisation of the talar

dome will be achieved under arthroscopy. The defect and the cyst will be confirmed arthroscopically, and graft transplantation will be performed for the OLTs with large lesion size, more than 10 mm in diameter or 100 mm² in size.

Graft transplantation will be performed by either arthrotomy (for lesions located in zone 1) or medial malleolar osteotomy (for lesions located in zone 4 or 7) as described by Flynn,¹⁹ with the osteotomised medial malleolus retracted inferiorly. After good exposure of the lesion is achieved, the surface of the defect will be debrided. The centre of the cystic lesion will be determined and drilled perpendicularly with a 2 mm pin. Then, the lesion will be drilled with a 4.5 mm cannulated bore until the cyst is reached, and a small bone socket will be created. A harvester tube (OATS, Arthrex, USA) with an 8 mm or 10 mm diameter will be used to enlarge the bone socket with care to avoid heat injury to the adjacent normal cartilage. The cyst will be debrided thoroughly, and the sclerotic wall of the cyst will be freshened up with awls or small pins. The number and size of grafts were determined intraoperatively with a sizing guide. Grafts with diameters of 6–10 mm have been commonly used in our previous studies.¹⁵ Lesions greater than 11 mm diameter required two grafts placed side by side in a figure-of-8 formation or 'nested', which minimised fibrocartilage fill of adjacent graft space.^{19 20}

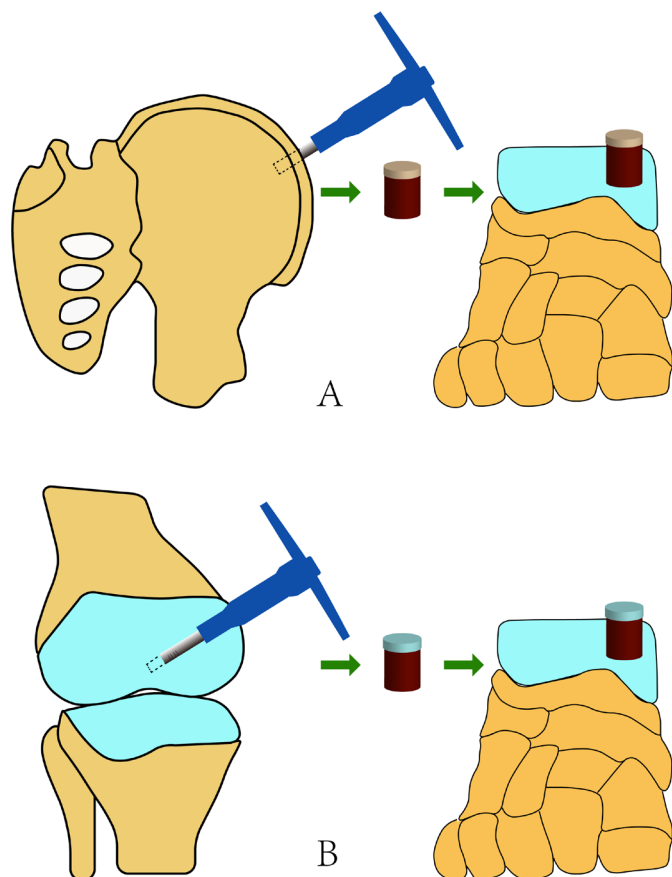


Figure 2 (A) Small pieces of cancellous bone harvested from the iliac crest will be used to fill the peripheral area of the cyst, and the osteoperiosteal graft will be implanted into the bone socket in the talus; (B) small pieces of cancellous bone harvested from the non-weight-bearing portion of the ipsilateral medial femoral trochlea in the ipsilateral knee will be used to fill the peripheral area of the cyst, and the osteochondral graft will be implanted into the bone socket in the talus.

Experimental group

According to Hu *et al.*,¹⁵ with the anterior superior iliac spine exposed, the periosteum will be preserved. A harvester tube with an 8mm or 10mm inner diameter will be driven deeply and perpendicularly 2cm proximal to the anterior superior iliac spine, and then the osteoperiosteal graft will be harvested. When the diameter of the bone socket in the talus is smaller than that of the cysts, small pieces of cancellous bone will also be harvested from the anterior superior iliac spine to fill the peripheral area of the cyst (*figure 2A*).

