



Allograft augmentation of hamstring autografts was not a cost-effective treatment option for middle aged patients undergoing primary anterior cruciate ligament reconstruction

Cale A. Jacobs¹, Chaitu S. Malempati¹, Eric C. Makhni², Darren L. Johnson¹

¹Department of Orthopedic Surgery, University of Kentucky, Lexington, KY, USA; ²Division of Sports Medicine, Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, MI, USA

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Correspondence to: Cale A. Jacobs, PhD. 740 S Limestone, Room K426, Lexington, KY 40536-0284, USA. Email: cale.jacobs@uky.edu.

Background: By lessening the rate of graft failure, augmentation of hamstring autografts with semitendinosus allograft tissue has been demonstrated to provide a cost-effective treatment option for adolescent anterior cruciate ligament reconstruction (ACLR) patients. However, with the overall rate of graft failure being much lower in older patients, it remains unclear if these so-called hybrid hamstring grafts are a cost-effective option in the middle-aged patient population. We hypothesized that hybrid hamstring grafts would not result in a clinically meaningful reduction in the prevalence of graft failure and, as such, would not be a cost-effective treatment option for middle-aged patients.

Methods: We retrospectively identified patients ≥ 25 years of age that had undergone ACLR by a single surgeon between 2010 and 2015. Patient demographics, graft type, and the need for secondary surgical procedures were compared between hamstring autografts (HAM) and hamstring autografts augmented with semitendinosus allograft tissue (HYBRID). The clinical results were then used to assess the potential cost effectiveness of HYBRID grafts in this group of middle-aged ACL patients.

Results: There were a total of 288 patients (HAM = 138, HYBRID = 150). The rate of graft failure did not differ between groups (HAM = 3/138, 2.2% *vs.* HYBRID = 4/150, 2.7%, $P > 0.99$). The cost-effectiveness analysis demonstrated that the HAM graft provided incremental cost savings of \$1,322.39 compared to the HYBRID graft, and the HAM graft was the preferred strategy in 85% of cases.

Conclusions: In younger patients, the initial cost of allograft augmentation is offset by a significant reduction in graft failure; however, similar findings were not realized in series of middle-aged patients. This information can assist surgeons as the both the techniques and patient selection criteria for hybrid grafts continues to evolve.

Keywords: Anterior cruciate ligament (ACL); graft failure; revision; complication; adult

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Introduction

By lessening the rate of graft failure, augmentation of hamstring autografts (HAM) with semitendinosus allograft tissue has been demonstrated to provide a cost-effective treatment option for adolescent anterior cruciate ligament

(ACL) reconstruction patients (1). However, with the overall rate of graft failure being much lower in older patients (2), it remains unclear if these so-called hybrid hamstring grafts are a cost-effective option in the middle-aged patient population. As such, the purpose of this study was to compare clinical results and cost-effectiveness between HAM

and so-called hybrid HAM augmented with semitendinosus allograft tissue in patients aged 25 years or greater in order to further establish evidence-based patient selection criteria for allograft augmentation. We hypothesized that hybrid grafts would not result in a clinically meaningful reduction in the prevalence of graft failure and, as such, would not be a cost-effective treatment option for middle-aged patients.

Methods

Patients

This study received IRB approval from our institution (protocol # 16-0077-P1H) and the current analysis included all patients aged 25 years or older that had undergone primary ACL reconstruction between 2010 and 2015 with HAM, either with or without allograft semitendinosus augmentation. Patients undergoing multi-ligament reconstruction or where revision anterior cruciate ligament reconstruction (ACLR) was the index procedure at our institution were excluded. Patients were not excluded based on the condition or treatment of the menisci or articular cartilage.

To compare clinical results of the two grafts, we identified patients ≥ 25 years old that had undergone ACLR by a single surgeon between 2010 and 2015 with either a HAM or hybrid autograft with semitendinosus allograft augment (HYBRID). Similar surgical technique, pre- and postoperative rehabilitation were used for both groups as directed by the single senior surgeon.

