Ultrasound assessment of response to intra-articular therapy in osteoarthritis of the knee

Helen I. Keen¹, Elizabeth M. A. Hensor², Richard J. Wakefield², Philip J. Mease³, Clifton O. Bingham III ⁴ and Philip G. Conaghan ⁴

Abstract

Objective. Assessment of the synovium in patients with knee OA is of great potential value for clinical trials. Ultrasonography could provide this but few data exist on its ability to assess synovial response to therapies. The aim of this study was to examine whether US can detect synovial response to IA corticosteroid (IACS) therapy and to explore associations between synovial characteristics and symptoms.

Methods. A total of 35 people with ACR radiographic knee OA were included, including those who required an injection of 80 mg of IA methylprednisolone. All participants completed a visual analogue scale for pain and underwent US of the knee at baseline, 1 and 4 weeks. Minimum clinically important improvement (MCII) in pain was $\geq 20$ mm.

Results. One week of data were available for 33 patients (19 received IACS and 14 others). Synovial thickness (ST) decreased in 16 IACS patients and 2 others [mean between-group difference 4.7 mm (95% CI 1.1, 8.2), $P = 0.012$]. Absolute reduction was not associated with absolute reduction in pain ($r = 0.20$, $P = 0.289$), but decreased ST was substantively associated with reduction in pain greater than or equal to the MCII (52.9% vs 23.1%, $P = 0.098$, $\psi = 0.30$). The power Doppler score decreased in 13 IACS patients and 3 others (median change in IACS patients $-1.0$ [interquartile range (IQR) $-5.0$ to $-0.0$], others 0.0 [-0.3 to 1.3], $P = 0.004$). Absolute changes in pain and power Doppler score were weakly associated ($r = 0.36$, $P = 0.049$) and a decreased power Doppler score was associated with reduction in pain greater than or equal to the MCII (64.3% vs 18.8%, $P = 0.011$, $\psi = 0.46$).

Conclusion. Ultrasonography can detect short-term synovial response in knee OA. In particular, power Doppler score may be both responsive to and associated with pain, warranting further investigation.

Key words: ultrasonography, osteoarthritis, corticosteroids.

Introduction

OA is the most common form of arthritis. The prevalence of symptomatic knee OA is estimated to be 10% in the North American elderly population [1, 2], while the prevalence of radiographic knee OA in the USA is estimated to be 33% in people $>63$ years of age [2]. In order to improve our understanding of the pathogenesis of OA, the relationship between symptoms and structural pathology and the relationship between OA processes and therapeutic interventions, novel imaging techniques such as US have been increasingly used in both trial and clinical settings. However, a recent systematic review demonstrated that while imaging techniques such as US are well placed to be used as objective outcome tools in knee arthritis, there is little published evidence that it can demonstrate changes in response to therapy in OA [3]. Until appropriate and responsive imaging outcome tools are developed,
the ability to rigorously examine the mode of action and efficacy of therapies in vivo is limited. The objectives of this study were 2-fold: first, to ascertain whether US can demonstrate response to IACS in OA of the knee and second, to compare the relationship of US response with clinical symptoms.

Methods

The study was undertaken in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Leeds West Research Ethics Committee, Leeds, UK. All subjects gave written informed consent before entering the study. Based on a previous report of a reduction in US-detected synovitis in 30 subjects with knee OA in response to repetitive shortwave diathermy [4] (there was no available information on the effects of IACS on US-detected synovitis in knee OA), we aimed to recruit 35 consecutive people from rheumatology outpatient clinics within the Leeds Teaching Hospitals Trust with symptomatic and radiographic ACR criteria OA [5]. The subjects completed a symptom assessment and US examination at baseline and returned for follow-up at 1 and 4 weeks. Those with clinical need, as determined by the treating physician (not the investigator, and independent of the study and therefore not randomized) received 80 mg of IACS (methylprednisolone) (n = 19, IACS cohort) mixed with 2 ml of lidocaine 1% (local anaesthetic) at the baseline visit (the standard dose in this unit). The remaining subjects (others) had no therapeutic intervention between baseline and week 4. Baseline levels of analgesia were not altered and subjects were asked to maintain stable doses of analgesics over the observation period, with no washout prior to study visits.