Then, the osteoperiosteal graft will be tapped into the hole with the periosteum outward without additional fixation. It is necessary for the graft to be flush with the normal cartilage. Passive motion of the ankle joint will be made to confirm that the graft is stable. The medial malleolus will then be reduced, and cannulated screws will be driven up from the tip of the medial malleolus into the cancellous tibia bone. The anatomic reduction will be confirmed by fluoroscopy. The ankle and iliac crest

wounds will be closed per routine, and a sterile compression dressing will be applied.

Control group

The osteochondral graft will be harvested from the non-weight-bearing portion of the medial femoral trochlea in the ipsilateral knee, with the harvester tube driven perpendicularly.²¹ The osteochondral graft will be tapped into the hole with the cartilage outward without additional fixation (*figure 2B*). The graft should be flush with the normal cartilage, and passive motion of the ankle joint will be performed to confirm that the graft is stable. In cases with a malleolus osteotomy, cannulated screws will be driven up from the tip of the medial malleolus into the cancellous tibia bone, and the anatomic reduction will be confirmed by fluoroscopy. The ankle and knee wounds will be closed per routine, and a sterile compression dressing will be applied.

Postoperative rehabilitation

On the first day after the operation, which will be non-weight bearing, the patients will be instructed to exercise the ipsilateral toe and knee joint by a physical therapist. Passive and active range of motion (ROM) training (15 min, three times a day) and ice will start 3 days after surgery. The patient will be immobilised in a short leg cast and non-weight bearing on the affected limb for 6 weeks after surgery, and partial weight bearing will be allowed 7–8 weeks after surgery. At 8 weeks after surgery, full weight bearing will be allowed, after healing of the osteotomy is confirmed by X-ray. After 3 months, low-impact sports, such as swimming, will be resumed, and high-impact activities, such as soccer or basketball, will be allowed 12 months postoperatively.

Outcome measurements

Primary outcomes

- ▶ The American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score and the Short Form 12 (SF-12) questionnaire will be recorded preoperatively and then at 3, 6, 12, 24, 36 and 60 months postoperatively (*table 1*).

Secondary outcomes

- ▶ The International Cartilage Repair Society score will be recorded during the second arthroscopy after 12 months.
- ▶ The Magnetic Resonance Observation of Cartilage Repair Tissue score will be recorded preoperatively and then at 3, 6, 12, 24, 36 and 60 months postoperatively.
- ▶ The Tegner activity level score will be used to assess sports level preoperatively and then at 3, 6, 12, 24, 36 and 60 months postoperatively.
- ▶ The visual analogue scale for pain of the ankle will be recorded preoperatively and then at 3, 6, 12, 24, 36 and 60 months postoperatively.

Table 1 The timeline of the study and the preoperative and postoperative follow-up

Follow-up schedules	Preoperative	Perioperative	FU 3 months	FU 6 months	FU 12 months	FU 24 months	FU 36 months	FU 60 months
Inclusion/exclusion criteria	x							
Clinical evaluation	x		x	x	x	x	x	x
Randomisation		x						
PROMS								
MOCART score			x	x	x	x	x	x
AOFAS score	x		x	x	x	x	x	x
SF-12	x		x	x	x	x	x	x
Tegner score	x		x	x	x	x	x	x
VAS score	x		x	x	x	x	x	x
ICRS score					x			
Routine X-ray	x		x	x	x	x	x	x
Complications			x	x	x	x	x	x

AOFAS, American Orthopaedic Foot & Ankle Society; FU, follow-up; ICRS, International Cartilage Repair Society; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; SF-12, Short Form 12 questionnaire; Tegner, Tegner activity level; VAS, visual analogue scale.