Surgical technique

As previously described, the gracilis and semitendinosus autograft harvest was identical between those receiving either HAM or HYBRID grafts (1). The gracilis and semitendinosus tendons were harvested using standard techniques, and were then either quadrupled or quintupled (3). For those having a HYBRID graft, the allograft tissue was whip-stitched on both ends. The allograft tissue was sterilized using the Allowash XG process including 1.2 to 1.9 Mrad irradiation (LifeNet Health, Inc., Virginia Beach, VA) (4). The allograft tissue was passed first with the autograft tissue then being placed around the allograft with the end goal of having as little of the allograft tissue exposed to the knee joint milieu *in vivo*. With the allograft strands placed in the middle of the autograft strands, the entire graft was doubled over forming six strands (1).

For both HAM and HYBRID grafts, the femoral tunnel was drilled using an accessory anteromedial portal. Femoral fixation was achieved using a suspensory fixation (Endobutton, Smith & Nephew, Andover, MA) and a BIORCI (Smith & Nephew, Andover, MA) bioabsorbable interference screw was used for tibial fixation with the free tendon ends wrapped around a bi-cortical 4.5 mm large fragment screw with a 20 mm washer (Geofit, Depuy Mitek, Norwood, MA) for backup fixation.

Statistical analyses

We retrospectively collected patient demographic information and the need for subsequent surgeries to the involved knee. In addition to the need for revision ACLR, we also included evidence of a failed graft on magnetic resonance imaging, or pathological laxity during the physical examination (positive Lachman test, marked anterior laxity, or a positive pivot shift test compared to the healthy knee), or patient-reported instability that affected the patient's ability to perform activities of daily living or sporting activities, in our definition of a failed graft. Any patient that met these criteria was considered to have a failed graft regardless of whether the patient chose to undergo revision ACL reconstruction (1,5,6). Continuous variables such as age and BMI were compared with independent *t*-tests and categorical variables such as sex and graft failure were compared between HAM and HYBRID groups using two-tailed χ^2 or Fisher Exact tests as appropriate. For all analyses, an α -level of $P \leq 0.05$ was considered statistically significant.

The clinical results were then used to compare the cost-effectiveness between HAM and HYBRID grafts when used in series of middle-aged patients. We utilized previously published methods and this study made the following assumptions: (I) patients underwent equivalent preoperative treatment with equivalent costs; (II) patients did not suffer contralateral ACL injury during the study period; and (III) those with complications or graft failures occurring after a tertiary surgery remained at the current health state (primary surgery = index ACL reconstruction, secondary surgery = revision ACL reconstruction or reoperation due to infection or arthrofibrosis, tertiary surgery = second revision ACL reconstruction or second reoperation for infection or arthrofibrosis; *Figure 1*).

The base case cost-effectiveness was assessed using Monte Carlo microsimulation of a simplified decision tree model created with 1,000 theoretical patients assigned

