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# Short-Term Progression of Functional Capabilities and Pain Levels Following Autologous Chondrocyte Implantation

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## Chapter 1: Introduction

Articular cartilage damage in the knee is a common pathology that can affect a large range of ages. It is estimated that 63% of patients receiving routine arthroscopies are found to have articular cartilage defects.[4] This type of cartilage has little blood supply; therefore, repair without surgery is highly unlikely. Surgical options to repair articular cartilage defects include autologous chondrocyte implantation (ACI), microfracture, osteochondral autologous transplantation (OATS), and mosaicplasty. However, a gold standard treatment for articular chondral defects has not been established.[8] Given that ACI is a novel procedure, there is limited data on patient-centered functional outcomes, and a lack of knowledge of long-term progression in these patients. There is also limited research providing the appropriate data needed to establish whether this procedure entails better patient outcomes than other chondral defect surgeries.

Autologous Chondrocyte Implantation (ACI) is a tissue-engineered articular cartilage repair procedure that patients can undergo to repair damaged articular cartilage. This is a two-step procedure in which the first surgical procedure involves an arthroscopic biopsy of healthy articular cartilage that is then sent to a cell expansion laboratory where the cells are allowed to replicate for 4-6 weeks. After the cartilage has grown, the second procedure follows and the cartilage is implanted in place of damaged tissue.

Since this is still a novel procedure, there is no set criterion for whether a patient should or should not get an ACI. With no predictors of a positive outcome, nor substantial research indicating success rates, insurance companies are hesitant in reimbursement. The ability to predict a successful outcome would benefit patients

financially in regards to reimbursement. Insurance companies are moving towards patient-centered outcomes to review the success of surgical procedures. Determining the level of reimbursement is based off of the data collected, where higher success rates reflect more substantial reimbursement. Higher reimbursement rates would mean the insurance companies would cover more of the rate and require less out of pocket money from the patient. By using patient-centered outcomes, we can trim physician bias and obtain personal outcome data from the patient population. This is beneficial because medicine is progressing toward patient-centered and functional outcomes vs. objective/surgeon/ clinician-based outcomes. Patient documented success is important as a true measure of success for surgeons, procedures, and predicting outcomes on future patients. Knee surgeries are expensive, and financial support from insurance companies is negatively correlated with the risk of a negative outcome. If data showed patient-oriented success following the ACI procedure, then insurance and healthcare companies are more likely to provide more money for the patients.

The purpose of this study was to evaluate patient-centered outcomes of functional capability and pain levels following ACI surgery, as well as compare results from previous studies.

## Chapter 2: Literature Review

### Surveys

When determining the efficacy of a procedure, physiological measures are important but they do, however, omit the patients' perception. Surveys allow the collection of more subjective patient data. This study pertains to patient surveys in the form of patient-centered outcomes (PCO's). Appleby describes PCO's as a measure of

quality that links effectiveness with efficiency of care.[18] These outcomes focus on purely subjective responses that more directly reflect a patients health status than physiological measures.

Patient-oriented improvement following ACI surgery in this study was evaluated using the International Knee Documentation Committee (IKDC), global rating of change scale (GROC), depression self-assessment (DSA) and the visual analog scale for pain (VAS). The IKDC presents a variety of questions surrounding symptoms, function, and sports activities that are ranked from 1 to 5 or 1 to 10 point scales. Summing the scores and dividing by the total possible score establishes an IKDC score. The minimum clinically important difference for the IKDC is reported to be 6.3 at 6 months and 16.7 at 12 months.[12]

The global rating of change (GROC) survey represents, on a -7 to +7 scale, the rate of change in overall functional capability. The lower end of the GROC is "a very great deal worse,' while the top is "a very great deal better." The GROC scale is used to quantify a patients improvement or deterioration over time usually to determine the effect of an intervention.[13] The Depression Self-assessment (DSA) is a 20-item self reported instrument that consists of symptom rating scales that provide a measure of depression symptom frequency and cutoff score indicating a probable diagnosis of depression.[16] An overall score out of 60 is determined with a score over 16 indicating depression. The VAS pain scale is used to measure pain intensity currently and at the moments where pain is the worst. These scales are from 0 to 100 mm. Patients with VAS pain scores of 30 mm or less would be categorized as having mild pain, those with scores of 70 mm or more were categorized as having severe pain and those from 31 mm to 69 mm, moderate

pain.[14] The minimal clinically significant difference (MCSD) in VAS pain score was defined as the mean difference between current and preceding scores when the subject reported "a little worse" or "a little better" pain.[14]

