Bridge-Enhanced Anterior Cruciate Ligament Repair: The Next Step Forward in ACL Treatment

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ABSTRACT

Anterior cruciate ligament (ACL) injuries are common in young and active patients. In this patient population, surgical treatment with an autograft tendon is recommended to reconstruct a new ACL. ACL reconstruction has a high patient satisfaction, improved patient reported outcomes and allows young patients to return to an active lifestyle, including sports. However, long-term follow-up shows these patients are at higher risk for degenerative arthritis, frequently at a young age. Recent research has focused on re-investigating the utility of performing an ACL repair rather than a reconstruction in the hopes that maintaining a patient's native ligament may not only restore knee stability, but provide improved knee kinematics and lessen the risk of late osteoarthritis and also limit donor site morbidity from autograft harvests. Historically, patients undergoing ACL repair suffered poor outcomes due to issues with intra-articular healing of the ligament; but now, with new bioengineering techniques, bridge-enhanced ACL repairs may provide a feasible alternative in the treatment of ACL injuries.

INTRODUCTION

ACL Tears and the Evolution of Surgical Treatment

Anterior cruciate ligament injuries are common and their incidence continues to increase.[1] The literature reports that approximately 200,000 ACL injuries occur per year in the United States[2,3,4] and that the incidence of reconstructions has increased from 86,687 in 1994 to 129,836 in 2006.[5] Unlike the medial collateral ligament (MCL), the ACL is unlikely to heal on its own due to both its intra-articular location and differences in stem cell characteristics.[6]

Because of this poor healing potential, it has consistently been shown that nonsurgical management of ACL tears in active patients results in recurrent episodes of knee instability and poor clinical outcomes. In fact, a delay of more than twelve months before reconstruction is associated with meniscal and chondral injuries, and a relatively longer time from injury to surgery results in the development of radiographic knee osteoarthritis.[7]

The first surgical treatment for ACL tears began in the early 1900s with attempted open primary repair in which surgeons sutured the torn ends of the ACL back to one another.[11] However, initial follow-up studies demonstrated both high failure rates (as high as 50–90%), recurrent instability, and low-patient satisfaction, therefore pushing surgeons to pursue ACL reconstruction rather than direct surgical repair.[8,9,10] ACL reconstruction has become an effective method for restoring knee stability in athletes and has demonstrated excellent clinical results, with some studies showing that over 89% of athletes return to previous level of competition.[11]

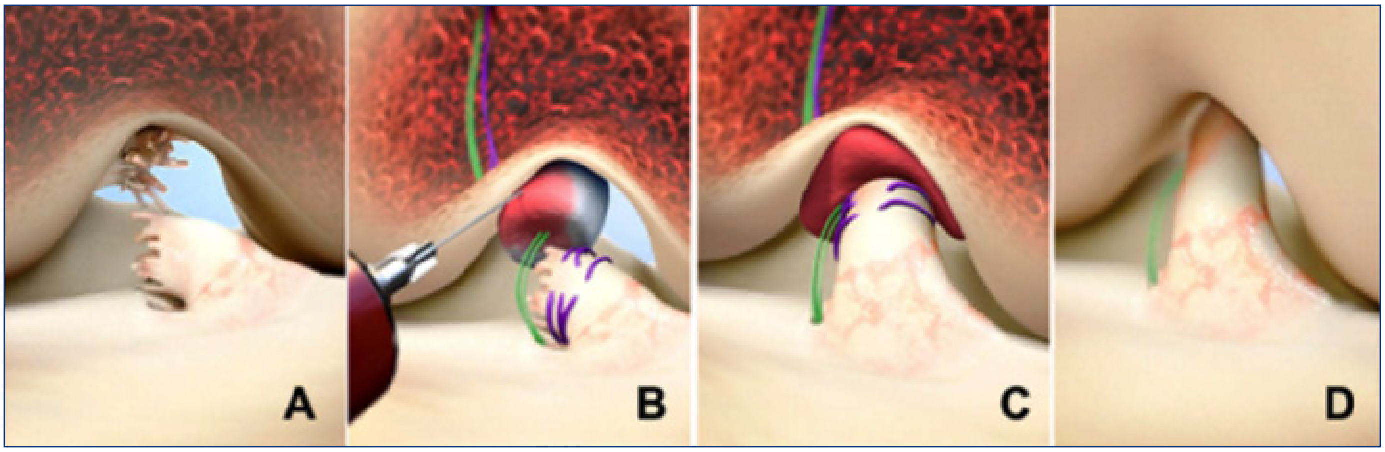
Furthermore, patients experience a significant improvement in patient reported outcome measures after ACL reconstruction with an autograft. Despite these successes, issues following ACL reconstruction remain and some patients' knees do not return to normal even two years after surgery.[12] Patients often experience quadriceps weakness and anterior knee pain from the patella tendon harvest or hamstring weakness if the hamstrings are the chosen donor tissue. Moreover, long-term follow-up of patients with anterior cruciate ligament tears show a significant risk of developing osteoarthritis, with and without ACL reconstruction.[13]