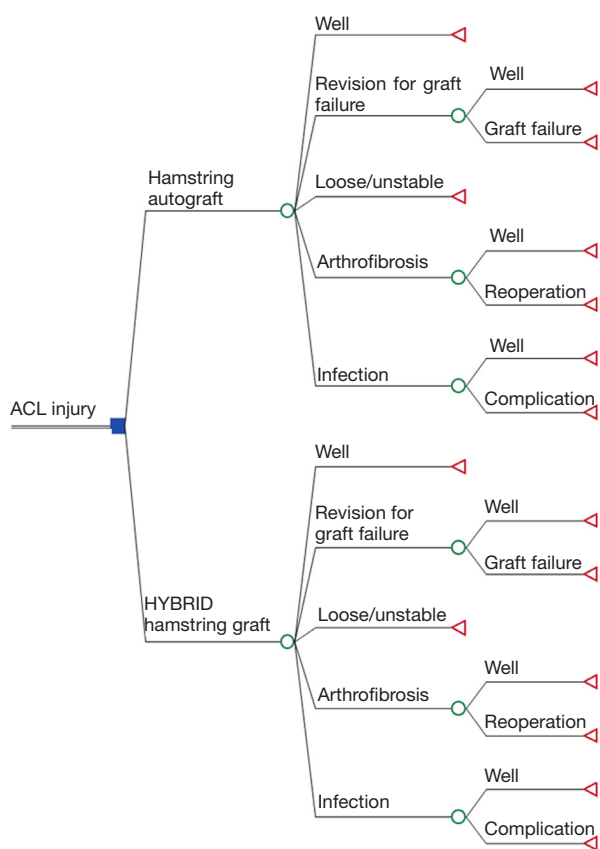


Figure 1 The simplified decision tree used to compare the base case cost effectiveness of hamstring autografts with or without being augmented with semitendinosus allograft tissue.

equally to HAM or HYBRID cohorts (Figure 1). These treatment arms were divided into outcome arms based on probabilities, utilities, and costs derived from both the current clinical results and from the literature (Table 1). Specifically, we included the probabilities of a successful outcome as well as revision due to graft failure, persistent instability, arthrofibrosis requiring reoperation, and infection. These values were taken directly from our clinical results or previously published literature on adult patients (Table 1). The incremental cost of the HYBRID graft was \$1201.56 greater than the HAM graft based on pricing at our facility. All other costs were consistent with the previous study by Genuario *et al.* (7). Terminal outcomes were assigned a health state/utility score and a societal cost, and the threshold for cost-effectiveness was set as an incremental cost-effectiveness ratio of \$50,000/quality-adjusted life year (QALY) (7).

To better estimate uncertainty within each model,

probabilistic sensitivity analysis of 1,000 first-order cases was used to vary probabilities, utilities and costs within the two models. Similar to the methods of Crall *et al.* (12) and Jacobs *et al.* (1), probability parameters were assigned beta distributions, utility parameters were assigned normal distributions, and cost parameters were assigned gamma distributions. All parameter distributions were centered about the baseline value and standard deviations were assumed to be 20% of the mean. We also determined the percentage of cases in which each strategy (HAM or HYBRID graft) would be the preferred strategy based on the willingness to pay (WTP) of \$50,000.

Results

Clinical results

There were a total of 288 patients, 138 patients in the HAM group and 150 in the HYBRID group (Table 2). The two groups did not differ in terms of age; however, the groups did differ in sex, BMI, and the duration of follow-up with the HAM group having significantly fewer females, lower BMI, and longer follow-up (Table 2). The prevalence of graft failure did not differ between groups (HAM = 3/138, 2.2% vs. HYBRID = 3/150, 2.7%, $P>0.99$).

Cost-effectiveness results

The HAM graft was the dominant strategy in the base case as it provided an incremental cost savings of \$1,329.92 with both treatment options demonstrating equal effectiveness (QALY = 0.94 for both groups). Probabilistic sensitivity analysis results were similar, with the HAM graft demonstrating mean costs of \$4,736.86±\$860.48 compared to \$6,059.25±\$1,056.04 for the HYBRID group. Again, both groups demonstrated similar effectiveness (QALY =0.94±0.15). The combination of lower cost and similar effectiveness made the HAM graft the preferred treatment strategy in 85% of the simulated cases.

