Cost-Effectiveness Analysis of Autologous Chondrocyte Implantation: A Comparison of Periosteal Patch Versus Type I/III Collagen Membrane

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What is This?
Cost-Effectiveness Analysis of Autologous Chondrocyte Implantation

A Comparison of Periosteal Patch Versus Type I/III Collagen Membrane

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Background: Autologous chondrocyte implantation (ACI) involves the use of a periosteal patch (ACI-P) as a cover for transplanted chondrocytes. Theoretically, this periosteal patch provides mesenchymal stem cells and growth factors that encourage chondrocyte development/differentiation. However, there is a significant rate of graft hypertrophy with the use of periostium compared with using a type I/III collagen patch (ACI-C). This type I/III collagen patch, although not approved by the United States Food and Drug Administration for ACI, has been used extensively in Europe and in an “off-label” nature in the United States as a cover during ACI.

Purpose: To examine the cost effectiveness of ACI and determine whether ACI-C is more cost effective than ACI-P.

Study Design: Economic and decision analysis; Level of evidence, 2.

Methods: Outcome data and complication rates from patients undergoing ACI (ACI-P and ACI-C) were derived from the best evidence in the literature. Costs were determined by examining the typical patient charges undergoing ACI at a local orthopaedic hospital. The costs, results, and complication rates were used to develop a decision analysis model comparing ACI-P to ACI-C.

Results: The cost of ACI-P was $66,752 and for ACI-C was $66,939.50 ($187.50 difference). The cost per quality-adjusted life year (QALY) for ACI-P was $9466 compared with $9243 for ACI-C. Sensitivity analysis was performed regarding the additional cost of the type I/III collagen patch ($780) in ACI-C as well as the rate of graft hypertrophy after ACI-P (25%). This analysis revealed that the cost of the type I/III collagen patch would have to reach $1721, or the rate of graft hypertrophy after ACI-P reduced to almost 11%, before ACI-P became more cost effective than ACI-C.

Conclusion: This cost-effectiveness analysis reveals that, while both ACI-P and ACI-C are cost effective, ACI-C is slightly more cost effective than ACI-P. This is likely secondary to the significant rate of patch-related complications associated with ACI-P, which is significantly reduced with ACI-C. Although the model is very sensitive to differences in outcomes between ACI-P and ACI-C, there is no high-quality evidence to suggest that there is a significant difference between the two. Thus, ACI-P becomes more cost effective if the cost of the type I/III collagen membrane is significantly increased or if the rate of graft hypertrophy after ACI-P were to be markedly reduced.

Keywords: autologous chondrocyte implantation; cost-effectiveness analysis; focal chondral injury

It has long been recognized that articular cartilage injury is a condition that causes significant dysfunction for the patient and presents serious treatment challenges for orthopaedic surgeons.2,20,36 This is likely due to the fact that articular cartilage is a “highly organized tissue with complex biomechanical properties and substantial durability.”26 p994 This complex tissue structure is difficult to recreate after significant cartilage injury. This raises an immense socioeconomic issue because significant chondral injury of the knee is quite common, being identified in over 60% of arthroscopic knee procedures,8,18,23 and the attempted treatment of these lesions is associated with a considerable economic burden.29,32

Various procedures have been proposed in an effort to treat focal chondral defects of the knee. These procedures range from marrow stimulation techniques, such as microfracture, abrasion arthroplasty, and subchondral drilling, to cartilage restoration techniques such as osteochondral...
autografts/allografts and mosaicplasty. While these techniques have shown some success in treating articular cartilage injuries of the knee, they have also been associated with some significant limitations. For instance, marrow-stimulating procedures result in the formation of a fibrocartilage repair tissue that has been associated with limited durability and functional decline with longer term follow-up. Concerns of cartilage restoration techniques include potential disease transmission, donor site morbidity, and chondrocyte viability after impaction.

