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Acellular Dermal Matrix Augmentation of Arthroscopic Rotator Cuff Repair Reduces Re-Tear Rates: A Meta-Analysis of Randomized Control Trials

Running Title: ADM for ARCR: MA of RCTs

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1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ABSTRACT

Purpose: The purpose of this study was to perform a meta-analysis of randomized controlled trials (RCTs) to compare the outcomes of arthroscopic rotator cuff repair (ARCR) with and without Acellular Dermal Matrix (ADM) augmentation.

Methods: A literature search of three databases was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. RCTs comparing ADM augmentation and a control for ARCR were included. Clinical outcomes were compared using Revman, and a p-value < 0.05 was considered to be statistically significant.

Results: Five RCTs with 307 patients were included. Overall, 11% of patients treated with ADM augmentation and 34% of patients in the control group had a re-tear ($p = 0.0006$). The mean Constant score was 90.1 with ADM augmentation, and 87.3 in controls ($p = 0.02$). Additionally, there was a significant higher ASES score with ADM augmentation (87.7 vs 82.1, $p = 0.01$).

Conclusions: The level I evidence in the literature supports the use of ADM augment as a modality to improve re-tear rates following ARCR.

Level of Evidence: Level I, Meta-Analysis of Level I Studies

Keywords; arthroscopy; rotator cuff; repair; patch augmentation; dermal; allograft; xenograft

INTRODUCTION

Rotator cuff tears are a common pathology, being prevalent in over half of the population over 50 years of age.[1] While the majority of rotator cuff tears can be treated non-operatively with physical therapy and injections, there is still an increasing incidence in those requiring arthroscopic rotator cuff repair (ARCR) annually with 165 repairs per 100,000 person-years performed annually between 2007 and 2016.[2] There is still a concern over re-tears with rates of 9.5%-63.2% reported at 10-year follow-up.[3] The suture-tendon interface is the weakest link in the ARCR construct, with failures occurring due poor tendon tissue quality and its inability to retain the sutures.[4] As a result, modalities to strengthen the suture-tendon interface and reduce the re-tear rates to improve patient outcomes and quality of life has become an important area of study for those performing ARCR.[5, 6]

Acellular Dermal Matrix (ADM) is a collagen matrix made of native elastin, proteoglycans, basement membrane and vascular channels.[7] ADM for reinforcement of rotator cuff repairs has shown significant increases in ultimate load to failure in biomechanical studies.[8-10] There are several meta-analyses in the literature with mixed levels of evidence and grouped multiple augmentation types into one analysis which makes it difficult to distinguish the utility of each, as well as the use of implants that have been withdrawn from the market.[11-15] More recently there have been new randomized controlled trials (RCTs) published, as well as ineffective potentially harmful implants, comprised of submucosa, withdrawn from the market allowing for an updated and more thorough review.[16, 17]

The purpose of this study was to perform a meta-analysis of randomized controlled trials (RCTs) to compare the outcomes of ARCR with and without ADM augmentation. Our hypothesis was that those augmented with ADM would have a lower re-tear rate and better functional outcome scores.

METHODS

Search Strategy & Study Selection

Two independent reviewers searched in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and then analyzed the search results (EH, AM). In the event of disagreement, a senior author would intervene (MD). The following were search terms that were used in The Cochrane Library, EMBASE, and Pubmed from their inception to March 2023: (patch or graft or dermal or allograft or xenograft or porcine) and (rotator cuff). Once duplicates were removed, the abstract and title were reviewed for all identified studies. Of those that qualified, a thorough review of each remaining full text was performed.. Furthermore, references included in the studies identified were reviewed for additional studies that met the inclusion criteria.

Eligibility Criteria

Inclusion criteria were as follows: 1) RCT comparing ADM augmentation and a control for ARCR, 2) published in a peer-reviewed journal, 3) published in English or full translation freely available, and 4) full text of studies available. All other studies were excluded.

