The Bridge-Enhanced ACL Repair

A Review

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ABSTRACT

The treatment of anterior cruciate ligament (ACL) injury is a prominent and costly component within orthopaedics. Even with success of the current gold standard of treatment, surgical ACL replacement, there are risks of postoperative comorbidities such as osteoarthritis (OA). A promising methodology that has emerged from Dr. Martha Murray's team at Boston Children's Hospital is the bridge-enhanced ACL repair (BEAR) procedure. This technique uses tissue engineering to regenerate and "bridge" together the severed ends of the ACL rather than constructing a new ligament. The BEAR procedure has shown great promise in early clinical trials, but longitudinal

follow-up is needed. The purpose of this study was to compile pre-clinical and clinical studies of the BEAR procedure to better understand its advances, limitations, and future directions; to our knowledge, this has not been done in the current literature.

Keywords: anterior cruciate ligament, bridge-enhanced ACL repair, osteoarthritis, graft, knee, sports medicine.

Abbreviations

ACL: anterior cruciate ligament

BEAR: bridge-enhanced ACL repair

OA: osteoarthritis

IKDC: International Knee Documentation Committee

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Introduction

Injuries to the anterior cruciate ligament (ACL) are estimated to affect up to 400,000 individuals per year¹ and cost over \$2 billion in healthcare-related expenses.² The ACL is 1 of 2 ligaments that make up the center of the knee joint and is responsible for preventing anterior translation of the tibia relative to the femur, more commonly referred to as hyperextension.³ The ACL is essential for maintaining stability and proper knee biomechanics.⁴ Although colloquially considered a sports injury, ACL tears and/or ruptures are becoming exceedingly

more common among non-athletes.⁵ The overall adjusted annual incidence of ACL tears was found to be 68.6 per 100,000 person-years with peak incidence in males 19–25 years of age and in females at 14–18 years of age.⁶ Given the prevalence and debilitating nature of ACL injuries, continuously improving treatment approaches remains of the utmost interest within orthopaedics and medicine as a whole.

As with any injury in the body, ACL tears can present at different stages and gravities. If the tear is minor or the individual has low physical demands of the knee joint, physical therapy is often the treatment of choice. However, if the tear is severe causing knee buckling or an active lifestyle is desired, the current standard of care involves surgically removing the torn ACL and replacing it with a tendinous graft via holes drilled into both the femur and tibia as anchors. This graft can be obtained from a number of sources. Autografts can be harvested from the patient during the same operation (hamstring tendon, patellar tendon, or quadriceps tendon) or cadaveric allografts; although autografts are more commonly used, there lacks a clear consensus as to which is superior.^{7–11}

ACL reconstructions are generally considered successful (75–97% patient satisfaction), necessary, and low-risk procedures.^{12–16} However, adverse consequences of the procedure can manifest beyond an immediate “successful” reconstruction.^{17–20} For example, 10–15% of ACL reconstruction surgeries require a secondary, revision surgery at some point.¹⁵ Overall, patient satisfaction and stability are improved by revisions but are significantly lower than in successful primary procedures.²¹ Although minimally invasive ACL reconstructions have been performed using arthroscopy, they pose a high incidence of complications compared to other orthopaedic arthroscopic procedures.²² There is evidence to show that patients are also at an increased risk of injury just 2 years following a primary ACL reconstruction, especially young athletes.²³ Interestingly, this increased risk involves both the operated knee

and the contralateral knee.²⁴ These mechanisms of susceptibility remain unclear.

Prior ACL injury and subsequent reconstruction lead to a greater likelihood of developing osteoarthritis (OA) and requiring a total knee arthroplasty (TKA), otherwise known as a knee replacement.^{25–34} Commonly referred to as “wear and tear,” OA is a degenerative joint disease that can affect any joint, but symptoms are exacerbated when weight-bearing joints are involved. OA results in the destruction of the meniscus, the rubber-like fibrocartilage wedged within the knee joint that acts as a shock absorber between the tibia and femur.³⁵ OA is the most common joint disorder and among the costliest to manage. Other risk factors for OA include but certainly are not limited to socioeconomic status, obesity, age, and past physical activity.^{36,37} Unfortunately, the meniscus is largely avascular, thus severely limiting repair following degeneration or tear; currently there is no curative treatment for OA besides a TKA.³⁷ The mechanism by which ACL repair contributes to the development of OA remains unknown, but substantial evidence supports an association^{38–45} with theories involving collateral damage during injury and abnormal distribution of forces following ACL injury and repair.^{46,47} Notably, patients who have had ACL reconstruction have been largely found to be at higher risk for developing OA compared to those with healthy knees. However, OA rates improve when comparing patients treated with ACL reconstruction to patients with untreated ACL injuries.⁴⁸ Preoperative and postoperative rehabilitation is essential surrounding ACL surgery to ensure regaining of proper gait biomechanics and weight distribution.^{49–51} Additionally, if a TKA is performed, a prior ACL reconstruction leads to a significant increase in TKA operative time.²⁵ Altogether, the conventional ACL reconstruction is a beneficial treatment, but there are substantial areas for perioperative improvement.