Subjects were asked to mark on a 100 mm visual analogue scale (VAS) how bad their knee pain had been during physical activities over the past 48 h. Patients also completed the WOMAC (100 mm VAS format; scores were summed within each subscale to produce a total score of 0–100) [8, 9] (as this is considered more sensitive than the neutral position) with no washout prior to study visits.

The knee was moved to the neutral position and the image acquisition filter, and gain was adjusted until the background signal was removed. The knee positioning and image acquisition were as described for greyscale synovial hypertrophy. Power Doppler was scored according to a semi-quantitative score of 0–3 (none, mild, moderate, severe) [12]. Reliability was determined by reading 48 stored US images (ST, effusion depth and power Doppler score) at two time points, 2 weeks apart.

Statistical analysis

No imputation was performed for missing data. The SPSS 19.0.0.2 software package (IBM, Armonk, NY, USA) was used for the analysis. The examination of the effects of IACS on US-detected pathology was an observational pilot study and, as such, was not powered to be confirmatory of significant findings. The results presented are exploratory and descriptive. Where P-values are provided, a two-sided P < 0.1 has been used as an indicator of potential difference between the groups that warrants further investigation; no corrections for multiple comparisons have been made.

Changes from baseline with regard to symptoms and US-detected features (summed over the five knee sites) are presented as absolute rather than percentage improvement. The minimum clinically important improvement (MCII) for the pain VAS was taken to be 20 mm, consistent with a published value for patients with knee OA [11]. Analysis of covariance (ANCOVA) was undertaken to assess for between-group differences in the change in US-detected pathology (ST and effusion) at follow-up, adjusting for baseline values. Residuals from the ANCOVA models were examined for normality and homoscedasticity. The Mann-Whitney U-test was used to detect between-group differences in the change in power Doppler score (an ordinal measurement) at follow-up with no adjustment for baseline values. Pearson’s product moment correlation (r) was used to examine associations between changes in pain, synovitis and effusion, while Spearman’s rank correlation (ρ) was used to measure the association between change in pain and change in power Doppler score. The ρ coefficient (equivalent to Pearson’s product moment correlation of two binary variables) was calculated to give an indication of the level of association between changes in pain and US measures when dichotomized into unchanged or worse or improved more than the MCII (pain) and reduced or the same or increased (US); ρ gives a measure of effect.
size for the chi-square test. Intrareader reliability was calculated by reading stored images of 35 subjects, with a minimum 4 week interval. Intraclass correlation coefficient (ICC1,2) was calculated for the continuous measures of ST and effusion depth and k for power Doppler signal. Levels of agreement measured by ICC and k were assessed according to rules of thumb proposed by Landis and Koch [13] (<0: poor; 0.00–0.20: slight; 0.21–0.4: fair; 0.41–0.6: moderate; 0.61–0.8: substantial; 0.81–1.0: almost perfect).

Results

The demographics of the cohort by treatment group are presented in Table 1, together with summaries of patient symptoms and US assessments. A total of 35 subjects were recruited, 19 to the IASC cohort and 16 others. As patient-reported symptoms were considered in determining the need for IACS, there were differences between the treatment groups with regard to pain. In addition, US-detected pathology differed between the groups, with the IACS group having greater ST and effusion.

In the IACS group, all subjects except one had the IA injection protocol; this subject declined local anaesthetic and requested both knees be injected at baseline, although only the most symptomatic knee was included in the study. One subject in the IACS group had an increase in pain at the 1 week follow-up and was investigated with a diagnostic tap of 5 ml to exclude septic arthritis after US assessment. All 19 subjects in the IACS cohort (100%) and 14/16 others (87.5%) attended the 1 week follow-up. Eighteen subjects in the IACS cohort (94.7%) and 14/16 others (87.5%) attended the 4 week follow-up. While US assessments were available for all patients who attended, some patients did not complete the pain VAS.

Synovial response to IACS therapy

Table 2 presents the change in US-detected ST and effusion scores at weeks 1 and 4 by treatment group. There was some evidence that both ST and effusion were reduced at 1 week in the IACS group, whereas no consistent reduction in either pathology was identified in the others. Changes in effusion were more variable than changes in ST. The change in total power Doppler score indicated that the groups differed at 1 week [median change, others 0.0 (IQR −0.3–1.3), IASC group −1.0 (−5.0–0.0); standardized statistic z = −3.48, P = 0.004]. At 4 weeks there were no longer substantive differences between the groups in ST, effusion size (see Table 2) or power Doppler score [control = 0.0 (IQR 0.0–2.0), injection = −0.5 (−3.0–2.0); standardized statistic z = −1.17, P = 0.241].