Data Extraction

Two independent reviewers collected all relevant information using a predetermined data sheet on Microsoft Excel. In the instance where required information was not offered in the text, authors were contacted via email. Level of evidence (LOE) was assessed using the criteria from the Oxford-Centre for Evidence Based Medicine. Risk of Bias was assessed using the Cochrane Risk of Bias Tool.

Outcomes Analyzed & Statistics

Statistical analysis was performed using Review Manager ((Revman) [Macintosh]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) Heterogeneity between studies was quantified using the I^2 statistic. Random-effects models were employed. Results were expressed as risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, with a 95% confidence interval (95% CI). A p-value of <.05 was considered to be statistically significant.

RESULTS

Literature Search, Study Characteristics & Patient Demographics

The initial literature search resulted 3,013 total studies. Once duplicates were removed, 1,958 studies were assessed for eligibility and full texts were reviewed as shown in Figure 1. Five RCTs met our inclusion criteria, with 156 patients augmented with ADM and 151 controls.[8, 16-19] The tear size was reported in 3 studies with 3.4 cm being the average among non-augmented patients and 3.7cm being the average among augmented patients ($p > 0.05$), with only one study reporting on the pre-operative tear characteristics[8]. The study characteristics & patient demographics are reported in Table 1, and the graft characteristics are reported in Table 2.

Clinical Outcomes

Re-tear Rate

The re-tear rate was reported in all 5 studies, comprising of 154 patients augmented with ADM and 149 controls. Retears were evaluated at final follow-up in all studies with MRI. There was an 11% re-tear rate in the ADM group and 34.9% in controls. There was a statistically significant difference in favor of ADM augmentation (RR; 0.36, 95% CI, 0.20 to 0.64, $I^2 = 20\%$, $p = 0.0006$). The forest plot of the overall re-tear rate is presented in Figure 2.

Constant Score

The Constant score was reported in 5 studies with 156 patients augmented with ADM and 151 controls. The average Constant score was 90.1 in the ADM group and 87.3 in controls. There was a statistically significant difference in favor of ADM augmentation (MD; 2.79, 95% CI, 0.31 to 5.28, $I^2 = 41\%$, $p = 0.02$). The forest plot of Constant score is presented in Figure

3.

American Shoulder and Elbow Surgeons Score

The ASES score was reported in 3 studies with 64 patients augmented with ADM and 61 controls. The average ASES score was 87. in the ADM group and 82.1 in controls. There was a statistically significant difference in favor of ADM augmentation (MD; 5.60, 95% CI, 1.32 to 9.87, $I^2 = 0\%$, $p = 0.01$). The forest plot of the ASES score is presented in Figure 4.

Minimal Clinically Important Difference (MCID)

The MCID was reported in 1 study of 20 patients augmented with ADM and 20 controls. A greater number of patients in the ADM group improved beyond the MCID in both ASES (90.0 vs 82.4%) and Constant score (100 vs. 73.7%) but these were not statistically significant ($p > 0.05$).

DISCUSSION

The most important finding was that the current level 1 evidence in the literature supports the use of ADM augmentation to improve re-tear rates and clinical outcomes in ARCR. All but one of the included studies found a statistically significant improvement in re-tear rate with ADM augmentation, which was a pilot trial to assess feasibility and determine the numbers needed for an RCT. However, there still are questions and areas for further study on the use of ADM augmentation, including when augmentation is required, whether allograft or xenograft is preferred and the cost-effectiveness of ADM augmentation.

ADM augmentation has been utilized to reinforce rotator cuff repairs, to improve the biomechanical strength of the construct and decrease tension of the rotator cuff repair tissue.[8-10]. Prior meta-analyses in the literature included a combination of mixed levels of evidence and graft use, with none focusing exclusively on the level 1 evidence for ADM, with many also including a now withdrawn from market porcine intestinal mucosal graft, which resulted in worse re-tear rates and an inflammatory response.[11-14] All of the studies in the included review utilized ADM, other graft patches have been trialed and resulted in controversy surrounding the use of patch augmentation. As opposed to previous metanalyses related to ARCR augmentation, this one focuses exclusively on ADM. [11-15] Mandalia et al.[20] in a metanalysis of both animal and human studies utilizing several different graft types found significant decreases in re-tear rates. Similarly, de Andrade et al.[12] reported significant improvement in retear rates and pain in the graft augmentation group, yet included intestinal and synthetic patches. The advantage of the current meta-analysis is the narrow focus on randomized controlled, ADM studies which have increased in recent years. Therefore, the findings of this study are noteworthy as they support the use of ADM augmentation which resulted in a one-third of the re-tear rate of non-augmented repairs.