A promising avenue for improving treatment of ACL injuries is the bridge-enhanced ACL repair (BEAR) procedure. BEAR was developed by

Dr. Martha Murray and her team at Boston Children's Hospital with the goal of mending many of the long-term detriments of the current gold standard. The theory behind BEAR is grounded in the principle that repairing the native ACL is preferred to introducing a graft that requires bone tunneling, thus presenting an invaluable tool for such work.⁵²⁻⁵⁴ Historically, bleeding occurs from the torn ACL, but fibrinolytic factors in the synovial (joint) fluid surrounding it inhibit clot formation as well as building of the proteinaceous scaffolding essential for healing.⁵⁴⁻⁵⁶ This is in contrast to tears of the medial collateral ligament (MCL), which connects the femur and the tibia as well but does so along the inner portion of the thigh and therefore is not within the joint itself. MCL tears do lead to clot formation and therefore allow severed ends to reconnect and heal without surgical intervention.⁵⁷ The capacity for the BEAR procedure to "bridge" this gap between torn ends addresses this significant obstacle in ACL repair.

The BEAR procedure begins with placing sutures in the 2 torn ends of the ACL and inserting a proteinaceous sponge in between these ends. Once the sponge scaffold is in place, a blood draw is performed from the patient's arm, and the blood is injected into the sponge to create an environment conducive to ligament healing. The sutures attached to the ends of the torn ACL are then pulled so that the ends of the torn ACL enter the sponge. Over the course of 8 to 12 weeks, the body naturally replaces the sponge and connects the ends of the torn ACL once again.^{1,54,58-60} The BEAR procedure has potential to offer preservation of nerve fibers at the ligament insertion sites pivotal for knee proprioception and biomechanics, which is especially important given the skeletal immaturity of younger patients.⁶¹

The purpose of this study is to provide a current report of preclinical and clinical studies implementing the BEAR procedure with elucidation of advantages and disadvantages at each step. To our knowledge, no other studies have compiled both preclinical and clinical data; we aim to fill this

gap and provide a concise report of in vivo evidence comparing the BEAR procedure with traditional ACL repair. Furthermore, we believe this work to be applicable to multiple areas of medicine outside of orthopaedics in that musculoskeletal injuries often present initially in the primary care setting where treatment and follow-up extend into fields such as radiology, physical therapy, pain management, physical medicine, and rehabilitation, as well as others.

Materials and Methods

Our approach consisted of qualitative review of the current PubMed literature on the bridge-enhanced ACL repair (BEAR) procedure. Being a new procedure, we aimed to compile the growing body of knowledge into a concise report detailing its efficacy and impact on the field of medicine. Dr. Martha Murray of Boston Children's Hospital has pioneered the procedure, and research from her group was the linchpin of our review. Other searched keywords for our review include ACL repair, sports medicine, BEAR, biomechanical outcomes, knee surgery, osteoarthritis, bioactive scaffold, injury, and ligament reconstruction. Inclusion criteria were based on reliability and rigor of study design with an emphasis on outcomes-based approaches. We did not include statistical analyses in our review.

Discussion

Biomechanical Advantages

There are numerous biomechanical advantages of the BEAR procedure to traditional ACL reconstructive surgery. From a structural and anatomical perspective, maintaining the inert ligamentous properties and alignment corresponds with minimized total cartilage lesion 1-year post-op. In both metrics, the BEAR procedure showed superior results as reported by Kiapour et al. They found that the BEAR was better able to maintain the natural properties and alignment of the native ACL, leading to a reduction in tibiofemoral cartilage damage.⁶² The repaired grafts have also been

shown to be comparable to reconstructed ones. In preclinical animal models, the strength of each type of graft was measured, and no statistical difference was found.^{63,64} These data were taken further and applied to current clinical trials in which similar results were shown in humans.^{59,60}

Additional data supporting the use of the BEAR procedure has recently emerged from clinical trials. These data include information on the post-operative comparisons between repaired and reconstructed groups as well as comparisons of strength, stability, and tissue integrity. As supported by Micheli et al, there were no statistical differences found when evaluating the 2 groups at 3 and 6 months post-op. In this same study, there were also no differences in International Knee Documentation Committee (IKDC) scores, effusion, range of motion, or AP laxity, all supporting the success and reliability of the BEAR procedure.⁶⁵ Lastly, all ten of the participants in the first in-human study showed tissue presence in the region of torn ACL at 3 and 6 months by MRI.⁶⁰ It should be acknowledged that analysis of long-term stability requires further study and patient follow-up.^{59,65} Preclinical and clinical studies using the BEAR procedure are outlined in Table 1.