Symptom response to IACS therapy

Changes in pain at 1 week were available for 18 patients in the injection group and 12 others. In those who did not receive IACS, none of the patients reported a clinically meaningful improvement in pain VAS (20 mm) at 1 week; one patient reported a substantive increase in pain of >20 mm. In the IACS group, all but one patient had seen at least some reduction in pain, and 13 of 19 patients (68.4%) reported clinically meaningful improvement. At week 4, one of the patients who did not receive IACS had substantively worse pain and in two patients (14.3%) pain had decreased relative to baseline levels. In the IACS group, nine patients (59.2%) reported substantively lower pain levels at 4 weeks than at baseline and none reported a substantive worsening of symptoms.

### Table 1 Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>IACS group (n = 19)</th>
<th>Control group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Median (IQR) 61.0 (64.0–70.0)</td>
<td>67.5 (66.0–77.5)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 62.0 (8.8)</td>
<td>66.5 (11.3)</td>
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<tr>
<td></td>
<td>95% CI 57.8, 66.3</td>
<td>60.5, 72.5</td>
</tr>
<tr>
<td><strong>Early morning stiffness, min</strong></td>
<td>Median (IQR) 10.0 (3.0–30.0)</td>
<td>5.0 (0.0–16.3)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 32.7 (70.3)</td>
<td>10.6 (16.6)</td>
</tr>
<tr>
<td></td>
<td>95% CI −1.2, 66.6</td>
<td>1.8, 19.5</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>Median (IQR) 29.4 (23.7–33.4)</td>
<td>29.0 (27.0–31.1)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 28.67 (4.81)</td>
<td>28.9 (3.4)</td>
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<tr>
<td></td>
<td>95% CI 26.01, 31.33</td>
<td>27.0, 31.0</td>
</tr>
<tr>
<td><strong>Pain VAS, mm</strong></td>
<td>Median (IQR) 73.5 (64.5–90.0)</td>
<td>36.0 (19.75–71.5)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 71.44 (18.89)</td>
<td>42.86 (26.70)</td>
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<tr>
<td></td>
<td>95% CI 62.05, 80.84</td>
<td>27.44, 58.27</td>
</tr>
<tr>
<td><strong>WOMAC pain (0–500)</strong></td>
<td>Median (IQR) 305.0 (212.0–429.0)</td>
<td>195.9 (76.25–220.75)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 315.68 (117.10)</td>
<td>156.50 (89.35)</td>
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<tr>
<td></td>
<td>95% CI 295.24, 372.13</td>
<td>108.89, 204.11</td>
</tr>
<tr>
<td><strong>WOMAC stiffness (0–200)</strong></td>
<td>Median (IQR) 153.0 (130.0–185.0)</td>
<td>89.0 (61.0–129.0)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 146.37 (40.15)</td>
<td>93.00 (52.36)</td>
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<tr>
<td></td>
<td>95% CI 127.02, 165.72</td>
<td>64.00, 122.00</td>
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<tr>
<td><strong>WOMAC function (0–1700)</strong></td>
<td>Median (IQR) 1014.0 (644.0–1448.0)</td>
<td>658.0 (349.5–851.75)</td>
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<tr>
<td></td>
<td>Mean (S.D.) 1020.95 (462.46)</td>
<td>627.14 (366.96)</td>
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<tr>
<td></td>
<td>95% CI 798.04, 1243.86</td>
<td>415.27, 839.02</td>
</tr>
<tr>
<td><strong>US total synovial thickness, mm</strong></td>
<td>Median (IQR) 13.0 (6.6–27.1)</td>
<td>7.8 (1.5–16.5)</td>
</tr>
<tr>
<td></td>
<td>Mean (S.D.) 16. (13.7)</td>
<td>8.5 (7.4)</td>
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<tr>
<td></td>
<td>95% CI 10.1, 23.4</td>
<td>4.5, 12.5</td>
</tr>
<tr>
<td><strong>US total effusion, mm</strong></td>
<td>Median (IQR) 13.3 (6.4–25.2)</td>
<td>4.4 (2.7–24.0)</td>
</tr>
<tr>
<td></td>
<td>Mean (S.D.) 16.1 (13.8)</td>
<td>10.8 (11.4)</td>
</tr>
<tr>
<td></td>
<td>95% CI 9.4, 22.7</td>
<td>4.7, 16.8</td>
</tr>
<tr>
<td><strong>US total power Doppler score</strong></td>
<td>Median (IQR) 3.0 (1.0–6.0)</td>
<td>0.5 (0.0–3.5)</td>
</tr>
<tr>
<td></td>
<td>Mean (S.D.) 4.0 (3.9)</td>
<td>2.3 (3.6)</td>
</tr>
<tr>
<td></td>
<td>95% CI 2.1, 5.9</td>
<td>0.3, 4.2</td>
</tr>
</tbody>
</table>

