Predictors of Outcome in Conservative and Minimally Invasive Surgical Management of Pain Originating from the Sacroiliac Joint – a Pooled Analysis

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ABSTRACT

Study Design. A pooled patient-level analysis of two multicenter randomized controlled trials and one multicenter single-arm prospective trial.

Objective. To identify predictors of outcome of conservative and minimally invasive surgical management of pain originating from the sacroiliac joint (SIJ).

Summary of Background Data. Three recently published prospective trials have shown that minimally invasive SIJ fusion (SIJF) using triangular titanium implants produces better outcomes than conservative management for patients with pain originating from the SIJ. Due to limitations in individual trial sample size, analyses of predictors of treatment outcome were not conducted.

Methods. We pooled individual patient data from the three trials and used random effects models with multivariate regression analysis to identify predictors for treatment outcome separately for conservative and minimally invasive surgical treatment. Outcome was measured using visual analogue scale (VAS), Oswestry Disability Index (ODI) and EuroQOL-5D.

Results. We included 423 patients assigned to either non-surgical management (NSM, n=97) or SIJF (n=326) between 2013 and 2015. The reduction in SIJ pain was 37.9 points larger (95% CI 32.5-43.4, P<0.001) in the SIJF group than in the NSM group. Similarly, the improvement in ODI was 18.3 points larger (95% CI 14.3-22.4), P<0.001). In NSM, we found no predictors of outcome. In SIJF, a reduced improvement in outcome was predicted by smoking (P=0.030), opioid use (P=0.017), lower patient age (P=0.008) and lower duration of SIJ pain (P=0.028).

Conclusions. Our results support the view that SIJF leads to better treatment outcome than conservative management of SIJ pain and that a higher margin of improvement can be predicted in non-smokers, non-opioid users, and patients of increased age and with longer pain duration.

Key words: low back pain; sacroiliac joint pain; disability; fusion of the sacroiliac joint; opioid use

Level of Evidence: 2
INTRODUCTION

The sacroiliac joint (SIJ) contributes to 15-30% of all chronic low back pain with an even higher contribution (35-43%) after lumbar fusion. Patients with SIJ pain have decreased quality of life with levels similar to other common surgically treated spine conditions. Non-surgical treatments for SIJ pain, including physical therapy, chiropractic, intraarticular SIJ steroid injections, and radiofrequency neurotomy of sacral nerve root branches, have some literature support, but high-quality evidence supporting long-term improvements and describing potential predictors of favorable outcomes lacking.

Surgical treatments for SIJ dysfunction include open and minimally invasive SI joint fusion (SIJF). Most published evidence on minimally invasive SIJF reports use of triangular titanium implants (TTI), including retrospective case series, a combined multicenter case series, systematic reviews, and three prospective multicenter clinical trials. Even though previously published results from the three prospective trials have shown concordant improvements in pain, disability and quality of life after SIJF compared to non-surgical management (NSM), the number of patients included in each of those trials was too low to identify potential predictors of clinical outcomes both for conservative management and SIJF. We therefore conducted a patient-level pooled analysis using the data from all three prospective multicenter TTI clinical trials to determine whether patient characteristics predicted clinical outcomes after either surgical or non-surgical treatment.

MATERIALS AND METHODS

Data sources. The three pooled trials are prospective clinical trials of SIJF with TTI. Trial characteristics are presented in table 1. Literature searches using Medline, Embase, and ClinicalTrials.gov (primary search terms: sacroiliac joint AND (arthrodesis OR fusion)) revealed no other ongoing prospective TTI trials.