**ACI procedure**

Chondral injuries are debilitating pathologies that can compromise the quality of life due to pain, swelling, and impaired mechanical movement.[6] The chondral tissue discussed in this study is hyaline cartilage. Hyaline cartilage does not receive an adequate blood supply to heal, so surgical intervention is often necessary.[4] The Autologous Chondrocyte Implantation (ACI) surgery is a two-stage operation, typically spread out over a 5 week time period. First, an arthroscopic surgery is performed to obtain 200-300 mg of healthy articular cartilage harvested from a non-weight bearing portion of the knee.[4] The cells are then sent to a tissue-engineering laboratory for chondrocyte expansion.[4] Once approximately10 million cells are collected, the cells are implanted underneath a periosteum flap obtained from the proximal end of the tibia.[7] It has been shown that a patient following a failed microfracture surgery can benefit greatly from the ACI procedure because of damage to the subchondral plate.[4] It is still unclear whether realignment procedure performed previous to or with the ACI is detrimental. In a study comparing the ACI procedure to mosaicplasty, an alternative approach, the ACI patients had significantly greater outcomes.[5]

**Successful outcomes**

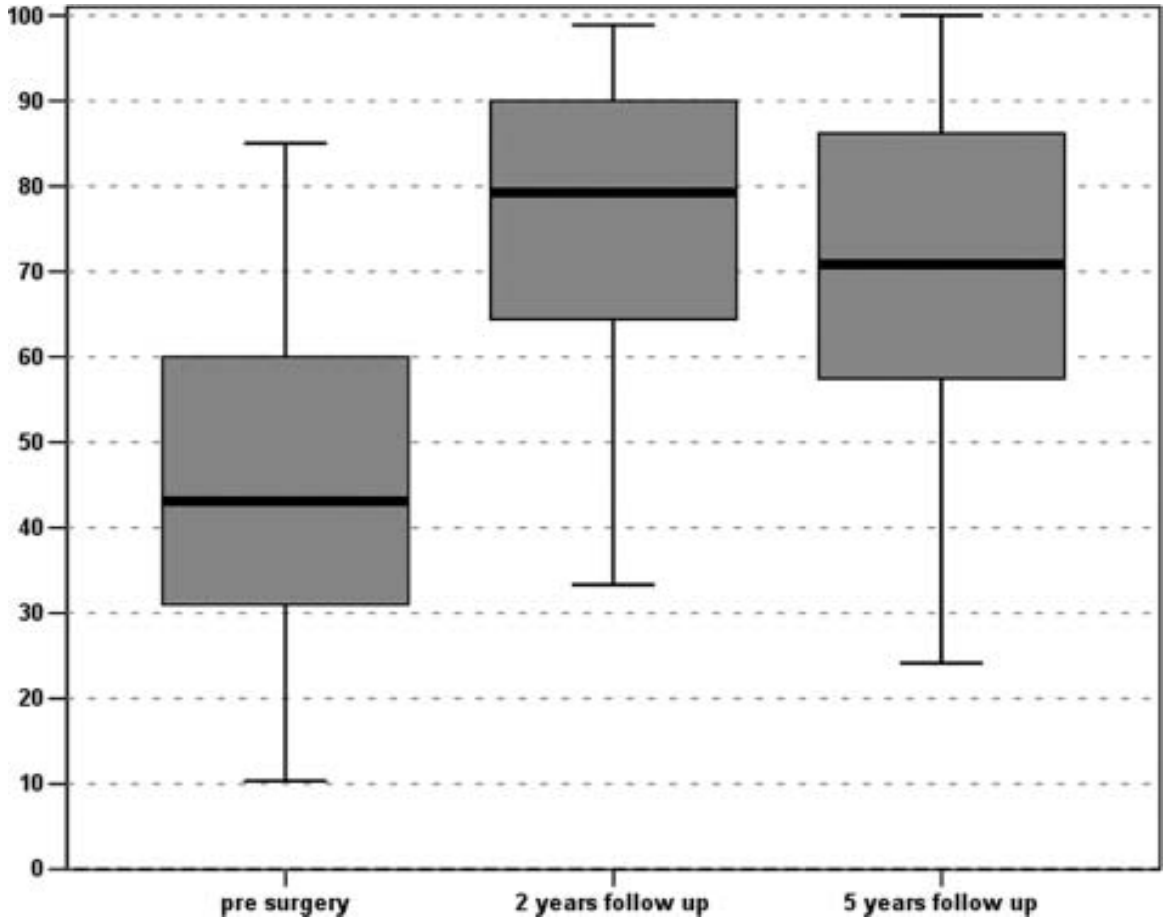
Evaluating ACI patients ≥ one year post-operation in overall knee condition, knee function, and patient symptomatology helps to establish the efficiency of the procedure. As shown in a study done by Micheli et al,[3] 84% (42 of 50) of patients were improved 36