Discussion

The purpose of this study was to compare clinical results and cost-effectiveness between HAM and hybrid hamstring autografts augmented with semitendinosus allograft tissue in patients aged 25 years or greater in order to further establish evidence-based patient selection criteria for allograft augmentation. Our hypothesis that hybrid grafts

Table 1 Baseline variables, sensitivity analysis ranges and distributions, and sources

Variable	Baseline values	Probabilistic sensitivity analysis distribution	Source
Probabilities of complications after primary ACL reconstruction*			
Revision for graft failure			
HAM	0.022	Beta	Current results
HYBRID	0.027	Beta	Current results
Arthrofibrosis			
HAM	0.007	Beta	Current results
HYBRID	0.007	Beta	Current results
Instability			
HAM	0.24	Beta	Genuario (7)
HYBRID	0.24	Beta	Genuario (7)
Infection			
HAM	0.013	Beta	Brophy (8)
HYBRID	0.013	Beta	Brophy (8)
Probabilities of secondary complications (assumed to be similar for both HAM and HYBRID)*			
After revision ACL reconstruction			
Re-revision for Graft Failure	0.137	Beta	Wright (9)
2nd reoperation for arthrofibrosis	0.151	Beta	Nwachukwu (10)
2nd infection	0.286	Beta	Calvo (11)
Utilities (QALY)*			
Well State	1	Normal	Genuario (7)
Arthrofibrosis	0.77	Normal	Genuario (7)
Instability	0.79	Normal	Genuario (7)
Infection	0.96	Normal	Genuario (7)
Well after revision	0.98	Normal	Genuario (7)
Secondary complication	0.70	Normal	Genuario (7)
Costs (US\$) [†]			
HAM	4,072	Gamma	Genuario (7)
HYBRID	5,274	Gamma	Current results
Infection	9,805	Gamma	Genuario (7)
Arthrofibrosis	3,000	Gamma	Genuario (7)
Revision	20,000	Gamma	Genuario (7)

*, probability and utility parameters were assigned beta distributions about the baseline value, with the standard deviation being assumed to be 20% of the mean (12). [†], cost parameters were assigned normal distributions about the baseline value (12).

Table 2 Comparison of patient demographics and complications between the HAM and HYBRID groups

Variables	HAM (n=138)	HYBRID (n=150)	P
Sex (females/males)	32/106	74/76	<0.001
Age (years)	37.7±9.1	38.6±8.9	0.42
BMI (kg/m ²)	28.9±5.2	30.9±6.3	0.03
Follow-up (years)	4.7±1.6	2.7±1.1	<0.001
Reoperations for arthrofibrosis	1 (0.7%)	1 (0.7%)	>0.99
Graft Failure	3 (2.2%)	4 (2.7%)	>0.99
Time between surgery and re-tear (months)	27.0±19.1	19.6±6.4	0.58

would not result in a clinically meaningful reduction in the prevalence of graft failure and, as such, would not be a cost-effective treatment option for middle-aged patients was supported by the current results.

There are limited published reports that have assessed the efficacy of hybrid HAM, and the current results represent the largest study in terms of the number of patients treated with hybrid grafts to date. In addition to the current results there have been four publications on the topic—two in adolescent patient populations (1,13) and two in more general populations (4,14). We have previously reported significantly reduced failure rates with hybrid grafts in select subsets of adolescent patients (1) and the current results suggest equitable efficacy between HAM and hybrid grafts in middle-aged patients. On the contrary, we recognize that all published results outside of our institution have reported inferior results with hybrid grafts. While there were differences between studies in terms of allograft tissue source (semitendinosus *vs.* Achilles tendon) and sterilization methods, we suggest that the dramatically different clinical results may have been due to differences in graft preparation technique. Specifically, the location of the allograft tissue within the graft may be important. Our technique involves incorporating the allograft tissue within the autograft tissue, theoretically minimizing the amount of allograft tissue exposed to the knee joint milieu. Unfortunately, the specific location of the allograft tissue within the hybrid graft was not clearly described by Darnley *et al.* or Pennock *et al.* (13,14); however, Burrus *et al.* (4), who reported significantly greater graft failure with hybrid grafts, stated that the hybrid grafts were rotated to place the allograft tissue anteriorly. Both on second-look arthroscopy and MRI, they reported that it was, indeed the anterior fibers of their hybrid grafts that had failed (4). Furthermore, Pennock *et al.* reported that hybrid grafts tended to fail

during the first postoperative year, and suggested that hybrid grafts may take longer to incorporate (13). The marked differences in clinical performance between our institution and others, combined with mean time to failure of more than 18 months in both our adolescent and middle-aged series, suggest that graft preparation methods that protect the allograft tissue may improve incorporation of the hybrid graft, thereby improving clinical performance.

