NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

The articular cartilage of the knee is the smooth white tissue covering the ends of the bones. People with damage to this cartilage often have pain, catching (a feeling that they cannot move the leg past a certain point), locking and swelling of the knee. This may cause degenerative changes in the joint (osteoarthritis). In this procedure, the damaged articular cartilage inside the knee is removed and tiny holes are drilled through the bone beneath to stimulate the growth of new cartilage. The affected area is then covered with a patch of special material (a microstructural scaffold) for the new cartilage tissue to grow into.

The National Institute for Health and Care Excellence (NICE) is examining microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects and will publish guidance on its safety and efficacy to the NHS. NICE's Interventional Procedures Advisory Committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The Advisory Committee has made draft recommendations about microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects.

This document summarises the procedure and sets out the draft recommendations made by the Advisory Committee. It has been prepared for public consultation. The Advisory Committee particularly welcomes:

- comments on the draft recommendations
- the identification of factual inaccuracies

- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.

- The Advisory Committee will meet again to consider the original evidence and its draft recommendations in the light of the comments received during consultation.
- The Advisory Committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 18 March 2016

Target date for publication of guidance: June 2016

1 Draft recommendations

1.1 The evidence on microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects raises no major safety concerns; however, current evidence on its efficacy is inadequate in both quality and quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to do microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects should:

- Inform the clinical governance leads in their NHS trusts.
- Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.
- Audit and review clinical outcomes of all patients having microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects (see section 6.1).

1.3 NICE encourages further data collection, including randomised controlled trials on microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects. Studies should clearly describe patient selection and adjunctive treatments. Outcome measures should include symptom relief, functional ability, long-term outcomes measured by appropriate imaging techniques and patient-reported outcomes.

2 Indications and current treatments

2.1 Chondral damage (or localised damage to the articular cartilage) in the knee can be caused by injury or arthritis, or it can occur spontaneously (a condition called osteochondritis dissecans). It may also happen because of knee instability, muscle weakness, or abnormal unbalanced pressures, for example, after an injury to a ligament or meniscal cartilage. In young people, the most common cause of cartilage damage is sporting injuries. Symptoms associated with cartilage loss include pain, swelling, instability, joint catching and locking, and may lead to degenerative changes in the joint (osteoarthritis).

2.2 There is no uniform approach to managing cartilage defects in the knee. Treatment options depend on the size of the defect and its location. There are 2 main categories of procedure: those intended primarily for symptom relief and those that also try to re-establish the articular surface. Interventions that aim to re-establish the articular surface include marrow stimulation techniques (such as abrasion arthroplasty, Pridie drilling and microfracture), mosaicplasty (also known as osteochondral transplantation), and autologous chondrocyte implantation (in which chondrocytes harvested from the knee are cultured and implanted into the damaged cartilage). Interventions that aim to relieve symptoms include knee washout (lavage) with or without debridement, osteotomy, and knee replacement.

3 The procedure

3.1 Microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects is

done with the patient under general or local anaesthesia, using an open or arthroscopic approach. The damaged articular cartilage is removed and standard bone marrow stimulating procedures, such as microfracturing or Pridie drilling, are done. The microstructural scaffold is cut to fit the size of the defect and then fixed in place over the damaged area using, for example, fibrin glue, resorbable suture thread or absorbable tacks. The position of the implanted scaffold is checked by bending and extending the knee and the wound is sutured. The aim of this procedure is that the graft or patch 'captures' the bone marrow cells and stem cells released by the microfracturing, and acts as a scaffold on which new articular cartilage can grow.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 In a randomised controlled trial of 38 patients with cartilage knee defects, autologous matrix-induced chondrogenesis (AMIC) techniques (sutured [n=13] or glued [n=15]) were compared with microfracture (MFx; n=10). In the interim analyses, the mean modified Cincinnati scores (assessing knee function [6–30 points], clinical pathology [0–20 points], and highest activity level without pain [0–50 points]; a maximum possible score of 100 points) increased significantly from baseline values of 47±20 to 82±14 ($p<0.001$) for the sutured AMIC group, 47±15 to 67±27 ($p=0.02$) for the glued AMIC group and 37±14 to 68±17 ($p=0.002$) for MFx

group respectively at 1-year follow-up. There were no statistically significant differences between the groups. At 2 years, mean scores increased significantly from baseline to 88±9 ($p<0.001$) for the sutured group, to 85±18 ($p<0.001$) for the glued AMIC group and to 83±8 ($p<0.001$) for the MFx group. There were no statistically significant differences between the groups. In a case series of 27 patients with 32 chondral lesions treated with AMIC, the mean Cincinnati scores improved significantly from baseline (46±18 to 66±23; $p<0.05$) at 1 year and further increased (to 74±23) at 2 years (level of significance not given). Non-significant declines in scores were seen at 36-month follow-up (62±26) and 48-month follow-up (37±9).