months postoperatively and only 6% (3 of 50) had graft failure. Failure of a graft usually leads to subsequent total knee replacement. Multiple studies have shown that ACI has a fairly low failure rate. One study with a large patient population (N=827) revealed that graft survival rate was 78.2% at 5 years and 50.7% at 10 years.[11] Another study, Pascual-Garrido et al,[4] found that only 7.7% (4 of 52) ACI grafts resulted in failure. A similar study of ACI patients age 45 and older recorded a failure rate of 4.9% (3 of 54) in non-workers compensation patients, and an overall failure rate of 14% (8 of 54).[6]

**Improvements in pain and overall function**

Studies have demonstrated that ACI patients typically improve in pain and overall function of health. One study, of 34 patients, obtained preoperative IKDC scores where only 8 knees were classified as normal and 26 were classified as abnormal or severely abnormal.[2] After 2 years, 32 of the 34 patients knees were classified as IKDC normal or nearly normal following the ACI procedure.[2] IKDC scores showed significant improvement in this study. Scores went from 46.09 ± 19.3 preoperatively to 77.06 ± 17.0 2 years after implantation, and then to 70.39 ± 21.4 at 5 years (Figure 1).[2]

**Figure 1.** IKDC score: improvement from preoperative to 2 and 5 years' follow-up.[2]




Pascual-Garrido et al[4] concluded that autologous chondrocyte implantation is a viable treatment option for chondral defects. This study included 62 patients and examined preoperative and follow-up (2-5 years) IKDC scores. The mean improvement for IKDC was 31-57.

Patients who undergo ACI surgery have been shown to experience a decrease in overall and functional pain levels. Gobbi et al[2] reported a preoperative mean EQ VAS score of 56.75 ± 18 that improved to 81.47 ± 13.3 at 2-year follow-up. Another study demonstrated similar results with VAS pain levels >60 evident in 64% (32 0f 50) of the patients preoperatively, but only 4 % (2 of 50) had pain levels >60 at follow-up. [15]

**Patient satisfaction**

One study of 56 patients ≥45 years of age who underwent cartilage repair with ACI.[6] Rosenberger et al[6] chose 45 years of age as their threshold because this is the common insurance age limit for ACI, despite weak supporting data. This study claims that results are comparable to younger ACI patients when comparing patient satisfaction, and four validated rating scales: Short Form-36, Modified Cincinnati Rating Scale, WOMAC Osteoarthritis index, and the Knee Society Score.[6] At their latest available follow-up, 72% of patients rated themselves as good or excellent, 78% felt improved, and 81% would again choose ACI as a treatment option (Table 1).[6]

**Table 1.** ACI patient satisfaction at latest follow-up (range, 2-11 years; mean, 4.7 years).[6]

Patient Satisfaction at Latest Follow-up

| Question | Statistic | Simple (n = 3) | Complex (n = 20) | Salvage (n = 31) | Overall (n = 54) |
|---|---|---|---|---|---|
| Compared to before surgery, how would you rate your joint? | | | | | |
| | Much better | 1 (33%) | 9 (45%) | 13 (42%) | 23 (43%) |
| | Somewhat better | 2 (66%) | 4 (20%) | 13 (42%) | 19 (35%) |
| | About same | 0 | 3 (15%) | 5 (16%) | 8 (14%) |
| | Somewhat worse | 0 | 3 (15%) | 0 | 3 (6%) |
| | Much worse | 0 | 1 (5%) | 0 | 1 (2%) |
| Would you choose to have this surgery again? | | | | | |
| | Definitely yes | 2 (66%) | 12 (60%) | 19 (61%) | 33 (61%) |
| | Probably yes | 1 (33%) | 3 (15%) | 7 (23%) | 11 (20%) |
| | Uncertain | 0 | 3 (15%) | 3 (10%) | 6 (11%) |
| | Probably not | 0 | 2 (10%) | 1 (3%) | 3 (6%) |
| | Definitely not | 0 | 0 | 1 (3%) | 1 (2%) |
| How would you rate the results of your surgery? | | | | | |
| | Excellent | 1 (33%) | 9 (45%) | 14 (45%) | 24 (44%) |
| | Good | 1 (33%) | 3 (15%) | 11 (35%) | 15 (28%) |
| | Fair | 1 (33%) | 4 (20%) | 3 (10%) | 8 (15%) |
| | Poor | 0 | 4 (20%) | 3 (10%) | 7 (13%) |