INSITE, a prospective 2-year multicenter randomized clinical trial (RCT) conducted at 19 centers in the US, included 148 patients with diagnosed SIJ dysfunction unresponsive to at least 6 months of conservative care. Patients were included between January 2013 and May 2014. Diagnosis was based on history, physical examination tests, and a ≥50% decrease in SIJ pain after image-guided joint block with local anesthetic. Subjects were randomized in a 2:1 fashion to either SIJF as previously described or NSM. NSM included anti-inflammatory and opioid pain medications, physical therapy, intra-articular SIJ steroid injections, and radiofrequency neurotomy, delivered serially as needed to manage pain and disability. Assessments included SIJ pain using a visual analog scale, Oswestry Disability Index (ODI), EuroQoL-5D (EQ-5D) and Short Form-36 (SF-36). In the NSM group, crossover to surgical care was allowed only after the 6-month visit was complete.

iMIA, a prospective multicenter randomized controlled clinical trial (n=103) was conducted at 9 European centers. Patients were included between June 2013 and May 2015. Key differences between iMIA and INSITE include: 1) iMIA used 1:1 randomization, 2) non-surgical treatment in iMIA included only physical therapy per European guidelines, 3) iMIA included Zung Depression Scale but not SF-36, and 4) iMIA included a functional test and self-reported walking distance.

SIFI is a prospective multicenter single-arm clinical trial (n=172) conducted at 26 centers in the US. Patients were included between August 2012 and December 2013. All subjects underwent SIJF. SIFI subjects underwent CT scan at 1 year; otherwise, study parameters were identical to INSITE.

Surgical revisions and wound infections. Adverse events, defined broadly using an international clinical trial standard were collected continuously during the trials. Events of interest included wound-related problems and early and late surgical revisions of the target SIJ.

Statistical analysis. We applied random effects models, performed using the nlme4 and lme4 packages, that used appropriate covariance structures to take into account individual patient characteristics (fixed effects) as well as repeated measures and site-level factors (random effects). Both univariate and multivariate regression techniques were used, including interaction terms. Outcomes assessed in a single trial only were not evaluated. Since both RCTs allowed crossover from NSM to SIJF after month 6, the treatment effect in the NSM cohorts...
was estimated using only 1, 3 and 6-month data. Models regarding patient age and pain duration used values grouped by quartiles. Opioid use was defined as continuous daily opioid use, including oral medication and/or transdermal application.

RESULTS

423 patients in 3 trials were analyzed, including 326 who underwent SIJF and 97 who underwent NSM. 2-year follow-up data were available from the 2 completed US studies; 1-year data are currently available from the European RCT.

Baseline Characteristics

In the 3 pooled trials, mean (SD) age was 50.4(11.2) years, most (70.4%) subjects were women, and pain duration averaged 5.5 years (SD 6.7, Table 2). Mean baseline SIJ pain (80 points, SD 12.5) and ODI scores (55 points, SD 12.7) were high. Quality of life was diminished (mean EQ-5D TTO of 0.43, SD 0.20 and mean SF-36 PCS of 31, SD 5.9). Body mass index, baseline pain scores, the proportion using opioids and the proportion with prior SIJ steroid injections were higher in the 2 US studies; smoking was less common in US patients. In the two RCTs, baseline characteristics (age, body mass index, pain duration, baseline pain, ODI and QOL scores) were distributed equally across groups. Current smoking and a history of prior RF ablation were more common in the SIJF group (p=0.0100 and 0.0197, respectively). Operative characteristics were similar across studies: Operating time averaged 48 minutes and 3 implants were used in most cases, with no significant variation in the mean number of implants used across studies (p=0.970). Mean hospital length of stay was longer in the European RCT (3.6 days) vs. US studies (0.8 days, p<.0001).

Treatment Effect

Taking into account all assessments prior to month 6, the adjusted reduction in SIJ pain was 37.9 points larger (95% CI 32.5-43.4, p<.0001) in the SIJF groups vs. the NSM groups. Similarly, the improvement in ODI was 18.3 points larger (95% CI 14.3-22.4, p<.0001) and the improvement in EQ-5D TTO index was 0.24 points larger (95% CI 0.17-0.30, p<.0001). Extensive modeling was used to evaluate for effect modifiers (i.e., interaction terms) but none were found.

