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Review Article

The non-reconstructive treatment of complete ACL tear with biological enhancement in clinical and preclinical studies: A systematic review

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ABSTRACT

Introduction: There is still controversy regarding the bio-enhanced non-reconstructive ACL treatment.
Materials and methods: A search for articles in databases was performed in February 2017. The objective and subjective evaluations of clinical studies and biomechanical and histological data of preclinical studies were extracted.
Results: Eighteen articles were included for analysis. In clinical studies, although subjective scores were significantly improved, the rate of re-operation rate was high. In preclinical studies, bio-enhancing techniques demonstrated promotion of the healing of ACL.
Conclusions: The efficacy of biological enhancement cannot be validated in clinical studies. Preclinical studies showed improved biomechanical and healing potential.

Contents

Introduction

Currently, anterior cruciate ligament (ACL) reconstruction has been considered as the primary treatment of active young adult patients with ACL complete tear. However, there is still controversy

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regarding the best treatment algorithm of ACL tear in adolescent,[1–4] the middle-aged to elderly,[5,6] skeletally immature and low-demanding adult patients. In addition, tendon-bone healing,[7] donor site morbidity,[8] destruction of proprioception and vascularity, and non-anatomic placement were all potential problems for reconstructive treatment. Non-reconstructive approach primarily avoids the use of graft and extra trauma caused by drilling bone tunnels, and probably preserves more proprioception with less destruction of ACL footprint.

Theoretically, torn ACL has healing potential.[9] However, the outcome of non-reconstructive ACL treatment was not promising. In a long-term follow-up study, Sanders et al.[10] demonstrated 18-fold likelihood of secondary meniscal tears, 14-fold of arthritis, and 5-fold of need of total knee arthroplasty with non-reconstructive treatment comparing with ACLR. Similarly, discouraging outcome of ACL single repair was also reported by a recent systematic review.[3] From the above discouraging results, it seems that the self-healing capacity of ACL is very low, biological enhancement of healing may be necessary to keep the advantages of non-reconstructive surgery and ensure sufficient healing responses and good clinical outcomes.

The biological enhancement technique in ACL reconstruction has been well discussed in a systematic review by Fu et al.[11] They suggested that biological modulation is able to promote healing at the tunnel-graft interface. But the healing of the intra-articular midsubstance of the graft was another consideration. We included clinical and extended to preclinical studies that may provide more advanced insight for the further ACL tear treatment. In the literature, “Healing Response Technique” (HRT) and “Dynamic Intraligamentous Stabilization” (DIS) are two mainly used techniques in clinical studies, while a variety of innovative techniques were also applied in animal studies. HRT was described as perforating cortical bone at the femoral origin and the rupture stump, while DIS is employing internal stabilizer to keep the unstable knee in a posterior translation, combined with microfracturing and platelet-rich fibrin induction at the rupture site to promote self-healing.

The purpose of the systematic review was to describe the clinical outcome and results of animal studies on non-reconstructive treatment of complete anterior cruciate ligament (ACL) tear with biological enhancement.

Materials and methods

We searched the Medline, Scopus and Ovid database in January 2018 to identify all clinical and preclinical studies about the treatment of complete ACL tear with non-reconstructive biological enhancement techniques based on the following criteria: (ACL OR anterior cruciate ligament) AND (repair OR healing) NOT (reconstruct*). The references of all included studies and related reviews were also checked. The inclusion criteria were (1) English original articles published from January 1, 2000 to January 20, 2018; (2) clinical or animal in vivo studies; (3) complete ACL tear; (4) and healing of ACL was enhanced by the use of bone marrow stimulation, mesenchymal stem cells, growth factors, biomaterials, drugs or biophysical intervention (biological enhancement). Articles were excluded if they (1) were reviews, meta-analyses, case reports, or technical notes; (2) had application of any type of graft; (3) included concomitant posterior cruciate ligament and posterolateral complex lesions and patellofemoral disorders. It should be noted that since the management for ACL partial tear is different from complete tear and the relevant articles of partial tear was too few to synthesize, articles about partial tear were also excluded. All included studies retrieved from the search engines were initially checked manually by 2 independent co-authors by reviewing titles, abstracts and full-text articles for final application of the inclusion and exclusion criteria. Any discrepancies were discussed and overcome by consensus.

The full texts of the filtered included articles were then obtained for data extraction. Data from clinical studies were mainly publication years, first author, type of biological enhancement and combined surgery, sample size, patients' demographic data, key objective and subjective outcome measures, and other major findings. Data from animal studies were mainly publication years, first author, type of biological enhancement and combined surgery, animal model, sample size, grouping methods, time of sacrifice, histological or radiological results, laxity data, and biomechanical data.

Assessment of quality of clinical studies and animal studies was then performed by two experienced clinicians and two senior researchers, respectively. Clinical studies were assessed with methodological index for non-randomized studies (MINORS).[12] Since there were four additional criteria for comparative study, the ideal score was 16 for non-comparative studies and 24 for comparative studies. Animal studies were assessed according to the criteria adapted from the checklist of Hooijmans et al.[13] The average score of the two reviewers were recorded as the final score.

Results

The initial research resulted in 1023 articles. After the filtered research, 508 articles were excluded for publication date, type and language. The review on titles was conducted on 515 articles. After the exclusion of 380 irrelevant articles, 135 articles were available for further screening. Twenty-two eligible articles were retrieved. It should be noted that the article written by Eggli et al., in 2015[14] included the same series as they published in 2016[15], so the earlier article was not included for analysis. So 18 articles were finally included for analysis. Among them, seven articles were clinical studies and 11 articles were animal studies. Of the 7 clinical studies, there were 5 level IV case-series studies,[2,15–18] 1 level III retrospective case-control studies[19] and 1 level III cohort study[20] (Fig. 1). There were three techniques discussed in all 7 articles, HRT in 3 studies, DIS repair in 3 studies and bridge-enhanced ACL repair. One of the level III studies compared the outcome of DIS repair with and without additional collagen application.[19] The other one compared the HRT and conservative treatment.[17] Of the 11 animal studies, six compared bio-enhanced ACL repair and suture repair only,[1,21–26] one compared bio-enhanced repair with ACL reconstruction,[27] and compared the outcome of bio-enhanced ACL repair with different fixation methods,[28] platelet-rich plasma (PRP) injection temperature,[29] concentration of PRP[30] and time of delay.[31]

Methodological quality assessment

For clinical studies, there were 4 cases-series studies, 2 case-control and 1 cohort studies. The quality scores were listed in the last column of Table 1. According to MINORS scoring system, comparative studies was evaluated by 4 more items than case-series studies. For animal studies, eight of twelve studies scores 5–8, while 4 studies scored lower than 5, and they were considered as low-quality studies. Good interobserver reliability was obtained between assessors (intraclass correlation coefficient, 0.882; animal studies, intraclass correlation coefficient, 0.807), and consensus on scoring was reached by discussion.

Clinical studies

In total, 193 knees (129 male, 64 female) were evaluated at a

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