IQR: interquartile range; VAS: visual analogue scale.
A similar response pattern was seen for WOMAC pain (see supplementary data, available at Rheumatology Online).

Relationship between symptoms and synovial response

In the majority of those who did not receive IACS [11/14 (78.6%)] there had been an increase in ST at 1 week. One patient reported a substantive increase in pain, and their ST had increased by 7 mm. There was no clinically important change in pain in the others who did not receive IACS. In the IACS group, ST was generally reduced after 1 week [16/19 (84.2%)] and corresponded with an improvement in pain, although the degree of reduction in ST was not strongly associated with the degree of change in pain; patients whose pain had not substantively changed still showed a mean reduction in ST at 1 week. Overall, when both groups were combined, there was not a substantive association between change in ST and change in pain (n = 30, r = 0.20, P = 0.289). Dichotomizing change in pain as unchanged or worse vs improved greater than the MCII and dichotomizing change in synovitis as the same or increased vs reduced indicated a moderate effect size for the association between substantive improvement in pain and reduction in synovitis (ψ = 0.30) (Table 3).

There was no consistent pattern of increase [7/14 (50.0%)] or reduction [4/14 (28.6%)] in effusion after 1 week in those who did not receive IACS. Effusion had not substantively changed in the patient whose pain had substantially increased. In the IACS group, effusion size was reduced in the majority of patients [14/19 (73.7%) but greater reductions in effusion were not observed in patients whose pain had improved during the week compared with those whose change in pain remained within measurement error. As was found for ST, when both groups were combined there was no association between 1 week changes in effusion and pain (n = 30, r = 0.05, P = 0.779). When changes in pain and effusion were dichotomized, the effect size was small (ψ = 0.25) (Table 3).

In those who did not receive IACS, the power Doppler score tended to remain stable [5/14 (35.7%)] or increase at 1 week [6/14 (42.9%)]. Total power Doppler score had increased by 4 units in the patient whose pain had substantively increased. In the injection group, total power Doppler score decreased in the majority of patients [13/19 (68.4%)]. When both groups were combined, the degree of change in power Doppler score was only weakly associated with the degree of change in pain (n = 30, ρ = 0.36, P = 0.049). However, when changes in pain and power Doppler score were dichotomized, the effect size was found to be moderate to large (ψ = 0.46) (Table 3).

None of the patients who did not receive IACS showed a consistent reduction in all three US pathology scores, compared with 10 patients in the IACS group, 7 of whom had reported a substantive decrease in pain (Table 3). This difference was largely driven by the power Doppler results. When power Doppler score had decreased, both ST and effusion were likely to have decreased as well, whereas reductions in ST and/or effusion were not always accompanied by a decrease in the power Doppler score. A similar pattern of results was found using MCII in WOMAC pain vs pain VAS (supplementary Table S1, available at Rheumatology Online).

Reliability

Intrareader reliability for ST and effusion was almost perfect (ICC = 0.824 and 0.94, respectively) and for power Doppler score was substantial (κ = 0.762).

Discussion

In this exploratory study there was some evidence that US may be able to demonstrate reductions in ST, effusion and power Doppler signal 1 week after IACS therapy, consistent with the concepts that these parameters reflect synovial inflammation and that IACS acts through an anti-inflammatory effect on the synovium.