Predictors of Treatment Outcome

Table 3 and Figure 1 show associations of clinical characteristics with treatment outcomes for NSM and SIJF. In the NSM cohort (n=97), none of the examined variables showed a significant association with pain, disability (ODI) or quality of life (EQ-5D) at 6 months of follow-up. For the SIJF group (n=326), predictors of treatment outcome were assessed over the 24-month follow-up period. For SIJ pain, we found that older age (effect size (ES) 9.1 points; p=0.0080) and longer pain duration (ES 7.7 points; p=0.0282) were associated with larger improvements after SIJF while current smokers (ES 5.9 points; p=0.0299) and patients using opioids at baseline (ES 6.4 points; p=0.0166) had smaller responses. For disability (ODI), improvements after SIJ were smaller amongst current smokers (ES 4.4 points; p=0.0292) and those using opioids at baseline (ES 6.1 points; p=0.0029). For EQ-5D, only longest pain duration was predictive of statistically significantly greater improvements after SIJF (ES 0.105 points; p=0.0035).

Surgical Revisions and Wound Infections

Of the 326 patients undergoing SIJF, 1.2% (n=4) underwent early surgical revision (<1 month). In each of those patients, one of the implants had been inadvertently placed into a sacral neuroforamen, causing postoperative neuropathic symptoms and requiring surgical repositioning of the implant. Late revision surgery (>1 month), performed in 2.8% (n=9), was typically done to address pain, sometimes associated with poor implant position, with placement of additional implants in most cases. Signs of wound infection occurred in 8 subjects overall, including deep wound infection requiring surgical washout (n=1), drainage from wound treated with antibiotics (n=3), redness treated with antibiotics (n=3) and slow healing treated with antibiotics (n=1). No subject had bony infection or implant removal for infection.
DISCUSSION

Combining data from three separate prospective studies allowed us to assess in more detail which patient groups may have a better chance of benefiting from conservative or minimally invasive surgical treatment of chronic SIJ pain. Our principal findings are that, within the patient cohort undergoing SIJF, 2 factors (current smoking and opioid use at baseline) predicted lower and 2 factors (higher patient age and longer duration of SIJ pain) predicted higher degrees of improvement in SIJ pain and pain-related disability. Older age also predicted higher improvements in quality of life (EQ-5D time trade-off index). Even though one may argue that each of these differences may be of relatively modest clinical significance, it is important to note that they all reached statistical significance. Moreover, subgroups with smaller improvements after SIJF, such as smokers or opioid users, still displayed larger and clinically important improvements compared to patients in the NSM cohort. Another important difference between SIJF and NSM was that within NSM we found no predictors of treatment outcome at all.

In the SIJF cohort, smokers showed reduced pain response (by 5.9 VAS points) and higher disability levels (by 4.4 ODI points) compared to non-smokers. These results are consistent with previously published data describing a significant negative association between smoking and spine surgery outcomes.47 Patients using opioids at baseline also benefitted less from SIJF (by 6.4 VAS points and by 6.1 ODI points) when compared to opioid-naïve patients. These findings add to the somewhat controversial discussion regarding opioids as part of LBP treatment overall, since current evidence suggests an absence of long-term superiority of opioids over placebo in the treatment of LBP, which has led some authors to call for avoiding any opioid use in LBP treatment.48,49 Opioid use may even increase the risk of recurrence of already existing depression as well as the risk of developing new onset depression.50

In the SIJF cohort, patients younger than 45 years displayed a reduced pain response (by 9.1 VAS points) compared to patients in the oldest age quartile. Whether young age reflects a true biologic effect or is a marker for more severe disability is not known but our results suggest that SIJF should be discussed with greater caution in younger patients. However, our findings are in line with previously published reports on patients undergoing lumbar fusion surgery, which found that older patients were not at higher risk of poor treatment outcomes.51

Within the SIJF cohort, we observed that patients in the third quartile of pain duration (3-6 years) had a larger improvement in pain. Also, patients in the fourth pain duration quartile (>6 years) had larger improvements in quality of life (EQ-5D). The significance of this finding is uncertain and is therefore the most difficult to integrate into decision-making during patient selection. However, since increased pain duration has been described to be a risk factor for poor treatment outcome in low back pain,52 our contrasting results provide reassurance that in patients with long-standing pain originating from the SIJ SIJF is a reasonable option.