**Microfracture**

Microfracture is a surgical substitution for the ACI procedure to revise chondral defects. Microfracture provides an enriched environment for tissue regeneration on the chondral surface by using the body's own healing abilities. After damaged cartilage has been removed, multiple holes are drilled in the exposed bone. Blood and bone marrow cells seep through and eventually form a clot that matures into firm repair tissue. Many long-term studies on microfracture have found increased complications compared to other procedures. Gudas et al[10] found that 4 year microfracture postoperative failure rate was 41% (9 of 22). Microfracture surgery can cause lingering pain and prolonged damage to the subchondral plate. One study suggests that microfracture surgery may cause damage to the subchondral plate compromising additional revision surgery.[9] Damage to the subchondral plate suggests the need for a second surgery, like ACI, to revise the defects.

## Chapter 3: Methods

This study included 10 patients, male and female, from a local orthopedic practice. Subjects were asked to complete a survey packet pre-operatively, and at three, six, and 12 months post-surgery as part of their standard medical files. These surveys included the International Knee Documentation Committee (IKDC), Visual Analog Scale (VAS) for Pain, Depression Self-assessment (DSA), and a Global Rating of Change (GROC) for overall functional ability. Once IRB approval was obtained, researchers picked up patient survey packets and entered their data, which was de-identified. The IKDC survey consists of 9 small surveys; data will be summed to denote a number value from 0 to 87 and divided by 0.87, representing patient’s knee function. The VAS scale

consists of a current and "when at worst" scale; these values will be collected and averaged to denote a number value for the patients overall pain level. The DSA is a survey that asks the patient to read ways they may have felt in the past week, and mark whether they were feelings lasting less than one day, one to two days, three to four days, or five-seven days. This data was summed to a value out of 60, where a number above 16 suggests depression. The GROC scale consists of an overall and specific functional capabilities scale; both values were assessed individually and given a value of -7 to 7. I reviewed these scores for each patient and entered them into spreadsheet software for data analysis.

**Statistical Analysis**

All variables were analyzed with descriptive statistics and percentages of patients were calculated. Select variables were analyzed using paired samples t-tests. Receiver operator characteristic curve analysis was conducted to determine cut points for select variables as potential predictors of successful outcome. To determine clinically relevant outcomes and predictive value, further 2X2 cross tabulation analysis was used to calculate sensitivity, specificity, and relative risk ratios.

## Chapter 4: Results

The time frame established for short-term success was determined by post-operative surveys, which varied in time (2.7 ± 0.9 months; range: 1-4 months) following surgery. Patient responses to short-term global rating of change (GROC) varied greatly (Table 2). Post-operative GROC analysis showed that 8 patients (80%) had at least "a little better" overall functional capabilities, 1 (10%) had "no change," and 1 (10%) failed

to respond. Post-operative GROC analysis of specific capabilities showed identical results with 8 patients (80%) having at least “a little better” overall functional capabilities, 1 (10%) with “no change,” and 1 (10%) failed to respond.

Pre-operative IKDC scores reported 3 patients as having 10-30% function, 2 with 30-50%, 1 with 50-70%, and 2 with 70-80% function. Post-operative IKDC scores showed 3 patients as having 10-30% function, 5 with 30-50%, 1 with 50-60%, as well as 1 unreported response. The difference in post-operation and pre-operation IKDC scores varied from better to worse (Table 3). With 1 failed response, 4 patients (40%) saw improvements in IKDC scores (range: 4 to 25 points). Five patients (50%) were found to have a decrease in IKDC scores (range: -1 to -34 points).

