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Review

Maximum load to failure of high dose versus low dose gamma irradiation of anterior cruciate ligament allografts: A meta-analysis☆,☆☆

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ABSTRACT

Background: The objective of this study was to systematically evaluate the existing literature to compare the biomechanical effects of low dose and high dose gamma irradiation on commonly used ACL allografts.
Methods: A systematic search was performed in PubMed, Cumulative Index for Nursing and Allied Health Literature (CINAHL), Cochrane Reviews, SCOPUS, and SportDiscus. Nine studies were identified that met the following inclusion criteria: 1) controlled laboratory study, 2) investigation of standard allografts for anterior cruciate ligament reconstruction (ACLR), 3) gamma irradiation (dose reported) and a negative control group, and 4) mechanical loading (results reported).
Results: Nine studies met all inclusion and exclusion criteria. There was a dose-dependent relationship between radiation and decreased mechanical tendon integrity. Low dose radiation (<2.5 Mrad [Mrad]) showed graft weakening with an average of 4.3% decrease in load to failure (standardized mean difference [SMD], 0.23; 95% CI 0.216, 0.68; $p = 0.31$), whereas high-dose radiation showed a significantly larger (32.4% average) decrease in load to failure (SMD, 1.79; 95% CI 1.194, 2.38; $p < 0.001$).
Conclusions: Gamma irradiation has a negative effect on tendon allograft strength that is dose-dependent, with particularly large effects noted at irradiation doses of ≥2.5 Mrad.

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1. Introduction

The anterior cruciate ligament (ACL) is among the most commonly injured ligamentous structures among athletes, with over 200,000 injuries each year in the United States [1]. Several graft types are available for ACL reconstruction, each with benefits and disadvantages [2,3]. Autograft reconstruction requires the harvest of tissue from the patient, potentially increasing operating room time and surgical morbidity. Alternatively, frequently used allografts include bone-patella-tendon-bone (BPTB), Achilles tendon, anterior tibialis tendons, and hamstring tendons. One potential concern with the use of allograft for ACL reconstruction is its potential to introduce infection [4–6]. Several methods are available to decrease the risk of transmission of infectious agents when using allograft tissue, including donor screening, fresh-freezing sterilization, Biocleanse®, ethylene oxide sterilization, gamma irradiation sterilization, and nucleic acid testing for infectious genetic material in donor tissue, with gamma irradiation being the most commonly employed method [7].

A major potential disadvantage of allograft tendon is increased failure risk in young, active patients, particularly when irradiated graft tissue is utilized [8,9]. Considerable debate exists regarding the appropriate amount of gamma irradiation (if any) to use for graft sterilization [10–12]. High-dose irradiation has been shown by some authors to degrade the biomechanical properties of grafts, while too little radiation may fail to accomplish the sterilization goals of gamma irradiation [13–16]. A recent systemic review demonstrated poorer clinical outcomes and higher revision risk of patients who received low dose (<2.5 Mrad) gamma irradiation compared to those who had not received gamma irradiation [17]. No reviews have been published assessing the biomechanical properties of allograft tendons after variable amounts of irradiation.

The purpose of this study was to systematically evaluate the existing literature to determine [1] the biomechanical effects of low dose and high dose gamma irradiation on commonly used ACL allografts, [2] to evaluate the methodological quality of the included studies, and [3] to perform a meta-analysis of available data. We hypothesized that high-dose gamma irradiation (≥2.5 Mrad) would result in a lower maximum load to failure of ACL allograft tissue than low-dose gamma irradiation (<2.5 Mrad).

2. Materials and methods

Using guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for standardized reporting of systematic reviews, a systematic search of the medical literature was performed to identify studies that evaluated the biochemical features of ACL tendon samples after variable amounts of gamma irradiation [18,19]. The PubMed MEDLINE, SCOPUS, CINAHL, SportDiscus, and Cochrane Collaboration Library databases were searched from their earliest entry points to January 28, 2016. All studies were reviewed independently by the authors and checked for potentially inclusive references. All disagreements over study inclusion criteria (i.e. patient age, definition of gamma irradiation, and irradiation type to include) were resolved by consensus among authors ACD and DCF. The search terms were "(knee OR anterior cruciate ligament OR ACL) AND (irradiation OR irradiated) AND (allograft or allogeneic)."