Procedure-related safety was reasonable in our analysis, with a low rate of wound problems and a low surgical revision rate consistent with a previously report in the commercial setting.53 Combined with retrospective case series, our findings provide high level evidence for the safety and effectiveness of SIJF with TTI and support its use as a relevant treatment choice in patients with SIJ dysfunction unresponsive to non-surgical management.

Minimally invasive SIJF is gaining increasing attention in spine surgery. Two different surgical approaches to SIJF have been reported. In the dorsal approach, which was not used in the trials evaluated in our analysis, a midline dorsal incision is made with dissection to the dorsal ligamentous recess followed by device placement. Stabilization is achieved through ligamentotaxis. Published outcomes from this approach are scant.58 In the lateral-to-medial approach, which was used in the trials analyzed by us, the implants transfix the SIJ. Published TTI studies include the 3 trials we summarized plus retrospective case series,13–18 including some with 3-, 4-, and 5-year follow-up, and comparative case series vs. open SIJF.15,20,21 Three additional case series report good outcomes with hollow modular anchor screws60–62 and a recent small case series suggests good

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outcomes with an additional transfixing device. Minimally invasive SIJF using TTI was shown to not only improve the LBP component of SIJ pain but also the referred leg pain component. Because of differences in approaches, device design, acute impact on the joint, and long-term fusion strategies, it is unclear whether results from our analysis apply to other laterally transfixing devices or to devices placed via a dorsal approach.

The main strength of our analysis is that all three pooled studies were of high quality, used standardized enrollment and diagnostic criteria, and were rigorously monitored. The two RCTs were designed to directly estimate the clinical value of surgery compared to a non-surgical treatment control group. However, certain limitations should be mentioned. First, because the study protocols of iMIA and INSITE allowed crossover from non-surgical to surgical treatment after 6 months and the majority of patients made use of this option, long-term information for NSM beyon(d beyond 6 months) was not evaluated in our analysis. Nevertheless, while crossover prevented calculation of treatment effect sizes after month 6, it allowed us to completely avoid early crossover, which has complicated interpretation of other surgery vs. non-surgery trials. Another limitation of our analysis is that all trials included were not blinded and therefore patient-specific expectations cannot be ruled out as potential confounders to overall outcome results. Nevertheless, the large observed effect sizes suggest a true underlying effect. Finally, the fact that all three trials included in our analysis were industry-sponsored may be viewed by some as a limitation. However, industry-sponsorship is the norm in spine surgery device trials.

CONCLUSIONS
Our pooled analysis suggests that the success of conservative management of SIJ pain is limited and difficult to predict. In contrast, improvements in pain, disability and quality of life with minimally invasive SIJF were large; moreover, the extent of improvement was modestly associated with smoking, opioid use, patient age and duration of pain. Procedure-related safety of SIJF was reasonable.

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**FIGURE AND TABLE LEGENDS**

**Figure 1.** Changes in pain (by VAS, left) and disability (by ODI, right) over time for NSM (dotted lines) and SIJF (solid lines) in relation to baseline smoking, opioid use, patient age, and pain duration.
Table 1. Trial characteristics of studies included in pooled analysis.

| Characteristic                                      | INSITE       | iMIA         | SIFI         |
|-----------------------------------------------------|--------------|--------------|--------------|
| NCT number                                          | NCT01681004 | NCT01741025  | NCT01640353  |
| Number of study centers                             | 19           | 9            | 26           |
| Number enrolled/treated                             | 148          | 103          | 172          |
| Geography                                           | US           | EU           | US           |
| Enrollment period                                   | 2013-2014    | 2013-2015    | 2012-2013    |
| Design                                              | RCT          | RCT          | SAT          |
| Randomization ratio (surgery:non-surgery)           | 2:1          | 1:1          | NR           |
| Control group                                       | NSM          | CM           | -            |
| Data availability, months                           | 24           | 12           | 24           |
| Percent of subjects with available data at long-term follow-up* | 85%          | 92%          | 87%          |

