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Terminal Sterilization of Anterior Cruciate Ligament (ACL) Allografts: A Systematic Review of Outcomes

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ABSTRACT

Introduction. Anterior cruciate ligament (ACL) injuries are common and reconstruction can be completed with either autograft or allograft tissue. However, there is concern about an increased failure rate with allograft tissue. The purpose of this study was to systematically review the available evidence to determine the effect of irradiation and level of dose on the failure rates of allograft in ACL reconstruction.

Methods. A literature search was performed using PubMed, Scopus, and Web of Science from January 2000 to September 2013. Inclusion criteria consisted of the following: (1) primary, unilateral, single-bundle allograft ACL procedure, (2) studies with data documenting graft type and terminal sterilization technique, (3) subjective assessments of outcome, and (4) objective assessments of outcome. Studies without reported subjective and objective outcomes and those pertaining to revision ACL reconstruction were excluded. Failures were defined and compared between irradiated and non-irradiated grafts, as well as between grafts irradiated with 1.2 - 1.8 Mrad and those with 2.0 - 2.5 Mrad.

Results. Of the 242 articles identified via initial search, 17 studies met the final inclusion criteria. A total of 1,090 patients were evaluated in this study, all having undergone unilateral primary ACL reconstruction with allograft tissue with 155 failures. The failure rate between non-irradiated (98/687, 14.7%) and irradiated (57/408, 14.0%) was not statistically significant ($p = 0.86$). Grafts in the high-dose irradiation group (27/135, 20.0%) had a statistically significant higher ($p < 0.001$) rate of failure than those in the low-dose irradiation group (30/273, 10.6%).

Conclusion. The irradiation of an allograft increases the risk of failure after an ACL reconstruction but the use of lower doses of radiation decreases that risk. ***Kans J Med 2020;13:23-28.***

INTRODUCTION

Anterior cruciate ligament (ACL) injuries are common and reconstruction can be completed with either autograft or allograft tissue. One study showed that the allograft in primary reconstruction had increased between 2002 and 2008.[1] The benefits of using allograft for ACL reconstruction are numerous and include shorter operative times, increased availability, and graft selection options, as well as decreased incidence of postoperative arthrofibrosis. In addition, there is no risk of donor site morbidity and complications, such as anterior knee pain, loss of knee extension, and loss of knee flexion strength, are avoided.

One of the disadvantages of using allograft tissue is a higher reported rate of graft failure. Different studies have shown rates of failure up to three times higher in patients who underwent ACL reconstruction with allograft compared to autograft.[2,3] Another disadvantage is the possibility of disease transmission from the allograft, although the risk is very low. Estimates of viral transmission risk from unprocessed tissues that are nucleic acid amplification test negative is 1 in 173,000 for human immunodeficiency virus (HIV), 1 in 421,000 for Hepatitis C, and 1 in 100,000 for Hepatitis B.[4] Fresh-frozen, freeze-drying, or cryopreservation are the different ways an allograft initially can be processed. These techniques reduce the graft's immunogenicity but do not eradicate the chance of bacterial or viral transmission. Donor screening procedures, such as the exclusion of high-risk groups and serologic testing, also reduce the risk of disease transmission. Despite the low risk of transmission, secondary sterilization of the graft often is completed. Ethylene oxide is no longer used due to higher graft failure rates[5] and reports of chronic synovitis.[6] Low-dose gamma irradiation between 1.0 and 2.5 Mrad is the accepted protocol for secondary sterilization by most tissue banks, as high levels (> 4.0 Mrad) have been shown to weaken the properties of the allograft.[7] However, up to 5.0 Mrad is necessary to inactivate viruses, such as HIV,[8,9] so the transmission risk is never eliminated completely.

The effect of graft sterilization on outcomes of ACL reconstruction has not been well studied. The purpose of this study was to systematically review and evaluate the available evidence to determine the effect of irradiation and different doses of irradiation on the failure rates of allograft in ACL reconstruction.

METHODS

A literature search was performed using PubMed, Scopus, and Web of Science from January 2000 to September 2013. Keywords used in this search were: anterior cruciate ligament, ACL, reconstruction, allograft, irradiated, non-irradiated, and surgery. This search resulted in 242 unique articles.

For our analysis, therapeutic prospective and retrospective studies were selected. The inclusion criteria consisted of the following: (1) primary, unilateral, single-bundle allograft ACL procedure, (2) studies with data documenting graft type and terminal sterilization technique, (3) subjective assessments of outcome, and (4) objective assessments of outcome. Studies without reported subjective and objective outcomes and those pertaining to revision ACL reconstruction were excluded.