In an attempt to improve upon previous cartilage treatments, and produce a hyaline or hyaline-like repair tissue, autologous chondrocyte implantation (ACI) was first reported in 1994 for use in treating chondral defects of the knee. The technique described utilizes a 2-step process including a cartilage biopsy, chondrocyte culture and expansion in vitro, and injection of these autologous chondrocytes back into the chondral defect under a periosteal graft (ACI-P) taken from the proximal medial tibia. Many studies have now been published demonstrating the significant and sustained improvement these patients experience with ACI-P. Despite this success, however, ACI-P is also associated with a significant rate of complications, most commonly graft hypertrophy, which can cause mechanical symptoms such as popping or catching. This often necessitates revision arthroscopic debridement, which significantly increases the costs associated with achieving a satisfactory outcome after ACI-P.

Recognizing the significant rate and effect of graft hypertrophy in ACI-P, and how this affects a patient’s quality of life, ACI utilizing a type I/III collagen patch (ACI-C) was developed. A type I/III collagen patch and other biological membranes have been used extensively for ACI in Europe. While these type I/III collagen patches are approved by the United States Food and Drug Administration (FDA) for use in rotator cuff repair, tendon reconstruction, and dental procedures, they are not currently FDA approved for use in ACI. Despite this, these collagen membranes are currently being used more commonly for ACI in an “off-label” nature. In a recent study, it was noted that in the United States, “close to half of all ACI procedures are now being performed using such membranes.” This is done in an effort to decrease the rate of graft hypertrophy and the need for subsequent surgical procedures often necessary in patients undergoing ACI-P who develop the frequent complication of graft hypertrophy. However, to achieve the benefit of a reduced rate of graft hypertrophy with ACI-C, one must be willing to accept the increased initial cost of the procedure utilizing this off-the-shelf product, which is associated with a significant cost as well.

The purpose of the study was to examine the cost effectiveness of ACI and determine whether ACI-C is more cost effective than ACI-P using outcomes based on the best level of evidence available in the literature and the average cost of patients undergoing ACI at a local orthopaedic specialty hospital.

### Materials and Methods

#### Design

The model used in this study assumes an otherwise healthy, young (age, 30 years) person with a focal chondral injury of the medial or lateral femoral condyle that satisfies the indications for repair using ACI. The model was run over a period of 10 years, which is based upon the longest term evidence (level IV) available in the literature regarding ACI.

The functional improvement of patients after ACI and the rate of graft hypertrophy after ACI-P and ACI-C was derived from studies identified as the best level of evidence available in the literature (levels I and II) regarding ACI-P and ACI-C, as determined by a recent Cochrane database review and systematic reviews by Harris et al and Bekkers et al. We believe that these level I and II studies identified by the Cochrane database review, as well as the 2 systematic reviews, most accurately represent the improvements that appropriately selected patients experience when treated with ACI for a focal chondral injury. Ideally, there would be level I or II studies regarding the long-term results of ACI. Unfortunately, this is not the case; however, there are 3 studies (level IV evidence) that report the results, sustained improvement, and failure rates of ACI at long-term follow-up (range, 7.4-12.8 years). All costs were obtained by examining the average costs experienced by patients undergoing ACI at a local orthopaedic specialty hospital that performs multiple cartilage restoration procedures yearly.

#### Decision Model

The decision tree model was constructed using publicly available software (TreeAge Pro 2011, TreeAge Software, Williamstown, Massachusetts). As stated above, the base case is a healthy, young person who meets the indications for cartilage repair with ACI. The model assumes 3 possible outcomes after the initial ACI procedure: doing well, graft hypertrophy, or graft failure (Figure 1). Patients suffering from graft hypertrophy were assumed to undergo revision surgery in the form of knee arthroscopy with graft debridement. These patients undergoing revision surgery could go on to do well (well hypertrophy) or have graft failure. The patients who did well after revision arthroscopic debridement, while improved from baseline overall, were assumed to do slightly worse than those without graft hypertrophy or revision surgery, as shown by Henderson et al. Patients who were initially doing well could continue to do well or subsequently develop graft hypertrophy or graft failure. An ACI graft failure was the termination point of the model. Complications other than graft hypertrophy or failure were assumed to be equal between ACI-P and ACI-C and were not specifically included in the model.