4.2 In the randomised controlled trial of 38 patients with cartilage knee defects comparing AMIC techniques (sutured [n=13] or glued [n=15]) against MFx (n=10), pain (measured on a visual analogue scale [VAS], 0 [no pain] to 100 [severe pain]) was rated less severe at 1- and 2-year follow-up compared with baseline and was comparable between the groups. At 1-year follow-up, pain decreased significantly from baseline for sutured AMIC (46±19 to 14±13; $p<0.001$), glued AMIC (48±20 to 16±13; $p< 0.001$) and MFx (54±21 to 19±17; $p=0.002$), and was further reduced at 2-year follow-up without statistical significance (9±6 for sutured AMIC; 10±13 for glued AMIC; 5±3 for MFx). In a case series of 57 patients, knee pain (measured with a VAS) decreased significantly from baseline at 1-year follow-up (7.0±1.8 to 2.7± 2.4; $p<0.001$) and at 2-year follow-up (2.0±2.1; $p<0.003$). The mean VAS improvement from baseline to 1-year follow-up was 4.2±2.6 ($p<0.001$), from 1- to 2-year follow-up was 0.5±2.3 ($p=0.003$), and from baseline to 2-year follow-up was 4.7±2.7 ($p<0.001$).

4.3 In the randomised controlled trial of 38 patients with cartilage knee defects comparing AMIC techniques (sutured [n=13] or glued [n=15]) against MFx (n=10), at 1-year follow-up, patients in all groups (n=30) rated their functional status as improved (n=24) or stable (n=6) (using the International Cartilage Repair Society [ICRS] Cartilage Injury Standard Evaluation Form 2000). At 2 years, patients in all groups rated their functional status as improved (n=12), stable (n=13) or deteriorated (from normal to nearly normal; n=2). Surgeon-rated assessments, based on the modified ICRS score (with respect to functional status, classification of the knee and crepitation using parts 3, 4 and 7 of the ICRS form), reported improvement in clinical symptoms and function and found no differences between the groups at 1- and 2-year follow-up. In the case series of 27 patients, mean ICRS scores improved significantly from baseline (31±15 to 59±24; $p<0.05$) at 1 year and further increased (to 68±22) at 2 years (level of significance not given). Scores declined non-significantly at 36-month follow-up (54±25) and 48-month follow-up (37±4).

4.4 In a retrospective case series of 38 patients (40 knees) treated with AMIC for full thickness chondral and osteochondral defects of the femoral condyles and patella, International Knee Documentation Committee (IKDC) scores (using the IKDC Subjective Knee Evaluation form 2000, score range 0–100, higher scores representing higher levels of function and lower levels of symptoms) improved significantly from baseline to a mean follow-up of 28.8 months in the osteochondral femoral condyle group (from 44±25 to 88±9; $p=0.005$) and the chondral patella group (from 51±25 to 74±17, $p=0.0025$). However, improvements in the chondral femoral condyle group were not significant (from 45±26 to

68±14). Significant differences were seen between the 3 groups (p=0.0016). There were no significant differences in outcomes in patients treated with AMIC alone compared with those who also had an osteotomy or realignment procedure. In a case series of 30 patients treated for chondral or osteochondral lesions with a cell-free collagen hydroxyapatite osteochondral scaffold, mean IKDC subjective scores improved significantly from 40.0±15.0 at baseline to 76.5±14.4 ($p<0.0005$) at 2–year follow-up and 77.1±18.0 ($p<0.0005$) at 5-year follow-up.

4.5 In the case series of 27 patients, mean Lysholm scores (a patient knee functional scoring scale with 8 items and a maximum possible score of 100) improved significantly from baseline (36±21 to 67±28; $p<0.05$) at 1-year follow-up and further increased (to 76±24) at 2-year follow-up (level of significance not given). Non-significant declines in scores were seen at 36-month follow-up (62±25) and 48-month follow-up (47±22).

4.6 In the case series of 27 patients, mean Meyer score (not defined in paper) improved significantly from baseline (9±3 to 14±3; $p<0.05$) at 1-year follow-up and further improved (to 16±3) at 2 years (level of significance not given). Non-significant decline in mean score was seen at 36-month follow-up (14±3).