### Inclusion criteria

- Age 21-70
- SIJ pain for >6 mo
- Diagnosis of SIJ dysfunction based on Fortin Finger Test, 3/5 positive exam and block
- ODI at least 30%
- SIJ pain at least 50 points

### Exclusion criteria

- Severe back/hip pain due to something else
- Other known sacroiliac pathology
- History of recent (<1 year) major pelvic trauma
- Previously diagnosed osteoporosis
- Osteomalacia or other metabolic bone disease
- Chronic rheumatologic condition
- Condition or anatomy making iFuse treatment infeasible
- Chondropathy
- Known allergy to titanium or titanium alloys
- Use of medication known to have detrimental effects on bone
- Neuropathy that would interfere with physical therapy
- Current local or systemic infection
- Currently receiving long-term worker's compensation, disability, involved in injury litigation
- Pregnant or planning pregnancy in next 2 years
- Prisoner
- Known or suspected alcohol or drug abuse
- Uncontrolled psychiatric disease
- Participating in another study
- Fibromyalgia
- Spine surgery in the past 12 months

*SIJF group only*  

**Abbreviations:**  
RCT = randomized controlled trial; SAT = single-arm trial; NSM = non-surgical management; CM = conservative management; mo=months; NR = not relevant
Table 2. Baseline characteristics of patients included in pooled analysis.

| Characteristic                  | INSITE (n=148) | IMIA (n=103) | SIFI (n=172) | Total | P-value across Studies* | P-value across Treatment** |
|---------------------------------|----------------|--------------|--------------|-------|-------------------------|---------------------------|
| Age, years, mean [range]        | 51.3 [26-72]   | 48.1 [23-70] | 50.9 [23-72] | 50.4 [23-72] | 0.2073                   | 0.7480                     |
| Women, n (% female)             | 103 (69.6%)    | 76 (72.8%)   | 120 (69.8%)  | 298   | 0.8322                  | 0.2425                     |
| Race, n (%)                     |                |              |              |       |                         |                           |
| White                           | 141 (95.3%)    | ND           | 166 (96.5%)  | 307   | 0.3370                  | 0.8681                     |
| Black                           | 5 (3.4%)       | ND           | 2 (1.2%)     | 7     | 0.7654                  | 0.1817                     |
| Ethnicity                       |                |              |              |       |                         |                           |
| Hispanic or Latino, n (%)       | 8 (5.4%)       | ND           | 7 (4.1%)     | 15    | 0.0085                  | 0.7567                     |
| Body mass index, mean [range]   | 30.4 [17-50]   | 27.1 [16-44] | 29.4 [17-51] | 29.2  | <.0001                  | 0.8458                     |
| Smoking status, n (%)           |                |              |              |       |                         |                           |
| Current smoker                  | 29 (19.6%)     | 39 (37.9%)   | 44 (25.6%)   | 112   | 0.0287                  | 0.0100                     |
| Former smoker                   | 43 (29.1%)     | 22 (21.4%)   | 49 (28.5%)   | 114   | 0.0287                  | 0.0100                     |
| Never smoker                    | 76 (51.4%)     | 42 (40.8%)   | 79 (45.9%)   | 197   | 0.9575                  | 0.0197                     |
| Prior lumbar fusion (n, %)      | 58 (39.2%)     | 37 (35.9%)   | 76 (44.2%)   | 171   | 0.3732                  | 0.8458                     |
| Years of pain, mean [range]     | 6.4 [4.8-11]   | 4.7 [4.0-5.4]| 5.1 [4.3-4.1]| 5.4   | 0.2515                  | 0.1052                     |
| Prior treatments                |                |              |              |       |                         |                           |
| Physical therapy                | 107 (72.3%)    | 75 (57.3%)   | 111 (64.5%)  | 277   | 0.0456                  | 0.9074                     |
| Steroid SI joint injection      | 127 (85.8%)    | 75 (72.8%)   | 162 (94.2%)  | 364   | <.0001                  | 0.2677                     |
| RF ablation                     | 25 (16.9%)     | 17 (16.5%)   | 27 (15.7%)   | 69    | 0.9575                  | 0.0197                     |
| Taking opioids (n, %)           | 99 (66.9%)     | 53 (51.5%)   | 131 (76.2%)  | 283   | <.0001                  | 0.1654                     |
| Questionnaire scores, mean (SD) |                |              |              |       |                         |                           |
| VAS                             | 82.3 (11.3)    | 75.3 (12.8)  | 79.8 (12.8)  | 79.6  | 0.0056                  | 0.0631                     |
| ODI                             | 56.8 (13.2)    | 56.6 (14.0)  | 55.2 (11.5)  | 56.1  | 0.4531                  | 0.3670                     |
| EQ-5D                           | 0.45 (0.18)    | 0.36 (0.25)  | 0.43 (0.18)  | 0.4   | 0.1837                  | 0.5518                     |
| PCS                             | 30.4 (6.2)     | ND           | 31.7 (5.6)   | 31.1  | 0.0476                  | 0.5709                     |
| MCS                             | 43.1 (11.6)    | ND           | 38.5 (11.3)  | 40.6  | 0.0029                  | 0.8356                     |