The current results represent an important step in defining appropriate patient selection criteria for hybrid grafts. We have previously reported that hybrid grafts significantly reduced graft failure rates in skeletally immature patients as well as those patients under the age 18 that the surgeon felt might have greater difficulty with postoperative rehabilitation following bone-patellar tendon-bone graft harvest (1). Some have expressed concern that augmenting a HAM in a small female patient may result in graft impingement; however, this was not borne out as there was no difference in reoperations for cyclops lesions, arthrofibrosis, or limited knee extension range of motion between the two grafts (1). The hybrid graft successfully reduced graft failure rates for both adolescent males (HYBRID: 4/24, 17% *vs.* HAM: 6/20, 30%) and females alike (HYBRID: 1/18, 6% *vs.* HAM: 7/26, 27%) (1), further suggesting that theoretical risk of graft impingement was not realized clinically. While this was the case, we do caution that the size of the graft must be customized in the small adolescent female or skeletally immature patient. We are in no way suggesting a one-size-fits-all approach be taken, or that all graft diameters should be ≥ 10 mm. On the contrary, the patient's anatomy and sporting demands should be taken into account so that the same graft would likely not be used in an 80 lb 16-year-old skeletally mature female *vs.* 200 lb 13-year-old skeletally-immature male.

While previously demonstrated to significantly reduce

graft failure rates in subsets of adolescent patients, the current results suggest that routine allograft augmentation may not be necessary in patients aged 25 years or older. Hybrid grafts did not yield inferior results in the middle-aged patients, but rather that the increased initial cost of the allograft tissue was not offset by a reduction in failure rates as was seen in adolescent patients. It is important to note that the current results suggest that routine allograft of all middle-aged patients is not cost-effective but that there may be subsets of middle-aged patients for whom hybrid grafts are indicated. While HAM were the dominant treatment strategy, the probabilistic sensitivity analysis results indicated that hybrid grafts were the preferred strategy in 15% of simulated cases. This suggests that there may very well be subsets of middle-aged patients that may be better served with a hybrid graft. Future studies are then necessary to determine if patients that place greater stress on the graft postoperatively (i.e., patients that resume cutting sports and/or those with greater BMI, etc.) may benefit from a hybrid graft.

This study was not without limitation. This study, while the largest sample of hybrid grafts reported in the literature to date, did not include patient-reported outcomes. Larger prospective studies are necessary to validate the current findings and examine potential effects on patient-reported outcomes. We also did not routinely capture postoperative sports participation and activity levels, which limited our ability to identify a potential subset of middle-aged patients that may benefit from hybrid graft selection. Second, this analysis was based on the United States healthcare system. Allograft augmentation may not be an available treatment option in other geographic locations, and the cost-effectiveness results may differ in other healthcare environments.

In conclusion, the cost-effectiveness of hybrid grafts previously seen in adolescent patients was not realized in an older patient population. Routinely augmenting HAM with semitendinosus allograft tissue did not result in a reduced rate of graft failure and, as such, was not a cost-effective treatment option for middle-aged patients when compared to HAM. HAM provided incremental cost savings of \$1,322.39 per patient compared to the hybrid graft, and the HAM grafts were the preferred strategy in 85% of simulated cases. This information can assist surgeons as both the techniques and patient selection criteria for hybrid grafts continue to evolve.

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Footnote

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Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study received IRB approval from our institution (protocol # 16-0077-PIH).

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