#### Graft Hypertrophy and Failure Rates

Studies identified as being of the highest quality of evidence available in the literature (levels I and II) were reviewed to obtain the rates of graft hypertrophy after
ACI-P and ACI-C, which were estimated to be 25% and 10%, respectively (Table 1). It was thought that the failure rate would be best estimated by examining the longest term evidence available in the literature regarding ACI. The rate of graft failure was assumed to be 16% at 7.4 years and 17% at 9.2 years (level IV evidence). The rate of graft failure was assumed to be equal between ACI-P and ACI-C, as there has not been, to our knowledge, any level I or II studies to suggest a difference in failure rates between the 2 techniques.

Cost

The cost of ACI-P was estimated based on the average patient undergoing ACI at a local orthopaedic specialty hospital. The costs included in the study consist of the initial consultation fee; all hospital, surgeon, and anesthesia fees; physical therapy; postoperative outpatient care; and

**Figure 1.** Diagram of the cost-effectiveness model used in the study.

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<tr>
<th>Cost-Effectiveness Model</th>
<th>Utility values</th>
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<td>Focal chondral defect</td>
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*ACI-P, autologous chondrocyte implantation with periosteal patch; ACI-C, autologous chondrocyte implantation with type I/III collagen patch.*
durable medical equipment (including hinged knee brace and continuous passive motion machine) (Table 2). The cost of ACI-C was derived by adding to this the cost of the type I/III collagen patch ($780) and subtracting the cost of the extra operating room time required for harvesting the periosteal graft ($592.50 = 15 minutes × $39.50 per minute), as this is not needed in ACI-C.

Patients with graft hypertrophy were assumed to undergo additional revision surgery in the form of arthroscopic debridement. The cost associated with this additional procedure, in addition to a decreased utility value, was $8278, which included the hospital, surgeon, and anesthesia fees for the procedure.

Discounting

All future costs and health benefits were discounted at 3%.

Effectiveness

Medical and surgical interventions are commonly compared by their respective cost per quality-adjusted life year ($/QALY).11 This value is obtained by dividing the cost of the intervention by the QALY, which is a measure of the effectiveness obtained with the intervention.11 One way to calculate QALYs is to multiply health-related utility values by the number of years lived in that particular state. These utility values, which correspond to health-related quality of life, are represented on a scale of 0 to 1.0, with 0 being death and 1.0 being perfect health.11

During our review of the literature regarding ACI, we were unable to identify any specific health-related utility value with respect to focal chondral defects or outcomes after ACI. However, a recent study has shown that the quality of life of patients with a focal cartilage defect is affected to the same degree as patients with severe osteoarthritis awaiting total knee arthroplasty.16 The utility value of “end-stage osteoarthritis” has been determined and reported in the literature to be 0.7.10,37 We, therefore, estimated the utility value of patients with a focal chondral defect (the base case in this model) to be 0.7. The utility value of patients doing well after ACI was subsequently determined utilizing Lysholm scores from studies representing the highest level of evidence available in the literature (levels I and II) regarding the outcome of patients undergoing ACI.19,43 Assuming that an otherwise healthy, young person with a perfect Lysholm score would have a utility value of 1.0 and that the utility value of those with focal chondral defects is 0.7, we were able to estimate a utility value representing outcomes following ACI (Table 1). The utility value representing the outcome of patients doing well after ACI was estimated to be 0.85. The Lysholm score has been determined to be both valid and reliable for use in assessing outcomes of chondral disorders of the knee.25 Comparing the outcome of patients who do well after ACI-P and ACI-C, there has been no high-quality evidence to suggest that there is a significant difference between these 2 groups, so their respective utility values were assumed to be the same. Patients who did well after revision arthroscopic debridement, while improved from baseline overall, were assumed to do slightly worse than those without graft hypertrophy or revision surgery, as shown by Henderson et al.17 The utility value of those who did well after revision surgery for graft hypertrophy was assumed to be 0.8. The quality of life of patients with graft hypertrophy and/or graft failure was assumed to be significantly affected, similar to having a focal chondral defect. Therefore, the utility value chosen to represent these states was 0.7.