Collected data included graft type, terminal sterilization technique, irradiation level, demographic data, and subjective and objective outcome assessments. Demographics included age, gender, mean follow-up, and time to failure when reported.

Subjective outcome assessments included International Knee Documentation Committee (IKDC), Lysholm, Tegner, and Cincinnati knee scores. Objective outcome assessments included functional IKDC scores, Lachman examination, Anterior Drawer test, Pivot shift test, instrumented laxity measurements with a KT-1000 arthrometer, and graft rupture and revision rates.

Failure rates, when not explicitly defined and reported in a study, were based on criteria determined by the authors, who defined failure as graft rupture, surgical revision, subjective IKDC score less than 80, Tegner Lyholm knee score less than 65, functional IKDC score of C/D corresponding to abnormal/severely abnormal, or laxity resulting in anterior translation greater than 5 mm measured via either KT-1000 arthrometer or Lachman examination. Whenever possible, or when failures rates varied between criteria, this study used functional IKDC scores, arguing that the patient reported outcome (PRO) more accurately reflects how well the patient is doing clinically.

Statistical Analysis. Data were analyzed using a Chi-square test in assessing relationships between irradiated and non-irradiated grafts, along with low-dose radiation (1.2 - 1.8 Mrad) and higher dose (2.0 - 2.5 Mrad) with regard to failure. An alpha probability of 0.05 was used as the threshold for statistical significance in two-tailed comparisons. Means are presented with standard deviations. All statistics were performed with Stata v. 12 (Stata Corp., College Station, TX).

RESULTS

Of the 242 articles identified via initial search, 120 studies were excluded by title because it illustrated that the study did not meet the inclusion criteria. Three reviewers analyzed the remaining 126 studies independently. Of these, 22 studies met initial inclusion criteria. Upon further review, four of these studies were excluded for failing to differentiate between terminal sterilization techniques when reporting graft failures, and one other study failed to note the graft type when reporting failure rates.

Seventeen studies eventually met the final inclusion criteria. With the exception of two studies,[10,11] minimum follow-up was 24 months. In a study by Gorschewsky et al.,[12] outcomes data were included from their two-year follow-up only to maintain consistency with other studies (Table 1). In total, 1,090 patients were evaluated in this study, all having undergone unilateral primary ACL reconstruction with allograft tissue with 132 failures. The characteristics are broken down by graft type in Table 2.

Terminal sterilization primarily consisted of irradiated and non-irradiated grafts. Of the non-irradiated allografts, the vast majority were fresh frozen tissue. Another study used allografts processed via cryopreservation, which was discontinued after report of infections.[13] The study switched to fresh frozen grafts, but the authors did not differentiate between terminal sterilization techniques when reporting failure rates.

Seven studies (n = 408) utilized irradiated allografts. Thirteen studies[14,31-42] (n = 682) utilized non-irradiated allografts. The demographics for these two groups are seen in Table 3. The failure rate between non-irradiated (14.7%) and irradiated (14.0%) was not statistically significant (p = 0.86). The characteristics of the failures of each group are summarized in Table 4.

The amount of radiation used to sterilize allografts fell into one of two categories. Allografts sterilized with 2.0 - 2.5 Mrad of radiation were considered high-dose irradiated allografts, and those sterilized with 1.2 - 1.8 Mrad were considered low-dose. These two groups were compared and the demographics are seen in Table 5. Grafts in the high-dose irradiation group had a statistically significant higher (20.0%) rate of failure than the low-dose irradiation group (10.6%, $p < 0.001$).

DISCUSSION

The principal result of this study did not find a statistically significant difference in failure rates between irradiated and non-irradiated grafts. However, when the data were analyzed further and adjusted for different levels of radiation, a statistically significant greater amount of graft failures was found in the high-dose irradiated group versus the low-dose irradiated group. A previous review by Park et al.[15] found lower clinical outcome scores in low-dose irradiation compared to non-irradiated grafts. However, their cutoff for low-dose radiation was less than 2.5 Mrad. The difference in outcome scores was not analyzed, but rather failure rate was compared. In our analysis, when the low-dose radiation was divided into different groups, very low radiation (1.2 - 1.8 Mrad) allografts had a statistically significant lower rate of failure compared to those between 2.0 Mrad and 2.5 Mrad.

Using low-dose gamma irradiation (1.5 - 2.5 Mrad) may reduce the risk of disease transmission and leave the mechanical properties of the graft intact.[16] The amount of irradiation needed depends on the pathogen that is being treated. This includes 0.5 Mrad for spore forming bacteria,[17] 2.1 Mrad for bacterial spores,[18] and 0.8 Mrad for yeast and molds.[19] Unfortunately, HIV can require anywhere from 1.5[20,21] to 4 Mrad[22] to be eradicated. Therefore, if using a very low dose of radiation (1.2 - 1.8 Mrad) as our study suggests, one would have to ensure there was extensive screening and testing to minimize the risk of transmission of HIV and hepatitis.