A plethora of research has been conducted over the past several decades on ways to improve the results of ACL reconstructions, but there has been very limited improvement in outcomes over the past twenty-five years. This has led to a resurgence in interest in primary repair techniques. The potential advantages of primary repair include preservation the native ligament tissues, its complex anatomy, and its proprioceptive capacity, while also being less invasive – thus eliminating complications from the graft harvest such as pain and weakness.[14]

Revisiting Repairs

The work of a group of researchers at Harvard and Brown University challenged the abandonment of ACL primary repair as an effective treatment option. Assuming that preservation of a patient's native ACL tissues and anatomy, rather than reconstruction, would lead to improve long-term knee function, they studied the science of ligament healing and developed a new alternative technique. Murray et al. determined that ACL repairs failed initially because intra-articular plasminogen in the knee joint breaks down any early clot that forms.[15] Typically, early clot forms to help heal other tissues, and without the ability to form this provisional scaffold in the knee joint to bridge the wound, there

Figure 1. Stepwise demonstration of the bridge-enhanced anterior cruciate ligament repair (BEAR) technique using the scaffold.
[**A**] The torn anterior cruciate ligament (ACL) tissue is preserved. A whipstitch of No.2 absorbable suture (purple) is placed into the tibial stump of the ACL. Small tunnels (4mm) are drilled in the femur and tibia, and a cortical button with two No. 2 nonabsorbable sutures (green sutures) and No. 2 absorbable sutures attached to it is passed through the femoral tunnel and engaged on the proximal femoral cortex. The nonabsorbable sutures are threaded through the BEAR scaffold and tibial tunnel and secured in place with an extracortical button. [**B**] The scaffold is then saturated with 5 to 10 ml of the patient's blood, and [**C**] the tibial stump is pulled up into the saturated scaffold. [**D**] The ends of teh torn ACL then grow into the scaffold, which is gradually replaced by healing ligament tissue.[17]



is no ability of the ACL to heal itself.[15] Tissue engineers then sought a way to implant a stable bridge by designing a collagen "bridge" that would be resistant to enzymes in synovial fluid that cause degeneration while at the same time maintaining the ability to stimulate cellular ingrowth and proliferation.[15,16]

This new technique is called bridge-enhanced anterior cruciate ligament repair (BEAR). With BEAR, a suture repair of the torn ACL is combined with a specific extracellular matrix scaffold (the BEAR scaffold). This scaffold has been designed from bovine tissue and includes proteins and collagen which have shown the ability to stimulate ACL healing.[16] The scaffold is placed in the space between the two torn ends of the ACL and activated with the patient's own blood (**Figure 1**).[17] The scaffold is used to bridge the gap between the two torn ends of the ligament, minimizing the necessity of absolute re-approximation of the torn ACL ends to promote ligament healing. The scaffold protects the ACL repair by keeping the blood between the torn ends of the ligament and the suture stent across the knee helps to stabilize the knee early on while the ligament begins healing itself.

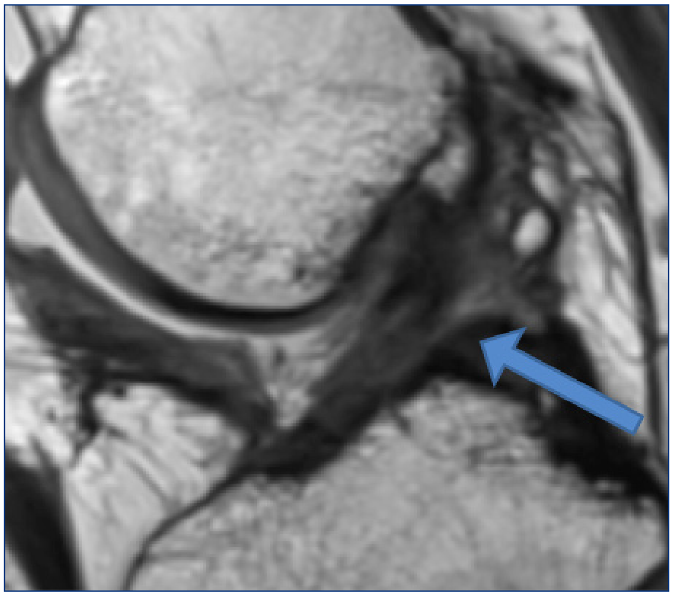
The BEAR implant has demonstrated equivalent rates of both deep joint infection and serious inflammatory reactions when compared to ACLR.[17] In addition, the BEAR technique does not require the compromise of other healthy tissues around the knee, as is required with an ACL reconstruction with an autograft. Thus, one possible benefit of the BEAR technique may be less loss of hamstring strength when compared with ACLR with a hamstring autograft, and less postoperative anterior knee pain that has typically been associated with ACLR using the classic bone-patellar tendon-bone autograft.[11]