Sensitivity Analysis

A sensitivity analysis was performed to determine how the results of the model change in relation to variations in the input values. Threshold sensitivity analysis was performed with regard to the additional cost of the type I/III collagen patch, the rate of graft hypertrophy following ACI (both ACI-P and ACI-C), utility values, and the discount rate.

RESULTS

Base Case

The results of the model showed the $/QALY of ACI-P was $9466 and that of ACI-C was $9243. In the base case, over the 10-year course of the model, ACI-C was both more effective by 0.07 QALYs and less expensive by $941.

Sensitivity Analysis

Cost of Collagen Patch. In the base case, the cost of the type I/III collagen patch was $780. Threshold analysis was...
performed in which the only variable that changed was the cost of the type I/III collagen patch. This analysis revealed that for ACI-P to become more cost effective than ACI-C, the cost of the type I/III collagen patch would have to reach $1721.

**Rate of Graft Hypertrophy.** The rates of graft hypertrophy after ACI-P and ACI-C were derived from the best level of evidence (levels I and II) available in the literature and determined to be 25% and 10%, respectively. Threshold analysis revealed that the rate of graft hypertrophy after ACI-P would have to be reduced from 25% to nearly 11% before ACI-P would be more cost effective than ACI-C. Similarly, the rate of graft hypertrophy after ACI-C would have to increase from 10% to almost 24% before ACI-P would be more cost effective.

**Outcome.** Threshold analysis revealed that small changes in outcome after ACI-P and ACI-C significantly change the results of this analysis. For instance, ACI-P becomes more cost effective if the utility value of patients doing well after ACI-P is increased slightly from 0.85 to 0.86 or that of ACI-C is decreased slightly from 0.85 to 0.84.

**Discount Rate.** Varying the discount rate from 0% to 10% did not affect the outcome.

**DISCUSSION**

The cost-effectiveness analysis presented in this study reveals that ACI is a cost-effective procedure and suggests that over the 10-year course of the model, ACI-C, offering both increased effectiveness (as measured by QALYs) and lower cost, is more cost effective than ACI-P. This appears to be because of patients experiencing similar improvements in their quality of life, while the rate of graft hypertrophy, and subsequent need for costly revision arthroscopic graft debridement, is significantly reduced after ACI-C when compared with ACI-P. However, there were several assumptions in this study that have yet to be proven.

This study presumed that the utility values of those patients doing well after ACI-P and ACI-C were identical. These utility values, which represent health-related quality of life, were estimated by taking into account the Lysholm scores of patients before and after ACI and the utility value of patients with a focal chondral defect, which has been shown to affect quality of life to the same degree as osteoarthritis. The Lysholm scores we utilized to estimate the utility values were those reported by studies conducted by Henderson et al (level III evidence). Their study compared the outcomes of 3 groups of patients who underwent ACI-P by a single surgeon (1 group that did not undergo reoperation after ACI, 1 group that underwent reoperation for reasons other than graft hypertrophy, and another group that underwent reoperation for graft hypertrophy). The authors of this study found that, while still significantly improved from baseline, those who underwent revision surgery for graft hypertrophy fared slightly worse than those who did well after the initial ACI procedure without any subsequent complications, as suggested by Henderson et al (level III evidence). Their study compared the outcomes of 3 groups of patients who underwent ACI-P by a single surgeon (1 group that did not undergo reoperation after ACI, 1 group that underwent reoperation for reasons other than graft hypertrophy, and another group that underwent reoperation for graft hypertrophy).