Biomechanical studies have shown that irradiation of greater than 2.5 Mrad are known to have detrimental effects on graft properties.[7,23] Other biomechanical studies have looked at 2.0 Mrad and have found a decrease in tensile strength when compared to non-irradiated controls.[23,24] Recently, a study by Yanke et al.[25] found that low-dose (1.0 - 1.2 Mrad) gamma irradiation decreases bone-patellar tendon-bone (BTB) graft stiffness by 20%, but it does not affect other failure or cyclic parameters. Therefore, they recommended low-dose (1.0 - 1.2 Mrad) gamma irradiation of central third human BTB allografts and concluded that it is not deleterious to pre-implantation biomechanical properties. This biomechanical study's conclusion was consistent with what we found in the literature, which is low-dose radiation (1.2 - 1.8 Mrad) had a statistically significant lower failure rate than higher dose (2.0 - 2.5 Mrad) irradiated allografts.[26]

Table 1. Summary of all articles.

Author	Level of Evidence	Total Number of Patients	Irradiated; Number (%)	Non-Irradiated; Number (%)	Definition of Failure	Irradiated Failures; Number (%)	Non-Irradiated Failures; Number (%)
Rappe[31]	3	75	33/75 (44%)	42/75 (56%)	> 5 mm	11/33 (33.3%)	1 (2.4%)
Sun[32]	1	66	32/66 (48%)	34/66 (52%)	> 5 mm	11/32 (34.4%)	3 (8.8%)
Rihn[10]	3	39	39/39 (100%)	0	> 5 mm	1/39 (2.6%)	0 (0%)
Singhal[33]	4	69	0 (0%)	69/69 (100%)	Rupture	0 (0%)	16 (23.2%)
Smith[34]	4	19	0 (0%)	19/19 (100%)	> 5 mm	0 (0%)	0 (0%)
Shah[11]	4	144	144/144 (100%)	0 (0%)	Rupture	8/19 (5.6%)	0 (0%)
Barrett[35]	3	78	0 (0%)	78/78 (100%)	Revision	0 (0%)	19/78 (24.4%)
Poehling[36]	2	41	0 (0%)	41/41 (100%)	IKDC	0 (0%)	11/41 (26.8%)
Gorchewsky[12]	2	97	97/97 (100%)	0 (0%)	Rupture	20/97 (20.6%)	0 (0%)
Kustos[37]	3	53	0 (0%)	53/53 (100%)	Rupture	0 (0%)	2/53 (3.8%)
Noh[38]	1	32	0 (0%)	32/32 (100%)	IKDC	0 (0%)	6/32 (18.8%)
Kim[39]	4	131	0 (0%)	131/131 (100%)	IKDC	0 (0%)	33 (25.2%)
Li[40]	3	30	0 (0%)	30/30 (100%)	TKLS	0 (0%)	0 (0%)
Noh[41]	2	67	0 (0%)	67/67 (100%)	Lachman	0 (0%)	3/67 (4.5%)
Lawhorn[42]	2	48	0 (0%)	48/48 (100%)	> 5 mm	0 (0%)	0 (0%)
Barber[43]	3	32	32/32 (100%)	0 (0%)	> 5 mm	2/32 (6.3%)	0 (0%)
Sun[14]	1	69	31/69 (45%)	38/69 (55%)	IKDC	4/31 (12.9%)	4/38 (10.5%)
Totals		1,090	408/1,090 (37%)	682/1,090 (63%)		57/408 (14.0%)	98/682 (14.4%)

IKDC: International Knee Documentation Committee

Table 2. Characteristics by graft type.

	Achilles	BPTB	Tibialis Anterior	Hamstring
Average age in years	25.9	31.7	32.2	31
Male gender	62.1%	44.4%	73.6%	79.7%
Mean follow-up in months	39.5	40.2	42.2	42.5
Mean time to failure in months	18.2	19.9	22	NA
Irradiated	177 (40.2%)	200 (54.8%)	0 (0%)	31 (12.9%)
Non-irradiated	263 (59.8%)	165 (45.2%)	216 (13.4%)	38 (10.5%)
Mean lysholm score	90.9	86.8	88.5	88.5
Mean tegner score	5.3	6.1	5.2	7.2
Mean subjective IKDC	NA	86.6	90.6	85.5
Functional IKDC A/B	286 (88.3%)	157 (77.7%)	145 (86.8%)	61 (88.4%)
Functional IKDC C/D	38 (11.7%)	41 (20.3%)	21 (12.6%)	8 (11.6%)

BPTB: Bone-Patellar Tendon-Bone; IKDC: International Knee Documentation Committee

Table 3. Terminal sterilization technique demographics.