ND = not done; *Mixed model across studies. **Mixed model across treatment groups (SIJF vs. NSM, RCTs only).
Table 3. Associations between baseline patient characteristics and treatment outcome

|                  | SIJ Fusion |                |                | Non-surgical management |                |                |
|------------------|------------|----------------|----------------|-------------------------|----------------|----------------|
|                  | VAS SIJ    | ODI            | EQ-TTO         | VAS SIJ                | ODI            | EQ-TTO         |
| Age quartile     |            |                |                |                         |                |                |
| 1 (<24 years)    | Ref        |                |                | Ref                     |                |                |
| 2 (42-50)        | -2.3 (0.5135) | 1.92 (0.4643) | -0.0294 (0.4219) | Ref                     |                |                |
| 3 (50-59)        | -4.7 (0.1750) | 0.17 (0.9482) | 0.0231 (0.5210) | Ref                     |                |                |
| 4 (>59)          | -9.1 (0.0080) | -1.39 (0.5921) | 0.0013 (0.9707) | Ref                     |                |                |
| Pain duration quartile |            |                |                |                         |                |                |
| 1 (<1.5 years)   | Ref        |                |                | Ref                     |                |                |
| 2 (1.5-3)        | -4.9 (0.1677) | 0.88 (0.7417) | 0.057 (0.1147) | Ref                     |                |                |
| 3 (3-6)          | -7.7 (0.0282) | -0.19 (0.9431) | 0.067 (0.0644) | Ref                     |                |                |
| 4 (>6)           | -5.2 (0.1384) | -0.26 (0.9235) | 0.105 (0.0035) | Ref                     |                |                |
| Current smoker   | 5.9 (0.0299) | 4.4 (0.0292)   | 0.0027 (0.9232) | -4.9 (0.3028)           | -1.2 (0.7189) | 0.112 (0.1423) |
| Male gender      | -1.3 (0.6324) | -2.4 (0.2453)  | -0.029 (0.3111) | 3.1 (0.4344)            | -0.52 (0.8493) | 0.030 (0.6416) |
| Bilateral SIJ    | 2.1 (0.5172) | 1.5 (0.5484)   | 0.027 (0.4155)  | -                        | -               | -              |
| History of lumbar fusion | 3.0 (0.2236) | 1.6 (0.3868)   | -0.027 (0.2841) | 1.9 (0.6403)            | 0.17 (0.9501) | 0.044 (0.4959) |
| Opioids at baseline | 6.4 (0.0166) | 6.1 (0.0029)   | -0.025 (0.3656) | 5.1 (0.1922)            | 2.2 (0.3970) | -0.042 (0.5001) |

Each entry shows the regression coefficient for the subgroup level for changes in SIJ pain, ODI or EQ-5D TTO index for the SIJF group and NSM group separately. Negative values indicate a decrease. Associated p-values are given in parentheses. Significant values (p<.05) are bolded.

Ref = reference level; VAS SIJ = visual analog scale sacroiliac joint pain; ODI = Oswestry Disability Index; EQ-TTO = EQ-5D Time Trade-off Index.