Pre-DSA scores ranged from 3-23 with 1 patient considered “depressed” (score ≥16). 8 patients (80%) scored <10, 1 (10%) scored a 12, and 1 (10%) scored a 23.

Current VAS pain scored, pre-operatively, showed a mean pain score of 2.45 ± 1.82 where 7 patients (70%) had pain levels between 0-3 and 3 patients (30%) had levels between 4-6. Post-operative current VAS scores showed a mean pain level of 1.32 ± 1.13 where all 10 patients scored between 0-3. Short-term pain levels decreased from pre-operation by a mean of 1.13 ± SD 2.21. 4 patients (40%) had an increase in pain levels between 0-1.5 points, 4 (40%) decreased by 1-3 points, and 2 (20%) decreased by 4-5 points.

"At worst" VAS pain levels before surgery averaged 7.6 points ± 1.37 with 4 patients (40%) scoring between 5-7 and 6 (60%) scoring between 8-10. Post-operative "at worst" averaged 6.15 ± 2.7 points with 4 patients (40%) between 2-4, 2 (20%) between 5-7, and 4 (40%) between 8-10. Pain, when at its worst, was shown to decrease by a mean

of 1.45 ± 3.05 points with 3 (30%) who experienced an increase in pain between 0-3, 3 (30%) with decreased levels between 0-3, 3 (30%) decreased between 4-7, as well as 1 (10%) with no change.

For the purpose of this study, successful short-term outcomes were established as a GROC score ≥3 or post-VAS pain levels ≤2. 8 patients (80%) had a successful outcome determined by GROC score, post-VAS score, or both. There were 8 patients (80%) that had success via GROC outcome and 5 patients (50%) who had success via VAS pain score.

Patients with pre-operative VAS scores ≥3 were more likely to have a successful short-term outcome, via GROC ≥3, with a relative risk of 1.5 (figure 2). Similarly, reviewing GROC scores ≥3 also showed patients with pre-IKDC scores <50 had more successful outcomes with a relative risk of 3. Patients with a DSA score >7 were found to have a 1.56 times greater chance of having a change in rating of function of ≤3 when compared to those who scored 7 or less on this survey (figure 2).

Patients below the age of 40 were found to have lower pain levels (≤2) more often than those ≥40 years of age with a relative risk of 1.67 (figure 3). Patients ≥40 had more successful outcomes, GROC ≥3, than patients below 40 (relative risk 1.8).

**Table 2.** Patient Global Rating of Change at Short-term Follow-up (range: 1-4 months; mean: 2.7 months; n=10).

| Question | Statistic | Response (n=10) |
|---|---|---|
| Since first starting treatment, how would you rate your change in overall functional capabilities | | |
| | A great deal better | 0 |
| | A good deal better | 1 (10%) |
| | Moderately better | 2 (20%) |
| | Somewhat better | 2 (20%) |
| | A little better | 3 (30%) |
| | Almost the same | 0 |
| | No change | 1 (10%) |
| | No response | 1 (10%) |
| Since first starting treatment, how would you rate your change in specific functional capabilities | | |
| | A great deal better | 1 (10%) |
| | A good deal better | 1 (10%) |
| | Moderately better | 2 (20%) |
| | Somewhat better | 1 (10%) |
| | A little better | 2 (20%) |
| | Almost the same | 1 (10%) |
| | No change | 1 (10%) |
| | No Response | 1 (10%) |

**Table 3.** Difference in Post-operation and Pre-operation IKDC scores (range: 1-4 months; mean: 2.7 months; n=10)**.**

| Difference in IKDC Score | Statistic (n=10) |
|---|---|
| 20 to 30 points | 1 (10%) |
| 10 to 20 points | 1 (10%) |
| 0 to 10 points | 2 (20%) |
| -10 to 0 points | 3 (30%) |
| -20 to -10 points | 1 (10%) |
| -30 to -20 points | 0 |
| -40 to -30 points | 1 (10%) |
| No response | 1 (10%) |