	Irradiated (n = 408)	Non-Irradiated (n = 682)
Age in years	31.7	29.2
Male	41.9%	57.2%
Female	58.1%	42.8%
Achilles allograft	177	263
BTB allograft	200	165
Tibialis anterior allograft	0	216
Hamstring	31	38
Mean follow-up in months	33.6	37.8
Mean time to failure in months	NA	25.3

Table 4. Summary of the failure results.

	Irradiated (n = 408)	Non-Irradiated (n = 682)	p value
Failure: n/Total n (percent)	57/408 (14.0%)	98/682 (14.7%)	0.86
Rupture	28 (6.9%)	37 (5.4%)	
IKDC C/D	5 (1.2%)	57 (8.4%)	
Laxity > 5 mm	24 (5.9%)	4 (0.59%)	
Mean lysholm score	89.2	89.3	N/A
Mean tegner score	6.8	5.6	N/A
Mean IKDC score	84.7	89.7	N/A
Functional IKDC			
A/B:	65/70 (92.9%)	252/309 (81.6%)	N/A
C/D:	5/70 (7.1%)	57/309 (18.4%)	

IKDC: International Knee Documentation Committee

Table 5. Summary of results by radiation dosage.

	2.0 - 2.5 Mrad (n = 135)	1.2 - 1.8 Mrad (n = 273)	p value
Age in years	33.6	31.9	N/A
Percent male	78.4%	57.2%	N/A
Follow-up in months	33.9	37.8	N/A
Time to failure in months	22	25.3	N/A
Failure: n/Total n (percent)	27/135 (20%)	30/273 (10.9%)	p <0.001
Rupture	0 (0.0%)	28 (10.3%)	
IKDC C/D	5 (3.7%)	0 (0.0%)	
Laxity > 5 mm	22 (16.3%)	2 (0.73%)	
Mean lysholm	90.5	89.3	N/A
Mean tegner	7.4	5.6	N/A
Mean IKDC	87.8	89.7	N/A
Functional IKDC A/B	97/102 (95.1%)	0 (0.0%)	N/A
Functional IKDC C/D	5/102 (4.9%)	0 (0.0%)	N/A

IKDC: International Knee Documentation Committee

Gamma irradiation causes molecules and ions in the allograft to undergo excitation and chemical reactions such as cross-linking, branching, and grafting.[27] This process destroys pathogens but also generates free radicals that can compromise the integrity of the allograft. Recent studies have investigated the use of free radical scavengers to minimize the amount of damage caused by irradiation. Thiourea, a free radical scavenger, results in less collagen damage and less brittle cortical bone in gamma-irradiated allograft bone tissue.[28] Seto et al.[29,30] have shown the radio-protective effects of cross-linking with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and glucose as well as radical scavengers such as mannitol, ascorbate, and riboflavin. These promising data suggested that further studies are needed to determine which radio-protective agent can be used to maintain the quality of irradiated allograft tissue while also minimizing the risk of disease transmission.

The limitations of this study include all of the limitations inherent to meta-analysis, which depends on the quality of the previous papers. In our review, only three papers were included that were level one evidence. Therefore, there was a lack of high-level of evidence papers among our analyses, which limited the conclusions that can be drawn. Due to there being multiple different papers and surgeons, there were multiple variables not accounted for between the two groups such as surgical technique, graft size, graft tensioning, and rehabilitation. Also, with there being multiple authors in the analysis, there was no standard definition of failure for each study. Therefore, when not explicitly defined and reported in a study, failure was defined as a graft rupture, surgical revision, subjective IKDC score less than 80, Tegner Lyholm knee score less than 65, functional IKDC score of C/D corresponding to abnormal/severely abnormal, or laxity resulting in anterior translation greater than 5 mm measured via either KT-1000 arthrometer or Lachman examination. Whenever possible, or when failures rates varied between criteria, this study used functional IKDC scores, arguing that the patient reported outcome (PRO) more accurately reflects how well the patient is doing clinically. Finally, one study[44] looking at BioCleanse was excluded due to the control group not being separated by sterilization technique. BioCleanse tissue sterilization process is a non-thermal combination of mechanical and chemical processes that has been reported to inactivate or remove all sources of infectious disease transmission while not compromising the biomechanical and physiological properties of allograft bone and soft tissue and may be a viable alternative to irradiation but was not able to be studied in this systematic review.

CONCLUSIONS

The irradiation of an allograft increases the risk of failure after an ACL reconstruction but the use of lower doses of radiation decreases the risk of failure.

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