Snow et al.[17] was the only included study not to show a statistically significant difference in the re-tear rate, but this was a pilot RCT to assess feasibility and determine the numbers needed for an RCT to be viable. They concluded that 150 was the number needed for an RCT to determine a statistically significant difference, which was surpassed by the cumulative number in this meta-analysis. Additionally, there were significant improvements in both the Constant and ASES scores. While these did not reach the MCID of 4.6 and 11.1 respectively, it should be noted that these are individual patient metrics and should not be applied to the whole population, rather the proportion of patients that meets the MCID.[21, 22] Although, Avanzi et al.[8] found in their RCT that ADM augmentation resulted in thicker repaired rotator cuff tendons and improved footprint coverage, which may lead to stronger tendons.

The 2019 AAOS CPG concludes there is limited literature to support the use of ADM in the setting of massive rotator cuff tears as there were only two studies of adequate evidence at the time.[18, 27] Since the report there have been 4 RCTs with greater than 20 patients that report significant improvement in re-tear rates and 3 reported significantly improvement in ASES scores. All these studies have been included in the current meta-analysis, which can potentially assist in updating the 2019 AAOS CPG recommendations.

These are still important areas of future study, as tendon healing has been shown to correlate with long-term patient reported outcomes.[23] It is imperative to determine when augmentation is required, and which patients should have it at the time of surgery. Jackson et al.[28] proposed that patients with a Rotator Cuff Healing Index score > 7 should have

augmentation at the time of ARCR, which is based on risk for re-tears (including age >70, anteroposterior tear size, retraction, infraspinatus fatty infiltration, bone mineral density and a high level of work activity).[29] The optimal graft requires future investigations, including whether allograft or xenograft is preferred as xenografts could result in an inflammatory response, and the optimal ADM thickness, which has been shown to influence outcomes in other procedures such as superior capsular reconstruction.[30]

Limitations

This study has several limitations and potential biases, including the limitations of the included studies themselves. There was moderate heterogeneity in several of the outcome measures, which shows inconsistency in the results between the studies. There was a mixture of different grafts used, including a mixture of allograft and xenograft. Additionally, there was a lack of consistency in reporting of secondary outcomes and while all of the included studies reported on the Constant score, other outcome measures were less commonly reported and it was not possible to meta-analyze for pain scores. There was a lack of reporting on MCID, with only one study reporting on this.

Conclusion

The level I evidence in the literature supports the use of ADM augment as a modality to improve re-tear rates outcomes following ARCR.