- ▶ Routine X-rays will be evaluated to assess joint space narrowing preoperatively and then at 3, 6, 12, 24, 36 and 60 months postoperatively.
- ▶ CT will be used to assess the size of the subchondral cysts preoperatively and then at 3 and 12 months postoperatively.
- ▶ Complications will be recorded, including infection, nerve symptoms, a deficiency of ROM of the ankle, donor-site morbidity, non-union or delayed union, fracture and osteoarthritis, at 3, 6, 12, 24, 36 and 60 months postoperatively.

Monitoring

Safety and data monitoring will be performed periodically during this study. All investigators in this study will undergo good clinical practice training, and the clinical outcomes will be collected and evaluated independently. All data will be recorded in both paper and electronic formats. All records of the case reports will be stored for 10 years in the secure research archives at Peking University Third Hospital with restricted access.

Sample size calculation

Based on current knowledge, no previous trial has used our randomised controlled study design, and the AOFAS score and SF-12 will be used as the primary outcome for this study. The postoperative AOFAS scores and SF-12 for autologous osteoperiosteal cylinder graft transplantations for the treatment of large cystic OLTs have been reported in our previous study (90 ± 6.5 , range 77–100). The mean and SD of the two groups are supposed to be the same. Based on the non-inferiority tests for two means, the estimated sample size for this trial is obtained as follows: $n = 2[(\alpha + \beta)s/\delta]^2$, $\alpha = 0.025$; $\beta = 0.2$; $s = 6.5$; $\delta = 5$. Under these conditions, the estimated sample size is equal to 27 patients. The 20% loss of data will include patients who crossover between interventions and those who are lost to

follow-up. After carrying out a two independent proportions power analysis using PASS software (Power Analysis and Sample Size) and allowing for a margin of 20% loss of primary outcome data, we propose to recruit a minimum of 70 patients who will be randomly allocated to either the experimental group or the control group at a ratio of 1. Therefore, a minimum of 35 patients randomised to each group will provide 80% statistical power to demonstrate non-inferiority at the 5% level.

Statistical analysis

Descriptive statistics will be presented first for demographic and other baseline characteristics, as well as for all outcome variables including complication variables by assigned treatment group, with normally distributed data by the mean and SD and skewed distributions by the median and IQR. Categorical variables will be presented using counts and percentages. SPSS Statistics V.24.0 will be used for all statistical analysis. Preliminary analyses will also compare treatment groups on characteristics at baseline to ensure that randomisation has succeeded. For baseline characteristics strongly correlated with the outcomes, outstanding (unlucky) imbalance will be adjusted in covariate analysis, when specified.

The primary analysis will compare treatment groups on their mean change in AOFAS score and SF-12 between baseline and 12 months. Differences between the two treatment groups will be summarised with the differences of the two means and 95% CIs for the difference between the means; p values from t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed distributions) may also be presented for hypothesis generating purposes, with a one-sided alpha of 0.025. The same analysis used to compare the two treatment groups as described in the primary analysis will be repeated for each time point. To identify the difference between the two treatment groups

over 5 years, multilevel, mixed-effects linear regression with an unstructured variance–covariance matrix was conducted to take into account of clustering on the same patient. A univariable model adjusting for preoperative AOFAS score and SF-12 was first performed. Fractional polynomial regression modelling was used to explore evidence of non-linear relationships. To obtain the average marginal effects to show the adjusted mean AOFAS score and SF-12 over time between the two treatment groups, the outcome was expanded to include both baseline AOFAS score and SF-12 and postoperative AOFAS score and SF-12 at all follow-up time points, and an interaction term was fitted between the treatment group and time of follow-up. To analyse differences of other outcome variables that was stated in the ‘Outcome measurements’ section between the two treatment groups, χ^2 tests will be used to compare categorical outcome variables at each follow-up time point. Differences between the two treatment groups will be summarised with the difference in percent and the Newcombe-Wilson score 95% CI for the difference of two percentages when specified. If the expected frequencies for all cells are ≥ 5 , then Pearson’s χ^2 test will be used to determine p values; otherwise, Fisher’s exact test will be used.

Depending on the distributional characteristics of continuous data, t-test or Wilcoxon rank-sum tests will be used to compare the mean changes of each outcome variable between baseline and postoperative results at each follow-up time point. A two-tailed alpha of 0.05 will be used as the statistical significance level.