A limited number of studies have evaluated the ability of US to detect synovial changes in response to therapy in inflammatory arthritis of the knee [4, 14–18]. Previous studies have assessed greyscale US-detected synovial

### Table 2 Change in US-detected pathology score (summed across five sites) in subjects receiving IACS

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Unadjusted</th>
<th>Baseline adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IACS, mean (s.e.)</td>
<td>Control, mean (s.e.)</td>
</tr>
<tr>
<td>Synovial thickness</td>
<td>−4.19 (1.05)</td>
<td>2.48 (1.57)</td>
</tr>
<tr>
<td>Effusion</td>
<td>−6.55 (2.17)</td>
<td>2.08 (3.06)</td>
</tr>
<tr>
<td>Synovial thickness</td>
<td>−1.22 (1.70)</td>
<td>0.56 (1.52)</td>
</tr>
<tr>
<td>Effusion</td>
<td>0.61 (3.00)</td>
<td>1.67 (2.04)</td>
</tr>
</tbody>
</table>

IACS: 1 week, n = 19; 4 weeks, n = 18; control (no treatment): 1 week, n = 14; 4 weeks, n = 14. ANCOVA: analysis of covariance.
change in pain was observed (a weak correlation between change in synovitis and was found in cross-section, reported that longitudinally, association between MRI-detected synovitis and pain subjects with knee pain and radiographic OA, in which no tween symptoms and MRI findings. A large study of 270 have found conflicting and only modest correlations be-
tween change in symptoms and change in synovial path-
ology in response to therapy. As might be expected from
the literature, the relationship was complex, and while a
second objective was to examine the relationship be-
tween symptoms and MRI-detected (grey scale and power
Doppler) changes [24]. While interesting observations
among patients with OA of the small joints of
a US model of knee OA that focuses on power Doppler
score may be more sensitive and discriminative than other
US parameters.

While the purpose of this study was to determine
whether US is able to detect early changes in synovial
pathology in response to anti-inflammatory therapy, the
second objective was to examine the relationship be-
tween change in symptoms and change in synovial path-
ology in response to therapy. As might be expected from
the literature, the relationship was complex, and while a
reduction in pain was generally associated with a reduc-
tion in US-detected ST and power Doppler signal, the
association was relatively weak. This is consistent with previous studies of large populations of OA patients that have found conflicting and only modest correlations be-
tween symptoms and MRI findings. A large study of 270
subjects with knee pain and radiographic OA, in which no
association between MRI-detected synovitis and pain was found in cross-section, reported that longitudinally, a weak correlation between change in synovitis and change in pain was observed ($r = 0.21$, $P = 0.0003$) [22]. Another longitudinal study of 570 subjects with knee OA found only trends between changes in MRI-detected synovitis and knee pain [23], confirming that the longitudi-
dinal relationship between structure and symptoms is
likely to be modest at best and that large participant num-erries are required to assess such relationships. In addition, inherent difficulties exist in attempting to quantify symp-
toms, coupled with the interaction of psychosocial factors
on the symptom experience. It may be that potential inter-
actions between US-detected pathology (particularly in-
flammation) and symptoms may be difficult to detect
and perhaps imaging-detected inflammation as a thresh-
old for symptoms should be investigated. In this study,
dichotomizing the variables of pain and pathology re-
sulted in a moderate effect size for the relationship be-
tween ST and pain and a moderate to large effect size
for the relationship between power Doppler score and
pain.

When considering further development of a US model, it
is interesting that subjects in our study with a reduction in
power Doppler score were likely to have had a com-
comitant reduction in ST and effusion. However, a reduction
in these two parameters was not always accompanied by a
reduction in power Doppler score. This may suggest that
a US model of knee OA that focuses on power Doppler
score may be more sensitive and discriminative than other
US parameters.

The current study has limitations. This was an explora-
tory study and was not powered. We previously published
a small study of 36 subjects with OA of the small joints of the hand that found no relationship between clinical re-
sponse to CS- and US-detected (grey scale and power
Doppler) changes [24]. While interesting observations
can be made, particularly with regard to the relationship
between symptoms and synovitis, the lack of statistical
powering means that our findings must be regarded with
this in mind. In addition, this study was purely observa-
tional, following patients who were treated according to
their clinical need, and no randomized control group was
available for comparison. Nevertheless, comparisons
changes in response to therapy with conflicting results as
to whether changes can be detected, with no greyscale
changes demonstrable when dichotomous or categorical
definitions of synovial pathology are used, although all but
one did not employ power Doppler techniques [4, 14,
19–21]. In this study, patients were scanned before and
after receiving an IA bradykinin 2 receptor antagonist [19].
Despite significant improvement in symptom parameters
in the active treatment group, no changes in power
Doppler signal were demonstrated with US [19].