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TABLE LEGEND

Table 1. Study characteristics & patient demographics

Table 2. Graft characteristics

FIGURE LEGEND

Figure 1. PRISMA

Figure 2. Forest plot of the re-tear rate

Figure 3. Forest plot of the Constant Score

Figure 4. Forest plot of the ASES Score

Table 1 Study Characteristics & Patient Demographics

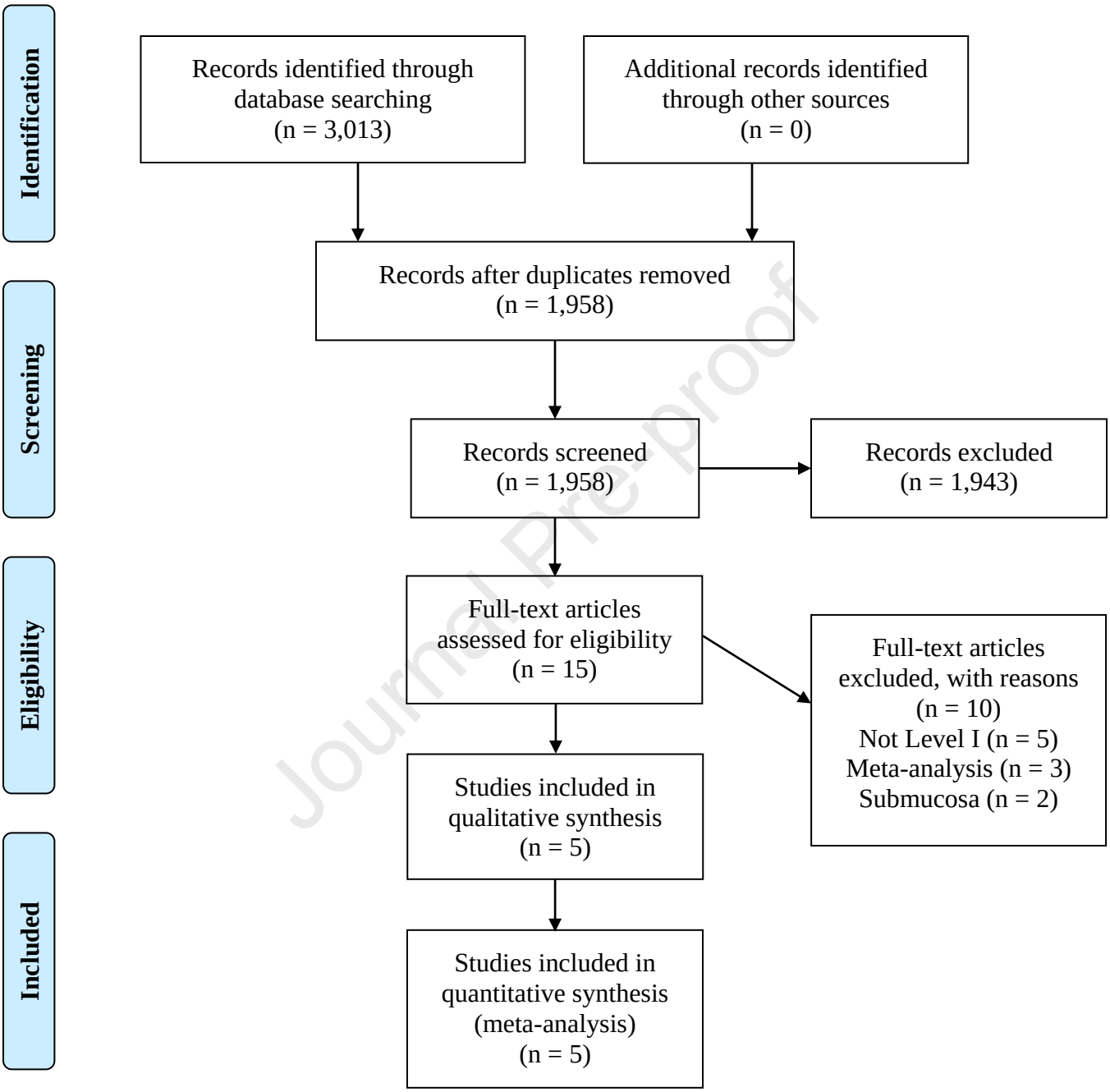
Author	**Study Patients**	**Control Patients**	**LOE**	**MQOE/ROB**	**Age (yrs)**	**Follow-up (mo)**
Avanzi et al. 2019[8]	41	37	I	Moderate	67 (6)	24
Barber et al. 2008[18]	22	20	I	Moderate	56 (N/R)	24
Cai et al. 2018[19]	51	53	I	Moderate	62 (6.3)	24
Lee et al. 2022[16]	22	21	I	Moderate	59 (9.8)	68
Snow et al. 2023[17]	20	20	I	Moderate	63.8 (9.6)	12

N; number, LOE; level of evidence. MQOE; methodological quality of evidence, ROB; risk of bias, yrs; year, mo; months