Quality of Life Benefits

Along with the outlined biomechanical advantages of the BEAR procedure, mounting evidence support its ability to improve patient quality of life. Following ACL reconstruction, patients are 3 times more likely to develop osteoarthritis (OA) in the reconstructed knee compared to their healthy contralateral knee.³⁹ The degenerative nature of OA causes debilitating pain and presents as a substantial comorbidity for ACL reconstruction patients.⁶⁶ Although preliminary, preclinical data provides significant evidence that the BEAR procedure can help minimize OA following ACL surgery.^{60,67} In conjunction with OA pain, implementing the BEAR procedure eliminates the need for a tissue graft and, therefore, reduces comorbidities associated with additional surgical trauma

and musculoskeletal compromise. As with any surgical intervention, the risk of infection is a concern following traditional ACL reconstruction and tissue grafting. In the case of the BEAR procedure, mid-term data from the first in-human study shows no infection or severe adverse reactions following the BEAR procedure in patients.⁶⁵ These findings are extremely promising and warrant more longitudinal studies, especially given the already low risk of deep joint infection during ACL reconstruction in conjunction with the sample size of the study.

Limitations and Future Directions

Despite the significant promise and innovation aforementioned, limitations of the BEAR procedure exist. The most prominent issue is the procedure's utility given current study inclusion criteria^{68,69}; more specifically, current research has focused exclusively on mid-substance tears, which does not account for 70% of repairs.⁷⁰ Furthermore, the published work on ACL tears has not included patients with more than 50% of the ACL length lost. This is a major potential detriment that needs to be addressed with future research as it may eliminate many future candidates. Moreover, there has been a longstanding correlation between sex and ACL tears, in which females are at a higher risk than males.⁷¹ Initial animal studies showed significantly lower biomechanical measurements of success in female pigs. These measurements include side-to-side comparisons and cartilage damage assessments, both of which favored males.⁶⁴ Interestingly, initial animal studies have also showed less favorable outcomes in female pigs who received dissolvable sutures during their BEAR procedure. However, the use of non-dissolvable sutures was shown to improve female outcomes to mirror those of males.⁶³ These data expose another potential loss of utility for the BEAR procedure that should be further researched in order to ensure equal efficacy across sexes. Finally, the long-term stability of the primary repair requires further follow-up as the BEAR procedure recipients have

TABLE 1. Summary of current studies available on the BEAR procedure.

Study	Model Organism	Study Type	Objective	Outcome	Adverse Events
Kiapour et al 2017	Mini pigs	Controlled laboratory study	Unilateral ACL reconstruction vs unilateral BEAR: analysis of cartilage damage at 1-year post-op	Less damage in bridge-enhanced repair compared to traditional reconstruction	Altered joint motion in ACL reconstruction group—joint damage
Vavken et al 2012	Skeletally immature pigs	Controlled laboratory study	Compare biomechanical outcomes in BEAR vs. ACL reconstruction at 15 weeks post-op	No measures of biomechanical differences were found to be statistically different between the 2 procedures	None
Murray et al 2016	Human	Non-randomized cohort study	Comparison of postoperative factors following BEAR vs. ACL reconstruction	No statistical difference	None
Micheli et al 2017	Human	Non-randomized cohort study	Determine if BEAR would be safe in humans and compare the early outcomes of this technique with ACL reconstruction	IKDC scores, effusion, AP laxity, and range of motion recovery all found to be similar between bridge-enhanced ACL repair and ACL reconstruction groups	None
Murray and Fleming 2013	Yucatan mini pigs	Controlled laboratory study	Compare the tensile properties of the repair grafts as well as the level of cartilaginous damage at 6 and 12 months post-op; BEAR vs conventional ACL reconstruction	Graft integrity after BEAR was not significantly different from conventional ACL reconstruction; less cartilage damage after BEAR	None

We have included all, to our knowledge, preclinical and clinical BEAR studies in the current literature. This includes respective study parameters and outcomes. The purpose of this table is to concisely summarize current data, and no statistical analyses were performed.

not experienced its effects sufficiently to acquire longitudinal data. Another limitation to the current review is that it does not heavily integrate the basic science literature, which emphasizes the tissue engineering and scaffold testing that has been done in the most primitive stages of the BEAR procedure's development.

Conclusion

Current methods of ACL reconstruction have offered patients sound therapeutic options and have led to restored knee stability and functionality. These traditional methods encounter significant drawbacks as patients are left more vulnerable to developing OA and subsequent surgical intervention. We have compounded preclinical and preliminary human trial data on the recently developed BEAR procedure. To date, the BEAR procedure continues to demonstrate great promise as a viable treatment for ACL tears. However, as aforementioned, it must continue to produce outcomes that rival the current gold standard and ameliorate its current limitations.

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