Inclusion criteria included the following:

- English language
- Human subjects
- Studies including the following conditions: ACLs treated with gamma irradiation sterilization, measurement of biomechanical properties of ACL samples in vitro, use of a negative control group.

Exclusion criteria included the following:

- Non-English language
- Animal studies
- Studies involving fascia lata grafts
- Expert opinion
- Letters to the editor
- Technique articles.

An initial search yielded 236 articles (Figure 1). Elimination of 53 duplicates among databases yielded 183 articles for screening. Limitation to studies published in English, involving only humans and the knee joint, and evaluating allogeneic ACL samples yielded 34 studies for possible inclusion. Full-text articles were assessed for inclusion. Further screening for studies evaluating in vitro biomechanical properties of ACL yield 14 studies. Two studies [20,21], were excluded because they evaluated electron-beam irradiation, not gamma irradiation. Differences in dose rate and penetration preclude comparisons between electron-beam and gamma irradiation [22]. Two other studies [23,24] were excluded as they did not include a negative (i.e. 0 Mrad) control group. Another study was not included due to analysis of non-irradiated tendons [25]. Thus, based on full-text review, the nine remaining studies met all inclusion and exclusion criteria and were included in the final qualitative analysis. Studies using the following graft types were included in the analysis: bone-patellar-tendon-bone (BPTB) grafts, tibialis anterior tendon grafts, and semitendinosus grafts.

Maximum load to failure (maximum load, failure load; reported in Newtons [N]) was chosen as the main outcome measure in the present review, because it was reported in all included studies and is the major reported outcome measure in biomechanical studies of ACL tissue grafts. Other biomechanical parameters also are included for completion but were inconsistently reported. We defined low dose irradiation as <2.5 Mrad and high dose irradiation as ≥2.5 Mrad. Irradiation doses of <2.5 Mrad (sometimes as low as 1.0–1.2 Mrad) are commonly defined as "low dose" and thus this definition served as the basis for our cut-points [13,17,26–28]. Studies included reported values as low as 0 Mrad (controls) and as high as 4 Mrad. Due to graft heterogeneity and the manner in which irradiation is applied in irradiation chambers, irradiation levels often are reported as ranges [29]. In these instances, if the range included 2.5 Mrad, it was considered high dose irradiation.

Study methodological analysis was evaluated according to a modified Coleman Methodology Score (CMS) [30,31]. Scores range from 0 to 100 (excellent, ≥85; good, 70 to 84; fair, 55 to 69; poor, ≤54). This scoring system was modified to better adhere to laboratory research study design, with the creation of a Modified CMS for laboratory research on tissue (Appendix Table 1).

2.1. Statistical analysis

All statistical tests were performed with a standard software package (STATA 13.0, StataCorp, College Station, TX). In order to account for between-study differences in baseline graft strength, treatment effect size was defined as the percentage decrease in graft strength after gamma irradiation (using a comparison between un-irradiated negative control groups and irradiated study groups within the same study). Only studies that included testing of grafts with and without gamma irradiation were included in the meta-analysis. A funnel plot of treatment effect versus variance was created as a semi-quantitative assessment of reporting bias among studies; Egger's test [32] was used to evaluate for statistical evidence of publication bias (Figure 2). A fixed effect meta-analysis then was conducted on the data. Effect heterogeneity was determined using the I-squared measure as described by Higgins et al. [33]. A Forest Plot then was created (Figure 3). As a consequence of high effect heterogeneity in at least one treatment category, a random effects model then was created by the DerSimonian and Laird method [34].

Studies were stratified by low vs high dose radiation; a low dose was defined as <2.5 Mrad, and a high dose was defined as ≥2.5 Mrad. The mean percentage decrease in load to failure due to low dose and high dose radiation then was determined as a weighted average with use of the same study weights as the random effects model.