Age is represented as mean and SD

Table 2. Graft Characteristics

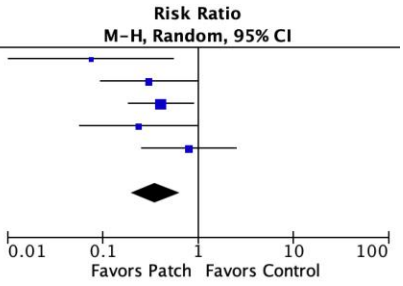
Author	Graft	Brand	Company	Method	Graft Thickness
Avanzi et al. 2019[8]	porcine dermal	Conexa	Tornier (Grenoble, France)	onlay	Not reported
Barber et al. 2008[18]	human dermal	GraftJacket	Wright Medical (Memphis, TN, USA)	onlay	Not reported
Cai et al. 2018[19]	3D type I collagen scaffold		Zhejiang Xingyue Biotechnology (China)	between cuff and footprint	Not reported
Lee et al. 2022[16]	human dermal	CGDerm	CGBio, Dae-woong Pharm, Seoul, Korea)	integrated	1.04–2.29 mm
Snow et al. 2023[17]	human dermal	D-cell	NHSBT, UK	integrated	1.5–2 mm



Study or Subgroup	Patch Augmentation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Avanzi 2019	1	41	12	37	8.1%	0.08 [0.01, 0.55]
Barber 2012	3	22	9	20	20.5%	0.30 [0.10, 0.96]
Cai 2018	7	51	18	53	35.8%	0.40 [0.18, 0.89]
Lee 2022	2	22	8	21	14.5%	0.24 [0.06, 1.00]
Snow 2023	4	18	5	18	21.0%	0.80 [0.26, 2.50]
Total (95% CI)		**154**		**149**	**100.0%**	**0.36 [0.20, 0.64]**
Total events	17		52			

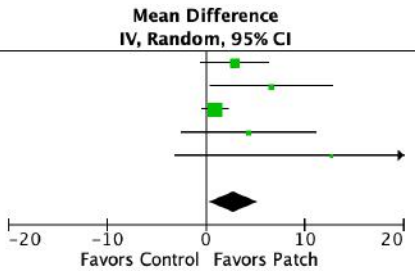
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.03$, df = 4 (P = 0.28); $I^2 = 20\%$

Test for overall effect: Z = 3.43 (P = 0.0006)



Study or Subgroup	Patch Mean	Patch SD	Patch Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Avanzi 2019	95.5	5.5	41	92.6	9.3	37	26.7%	2.90 [-0.54, 6.34]
Barber 2012	91.9	9.2	22	85.3	11	20	12.5%	6.60 [0.43, 12.77]
Cai 2018	90.8	3.5	51	89.9	3.2	53	47.7%	0.90 [-0.39, 2.19]
Lee 2022	71.1	7.7	22	66.8	14	21	10.7%	4.30 [-2.50, 11.10]
Snow 2023	83.9	16.6	20	71.2	32.1	20	2.4%	12.70 [-3.14, 28.54]
Total (95% CI)			**156**			**151**	**100.0%**	**2.79 [0.31, 5.28]**

Heterogeneity: $Tau^2 = 2.94$; $Chi^2 = 6.67$, df = 4 (P = 0.15); $I^2 = 40\%$
Test for overall effect: Z = 2.20 (P = 0.03)



Study or Subgroup	Patch Mean	Patch SD	Patch Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barber 2012	98.9	4.2	22	94.8	14.2	20	43.7%	4.10 [-2.37, 10.57]
Lee 2022	78.9	12.8	22	71.7	7.7	21	46.3%	7.20 [0.92, 13.48]
Snow 2023	79.6	17.7	20	74.9	25.3	20	10.0%	4.70 [-8.83, 18.23]
Total (95% CI)			**64**			**61**	**100.0%**	**5.60 [1.32, 9.87]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, df = 2 (P = 0.79); $I^2 = 0\%$
Test for overall effect: Z = 2.57 (P = 0.01)