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tional, following patients who were treated according to
their clinical need, and no randomized control group was
available for comparison. Nevertheless, comparisons

<p>| TABLE 3 | Effect size of change in US-detected findings on pain when both US pathology and pain are dichotomized |
|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>US parameter</th>
<th>At 1 week</th>
<th>At 4 weeks</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pain reduced &gt; MCII, n/N (%)</td>
<td>Chi-square test result</td>
</tr>
<tr>
<td>Synovial thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same or increased</td>
<td>3/13 (23.1)</td>
<td>2.74 ($P = 0.098$)</td>
</tr>
<tr>
<td>Decreased</td>
<td>9/17 (52.9)</td>
<td></td>
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<tr>
<td>Effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same or increased</td>
<td>3/12 (25.0)</td>
<td>1.88 ($P = 0.171$)</td>
</tr>
<tr>
<td>Decreased</td>
<td>9/18 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Power Doppler score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same or increased</td>
<td>3/16 (18.8)</td>
<td>6.45 ($P = 0.011$)</td>
</tr>
<tr>
<td>Decreased</td>
<td>9/14 (64.3)</td>
<td></td>
</tr>
<tr>
<td>Synovial thickness, effusion and power Doppler score</td>
<td>5/20 (25.0)</td>
<td>5.63 ($P = 0.018$)</td>
</tr>
<tr>
<td>At least one same or increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistently decreased</td>
<td>7/10 (70.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Change in pain dichotomized as unchanged or increased vs reduced greater than the MCII and change in synovitis dichotomizing as the same or increased vs reduced.** aToo few patients showed a consistent reduction in US pathology at 4 weeks ($n = 3$) to make meaningful comparisons at this visit. MCII: minimum clinically important improvement.
have been made between those who received IACS and those who did not, as to date there are few published data concerning the natural history of US-detected pathology in knee OA, and we believe this information is therefore of interest. Due to the lack of randomization, the two groups studied were not matched in terms of symptom levels and synovial hypertrophy at baseline. We attempted to control for this by obtaining baseline-adjusted estimates, but it is possible that the patients differed in other ways not directly measured in this study. This would be an important limitation if the study had aimed to test the efficacy of IACS in knee OA. However, in the setting of a study designed to assess whether change in US parameters can be detected, the inclusion of participants likely to demonstrate a good response is sometimes preferred to facilitate demonstration of a difference, recognizing that effect size may be overestimated [25]. Although the effects of CS on OA synovium are assumed, this assumption has been largely extrapolated from the RA literature, thus the actual effects of CS on OA synovium are uncertain. Because the no IACS group was not matched for disease duration, symptoms or pathology at baseline, this study cannot necessarily discern our observed changes from natural history, and since the effects of IACS on OA synovium in vitro are unknown, we may have overestimated the effect size, particularly with regard to the semi-quantitative power Doppler score, where adjustments for baseline differences were not made.

The imaging was undertaken with the knee in 30° of flexion. It is possible that with this degree of flexion, quadriceps contraction may affect the Doppler signal. The subjects were imaged with the knee supported by a pillow to minimize quadriceps contraction, and recent evidence suggests that imaging the knee in 30° of flexion is associated with the highest detection of both GS and Doppler pathology [8, 9].

Pain is often a difficult symptom to measure. In this study we asked patients to rate pain over the previous 48 h during activity using a VAS. The rationale for a 48 h time anchor was based on the strength of patient recall [26, 27], although time anchors vary somewhat in reported OA trials. We acknowledge the limitation of not using a more complex but global question or patient-reported outcome measure such as the WOMAC pain subscale, however, post hoc analysis using the WOMAC pain subscale in place of the pain VAS demonstrated similar results.

In spite of these limitations, the findings from this study are of importance in both the development and testing of IA therapies in OA. A US model of short-term synovial response has great potential, and in particular the validity and utility of power Doppler in assessing synovitis in knee OA requires investigation in future studies. In particular, a well-designed, adequately powered trial randomizing patients to a potent anti-synovial therapy (most likely CS) or placebo would further aid development of a US outcome tool in OA. In particular, further investigation into the added value of examining the medial and lateral recesses is required to optimize sensitivity and responsiveness, while remaining feasible, would also be of interest.

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**Supplementary data**

Supplementary data are available at *Rheumatology* Online.

**References**