BEAR Success thus Far

Initial research showed promising results for the BEAR implant. In animal models, implants were shown to be completely populated with cells as soon as one week after surgery, and by four weeks they contained new vessel and nerve ingrowth.[18] Subsequent large animal porcine models had promising results as well, as pigs with the BEAR implant showed a fibrovascular bundle at the healing ACL tear site via histological analysis three months after surgery when compared to pigs having undergone suture repair alone.[20] Animal models have also shown the BEAR technique has shown comparable mechanical properties when comparing BEAR to ACL reconstructions both at three months and twelve months post-operatively.[22] Additionally, the BEAR technique has shown a lower incidence of posttraumatic osteoarthritis at one year when compared to those pigs who underwent reconstructions.[19,20,21,22]

The first human study, the BEAR 1 Trial, which sought to assess safety in humans, consisted of a cohort of ten patients age 18–35 who underwent the BEAR procedure and ten patients who underwent an ACL reconstruction using hamstring autograft.[17] There were no joint infections or signs of significant inflammation in either group. There were no differences between groups in effusion or pain, and no failures by Lachman examination criteria. No patients required revision ACL surgery at two years.[17] Magnetic resonance images from all of the BEAR and ACL-reconstructed patients demonstrated a continuous ACL or intact graft (**Figure 2**). In addition, hamstring strength at three months was significantly better in the BEAR group than in the hamstring autograft group.[17] These favorable results in the first human study led to further trials in a larger group of patients.

Figure 2. T1-weighted MRI of a patient's knee 9 months post-op after undergoing BEAR procedure. Visible in center of image is reconstituted ACL (blue arrow).



The BEAR 2 trial was a double-blind randomized control trial including 100 patients randomized into either the BEAR procedure (n = 65) or an ACL reconstruction with autograft hamstring tendon (n=35). A 2:1 enrollment scheme was used to help detect for rare negative events. The study included younger adolescents with patients ranging in age from 14–35 years old, with patients having to undergo surgery within six weeks of injury. Again, there were no issues with safety after BEAR implant use. The findings at two years show patient-reported outcome scores between the BEAR group and reconstruction group to be similar. There was also comparable knee stability using the KT-1000. The BEAR cohort had improved hamstring muscle strength at two years when compared to the ACL reconstruction group, and the reinjury rate was found to be similar to that of ACL reconstructions (paper currently in press at AJSM).

Future Directions

The BEAR procedure already appears to be a safe and effective surgery for ACL tears.[17,23] The BEAR technique does not require the compromise of other healthy tissues around the knee, as is required with ACL reconstruction with an autograft. This new technique provides promise that soon surgeons will be able to repair and regenerate the ACL instead of replacing it. Further work is planned for the future to better examine how outcomes and surgical techniques can be improved. For example, the BEAR III trial is a current FDA-approved cohort study that has been approved for up to 250 patients and will be performed by seven surgeons across two centers: University Orthopedics group in Rhode Island and Boston Children's Hospital. Those eligible for recruitment include patients between the ages of 12–80 years-old who experienced an acute ACL tear within the past 50 days. In addition to the BEAR III trial, Rhode Island Hospital is one of six planned sites for an NIH-funded, multicenter, randomized controlled trial of BEAR versus patella tendon autograft reconstruction for acute ACL tear (https://clinicaltrials.gov/ct2/show/NCT03776162?term=MOON&cond=acl&draw=2&rank=1).

SUMMARY

There has been a resurgence of work on ACL repair and excitement for its potential. With the addition of a basic science and translational approach, the BEAR technique offers the potential to change the current treatment paradigm for ACL injury.

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