4.7 In the case series of 27 patients, mean Tegner score (a patient activity level scale; score range 0-10, with higher scores representing participation in higher-level activities) improved significantly from baseline (not reported) to 3.4 ($p<0.05$) at 1-year follow-up and further increased to 4.1 at 2-year follow-up (level of significance not given). Non-significant decline in scores was seen at 36-month follow-up (4.0). In the case series of 30 patients with

chondral or osteochondral lesions treated with a cell free collagen hydroxyapatite osteochondral scaffold, mean Tegner score improved significantly from 1.6±1.1 at baseline to 4.0±1.8 ($p<0.0005$) at 2-year follow-up and to 4.1±1.9 ($p<0.0005$) at 5-year follow-up.

4.8 In a case series of 23 patients with symptomatic knee osteochondritis dissecans, EQ-VAS score (a measure of patients' own global rating of their overall health, on a scale 0 [worst imaginable health state] to100 [best imaginable health state]) had improved significantly from baseline at 2-year follow-up (3.15±1.09 to 8.15±1.04; $p<0.0005$).

4.9 In the case series of 38 patients (40 knees), patient satisfaction (rated on a scale of 0–100%, 0 indicating completely dissatisfied to 100 indicating completely satisfied) was high in all subgroups and there was no significant difference between groups (osteochondral femoral group 94±8; chondral patella group 84±24; chondral femoral condyle group 74±43). In the case series of 23 patients with symptomatic knee osteochondritis dissecans, satisfaction was recorded in 85% (absolute numbers not given) of patients.

4.10 In the case series of 30 patients with chondral or osteochondral lesions treated with a cell free collagen hydroxyapatite osteochondral scaffold, MRI evaluation showed an improvement in both the magnetic resonance observation of cartilage repair tissue (MOCART) score and subchondral bone status (part of MOCART, 5 variables rated on a scale of 1–3) at 2- and 5-year follow-up. At 5–year follow-up, complete filling of the cartilage was shown in 78% of lesions (absolute numbers not given), complete integration of the graft was detected in 70% of cases, the repair tissue surface was

intact in 61% of cases and the structure of the repair tissue was homogenous in 61% of the cases. No correlation was found between MRI findings and clinical outcome.

4.11 The specialist advisers listed key efficacy outcomes as improved clinical benefit, MRI evidence of chondro-regeneration (for example, T2 mapping and d-GERMIC) and delayed replacement arthroplasty.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 Haematoma, after the autologous matrix-induced chondrogenesis (AMIC) procedure, developed in 1 patient in a case series of 38 patients (40 knees) with full thickness chondral and osteochondral defects of the femoral condyles and patella. The haematoma was excavated.

5.2 Muscle vein thrombosis was reported in 1 patient in a case series of 27 patients with 32 chondral lesions treated with AMIC. This complication resolved after treatment.

5.3 Effusion ‘after tumbling’ was reported in 1 patient in the case series of 27 patients. This complication resolved after treatment.

5.4 Knee stiffness was reported in 23% (9/40) patients in the case series of 38 patients (40 knees) after the procedure. This was

reported in patients in the chondral patella group. Patients regained full range of motion after mobilisation under anaesthesia.

5.5 Revision surgery, because of pain and limited function of the knee, was done in 10% (5/49) of patients in a case series of 49 patients with large osteochondral knee lesions treated with a biomimetic osteochondral scaffold. In 2 patients with osteonecrosis of the medial femoral condyle, unicompartmental knee replacement was done in 1 patient and a valgus high tibial osteotomy was done in the other patient. In 2 patients with osteochondritis dissecans, autologous osteochondral transplantation revision surgery was done in 1 patient and osteochondral allograft transplantation and varus femoral osteotomy was done in the other patient. The fifth patient, who was lost to follow-up, had treatment at another centre. Revision surgery was done in 8% (2/27) of patients due to symptoms of grinding, catching, pain or swelling after the procedure in the case series of 27 patients. Clinical improvement was not seen in these patients.

5.6 Bleeding and swelling of the knee after surgery was reported in 12% (6/49) of patients in a case series of 49 patients, all of which resolved spontaneously within 1 week. Swelling, which resolved in a few days, was reported in 22% (17/79) of patients in a case series of 82 patients with chondral or osteochondral knee lesions.

5.7 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: delamination of repair tissue

and the need for surgical removal of this tissue, and hypertrophy. They considered that allergic reaction to materials used in preparation or preservation of scaffold was a theoretical adverse event.

6 Further information

6.1 For related NICE guidance, see the NICE website.

6.2 This guidance requires that clinicians doing the procedure make special arrangements for audit. NICE has identified relevant audit criteria and is developing an audit tool (which is for use at local discretion). This tool will be available when the guidance is published.

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