**Figure 2.** Comparing Patient Pre-DSA, Age, and Pre-VAS Data to Short-term GROC Outcomes.

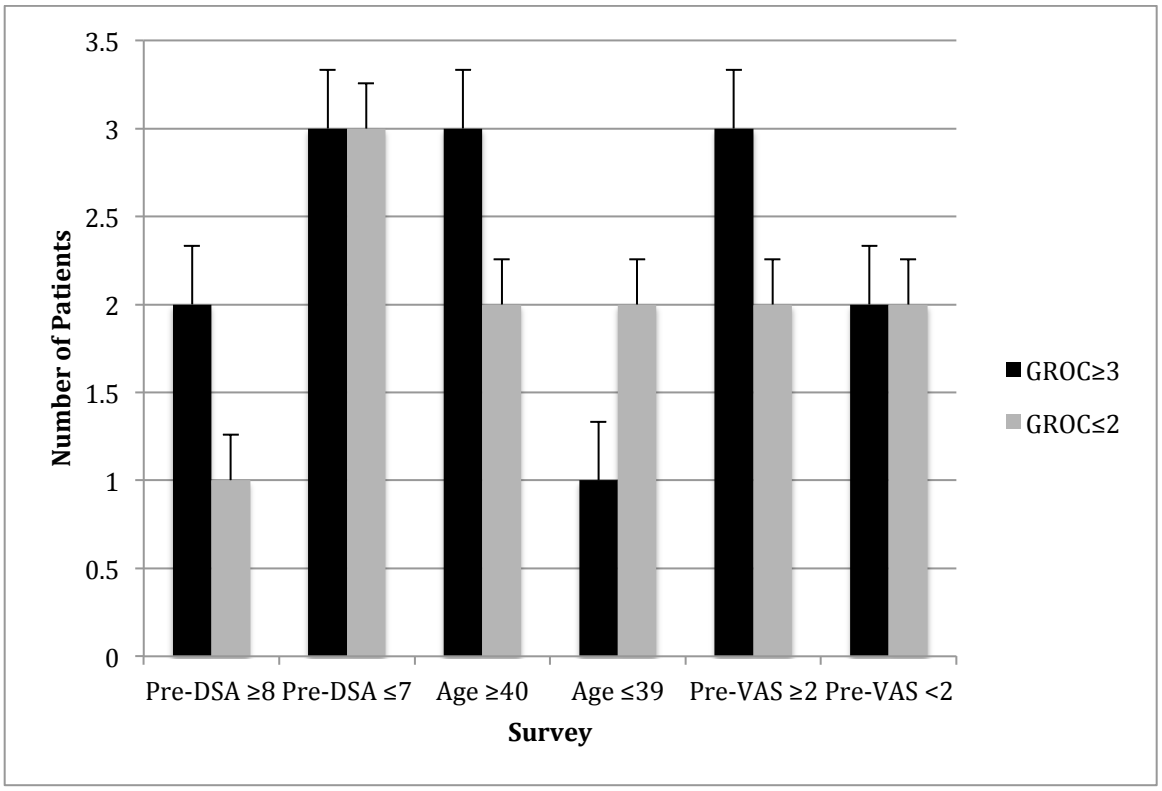
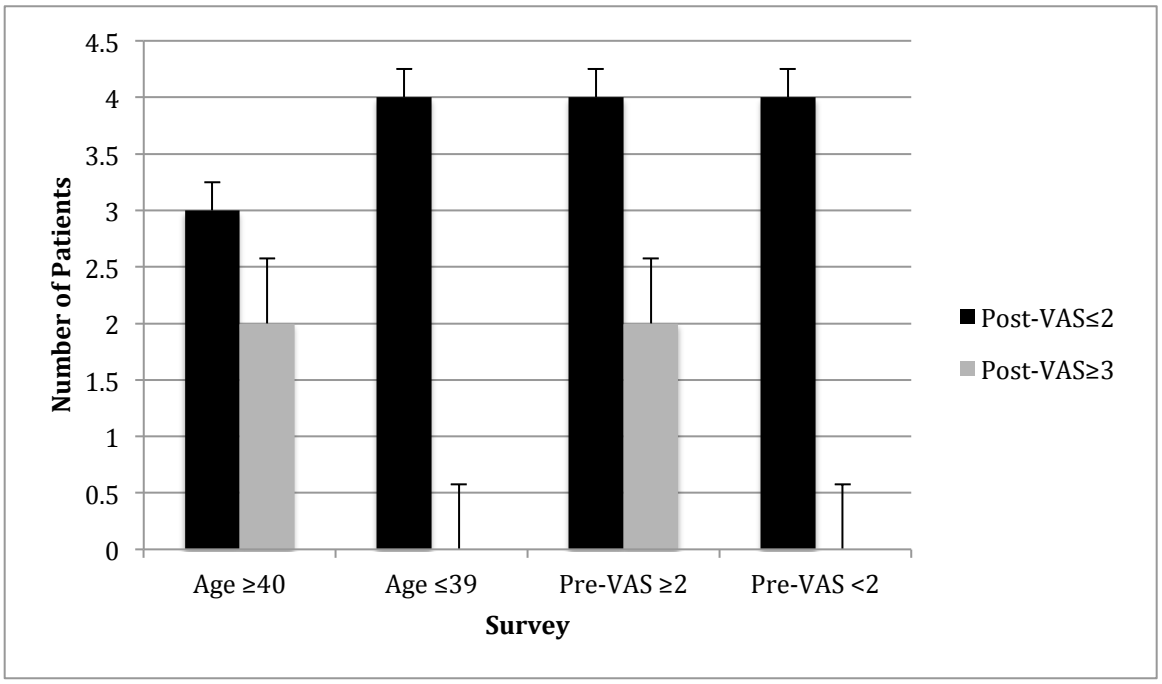