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The cost effectiveness of ACI has been previously studied. Minas, in 1998, reported the cost effectiveness of ACI-P to be $6791/QALY in 1997 dollars; converted to 2011 dollars, that value would be $9585/QALY. This is almost identical to the values obtained in the present study, with the cost effectiveness of ACI-P and ACI-C being $9466/QALY and $9243/QALY, respectively. This, we believe, lends further validity to the model created for this study. In addition, these values compare favorably with the cost-effectiveness values of routine orthopaedic procedures such as hip or knee arthroplasty, $7300/QALY and $20,000/QALY, respectively, and anterior cruciate ligament reconstruction ($7800/QALY). These values are also
less costly than other commonly accepted routine medical and surgical interventions such as carotid endarterectomy ($11,000/QALY), coronary artery bypass grafting ($42,000/QALY), lumbar discectomy ($51,000/QALY), and hemodialysis (> $90,000/QALY) (Figure 2).7,27,31,42

This study is not without some significant limitations. First, we derived the utility values, outcome scores, graft hypertrophy, and failure rates from the literature. When possible, we tried to accept only those values from level I or II studies. The Lysholm outcome scores19,43 and rates of graft hypertrophy1,24 were obtained from studies representing the highest quality evidence (levels I and II) in the literature regarding ACI, as identified by a recent Cochrane database review40 as well as systematic reviews by Harris et al15 and Bekkers et al.3 To our knowledge, there are no level I or II studies reporting the “long-term” outcomes of ACI. However, there are 3 level IV studies that report the long-term outcomes and failure rates of ACI at 7.4 to 12.8 years’ follow-up.33-35 It was thought that the failure rate after ACI would be best determined by examining the longest term evidence available for ACI. While the overall cost effectiveness of ACI could be affected by changing the failure rate, the fact that ACI-C appears to be more cost effective than ACI-P would not change, as there has been no evidence to suggest that there is a significant difference in the rate of failure between ACI-P and ACI-C.

As stated above, a significant limitation of the study is the lack of high-level evidence, long-term data regarding ACI, especially ACI-C. The current cost-effectiveness analysis was run over a period of 10 years, as this approximates the longest term data available in the literature regarding ACI.33,35 In fact, the longest term data evaluating ACI-P were reported by Peterson et al35 in 2010 with a mean follow-up of 12.8 years. The longest term data reported in the literature regarding ACI-C are only 3 years.39 At 12.8 years, Peterson et al39 found that 74% of their patients reported that they were “better or the same” as they were in previous years, indicating that these patients continued to derive benefit from their original ACI procedure. At the present time, it is unknown how long these patients will continue to benefit from, or experience the effectiveness of, their initial ACI procedure. Recognizing that, at almost 13 years after ACI, 74% of patients were still experiencing functional improvement over their baseline, it follows that the actual $/QALY is lower than the model used in this study, which was carried out over 10 years, because the patient continues to derive benefit from the procedure while the initial cost stays the same.

While the authors of this work are not specifically advocating for the “off-label” use of a type I/III collagen patch in ACI, recognizing the significant rate and effect of graft hypertrophy on a patient's quality of life after ACI-P has led to these products being used more extensively.1,12,26,43 And while these type I/III collagen patches are approved by the FDA for use in rotator cuff repair, tendon reconstruction, and dental procedures,12 they are not currently FDA approved for use in ACI. Despite this, these collagen membranes are currently being used more commonly for ACI in an “off-label” nature in the United States, and in a recent study, it was suggested that “close to half of all ACI procedures are now being performed using such membranes.”15

Finally, the costs of ACI utilized in this study were derived from the typical charges of patients undergoing ACI by one experienced orthopaedic surgeon at a local orthopaedic specialty hospital. These costs could differ significantly based on location, insurance status, varying rehabilitation protocols, and so on. Therefore, the results of this study may not be generalizable to the community as a whole.

CONCLUSION

This cost-effectiveness analysis shows that ACI is a cost-effective procedure and compares favorably with many other commonly accepted medical and surgical treatments. It also reveals that while ACI-C is initially more costly than ACI-P ($187.50 difference), over the course of 10 years, ACI-C is actually more cost effective. The initial increased costs associated with using a type I/III collagen patch instead of periosteum are eventually recouped by reducing the rate of graft hypertrophy and subsequent revision arthroscopic debridement associated with ACI-P. The analysis also revealed that the cost of the type I/III collagen patch would have to increase significantly (more than double) or the rate of graft hypertrophy after ACI-P would have to be significantly reduced (25% to 11%) before ACI-P would become more cost effective than ACI-C.
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