For all analyses, the per-protocol population, that is, the set of people who have taken their assigned treatment and adhered to it, will be used for primary analysis. The intention-to-treat population analysis will be performed for sensitivity analysis, in which case all randomised patients are analysed according to the treatment to which they were randomised.

TRIAL STATUS

Recruitment to the trial commenced in the Peking University Third Hospital in June 2018; 24 participants had been registered and randomised by 24 August 2019.

DISCUSSION

Previous studies have reported clinical outcomes of osteoperiosteal cylinder graft transplantation and autologous osteochondral transplantation. However, whether osteoperiosteal cylinder graft transplantation is as safe and effective as autologous osteochondral transplantation for large cystic OLTs has not been verified in any research study with high-quality evidence.

Talar cartilage is supported by the subchondral bone and the subchondral bone plate, and the importance of the subchondral bone plate and subchondral bone has been well discussed.²² After trauma causing the breakdown of the subchondral bone plate or cartilage over the talus, liquid flows into the subchondral bone, which

results in the formation of talar cysts.²³ However, the damaged subchondral bone plate and talar cysts allows more liquid to flow into the subchondral bone, which may cause subsequent degeneration of the cartilage over the talus and articular damage, with loss of proteoglycans and glycoprotein.^{5 24} Hence, in surgical treatment for large cystic OLTs, large cysts need to be filled in order to promote the healing of talar cartilage.

To preserve the normal cartilage and subchondral bone plate as much as possible, an 8 mm diameter reamer, as described by Takao *et al*,²⁵ will be used to perform the procedures in the trial. The diameter of the cysts will be larger than that of the cylinder graft in both groups; as a result, small pieces of cancellous bone will also be used to fill the remaining space occupied by the cysts. In addition, freshening of the sclerotic wall of the cyst is important for good incorporation.¹⁵ Thus, the sclerotic wall of the cyst will be freshened with awls or small pins in both groups.

In this trial, we designated the autologous osteochondral transplantation group as the control group to identify the clinical outcomes of autologous osteoperiosteal cylinder graft transplantation. In the proposed study, it is hypothesised that both procedures offer good results for the treatment of patients with large cystic OLTs, and all of the lesions in the osteoperiosteal group will be filled with ‘cartilage-like tissue’, softer than and levelled to the adjacent normal cartilage, similar to the osteochondral group. In addition, we will determine whether autologous osteoperiosteal cylinder graft transplantation is as safe and effective as autologous osteochondral transplantation and whether it is superior in reducing donor-site morbidity of the normal knee joint.

The key limitation of this trial is the lack of blinding of the participating surgeons and participants. In addition, we acknowledge that a large sample is not proposed, but large cystic OLTs are still rare. The efficacy of the new surgical technique will be based on the primary analysis, which focuses on the change in the AOFAS score and SF-12 between baseline and 12 months. Secondary analysis including the modelling of the trend over time will be performed to provide inference for further studies. In addition, second-look arthroscopy could show whether the repaired tissue appeared as nearly normal cartilage, but histological analysis would be absent because of ethical limitation and lack of the dedicated medical puncture instrument.

If our hypothesis is confirmed, the consequences would have an important value in the scheduling and developing of treatment options for patients with large cystic OLTs. We anticipate that the results will provide more reliable evidence and clarify the value of autologous osteoperiosteal cylinder graft transplantation as a safe and effective treatment of large cystic OLTs without complications such as donor-site morbidity of the normal knee joint. In treatment of large cystic OLTs, for patients with chondral lesion of patellofemoral joint that are unsuitable for autologous osteochondral transplantation, autologous

osteoperiosteal cylinder graft transplantation may be a safe and effective choice.

Contributors ED and WS contributed equally to this work. YJ and QG conceived and designed the study. ED and WS developed the first draft of the manuscript. All authors contributed to the development of the study protocol and approved the final draft of the manuscript. We also thank YJ for being a patient adviser for this study.

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Competing interests None declared.

Patient consent for publication Not required.

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