**Figure 3.** Comparing Patients Age and Pre-VAS data to Post-VAS pain scores.



## Chapter 5: Discussion

After analyzing and comparing pre- and post-operative surveys, it is evident that most patients experienced short-term success. For the purpose of this study, successful short-term outcomes were established as a GROC score ≥3 or post-VAS pain levels ≤2. With an 80% success rate, data suggests that the ACI procedure does elicit short-term success.

### Success Rate

Since the complete recovery time for this surgery is 1 year, it must be noted that these short-term success rates are in a time frame that is only about 33% through post-surgical treatment. The small change in overall function with the GROC scale was expected because of this. This explains the small decrease in pain levels (mean 1.13) as well. Patients were enduring intense rehabilitation programs and most are only just recently off of crutches or still using them. Function was expected to be low and pain levels can stem from the intense rehab as well.

### Possible Predictors

Age, VAS pain scale, IKDC, and DSA scores, pre-operatively, were found to be possible predictors of a short-term successful outcome. Patients below the age of 40 displayed a 1.67 times greater chance of experiencing pain levels ≤2 during their short-term follow-up. According to Woodrow et al,[17] pain tolerance decreases linearly with age, so it is relevant that younger patients would record lower pain levels.

Patients 40 years of age or older were shown to have a 1.8 times greater chance of having a GROC score of ≥3 than those under the age of 40. Older patients generally have

less function overall, so younger patients most likely felt that they had not progressed much in getting back to their original functional capabilities.

Pre-VAS pain scores suggest that patients with a score of ≥3 pre-operatively will be 1.5 times more likely to score ≥3 on the GROC survey than those who scored <3. Patients experiencing more pain pre-surgery seem to be capable of noticing a greater change in their short-term function than those who had less pain.

Lower functioning patients, via pre-IKDC data, shows that a patient with <50 points is 3 times more likely to have a GROC score of ≥3. Less function pre-surgery suggests that the patient will have greater improvements in their function overall. If a patient has a low functional score, then it is understood that they will notice a greater change in function more than someone with a higher pre-surgical score.

DSA data suggests that a patient with a score >7 will have a 1.56 times greater chance to have a negative outcome in regards to the GROC scale (≤3). A patient showing depressive symptoms would generally have a negative outlook on treatment and progress in functional capabilities. Therefore, a depressed patient would generally see their progression of function as slower, or less significant than those who are not depressed.

**Previous Studies**

Success rates in this study support data collected by Micheli et al.[3] Eighty-four percent of patients in his study reported a successful outcome, where an 80% success rate was reported in this study. This would suggest that throughout recovery from this operation, patients generally feel that they are progressing and will have a successful outcome. A decrease in pain levels also aligned with previous studies.

## Conclusion

With our small population size and relatively short time frame, data collected from this study was unable to confidently declare whether the ACI procedure is successful. However, our evidence shows that most patients see improvements in pre-operative function and pain levels in an average of 2.7 months post-op. Data suggests that patients with pre-VAS ≥3, pre-IKDC <50, and age >40 are most likely to have a successful outcome in regards to improved overall functional capabilities. Also, it can be predicted that younger patients (<40) will have a greater chance to have a successful outcome with a decrease in pain levels. Conversely, a patient with a score of >7 on the DSA is more likely to have an unsuccessful outcome.

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