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Concise report

Influence of non-steroidal anti-inflammatory drugs on the inflammatory sonographic features in erosive hand osteoarthritis: an intervention study

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Abstract

Objective The aim was to examine whether inflammatory US features in erosive hand OA patients change when discontinuing intake of NSAIDs before US examination in a non-randomized study.

Methods Patients ($n = 99$) were allocated to the NSAIDs or control group according to their intake at baseline. US was performed at baseline (T0) and 2 weeks after discontinuation of NSAIDs (T1). Inflammatory features (i.e. synovial proliferation, effusion and power Doppler signal) were scored using a semi-quantitative scale (from zero to three). Pain levels were scored on a numerical rating scale. Binomial mixed models were fitted for US features, and odds ratios of having a US score of at least two *vs* at most one for synovial proliferation and effusion, and zero *vs* at least one for power Doppler were calculated.

Results At baseline, both groups [NSAIDs group ($n = 47$) *vs* control group ($n = 52$)] were comparable for numerical rating scale pain, disease duration, number of radiographically affected joints, BMI and US baseline data, but not for age ($P = 0.005$). At T1, more synovial proliferation and power Doppler signal was seen compared with T0 in the NSAIDs group ($P = 0.018$ and 0.031, respectively). However, the interaction term time*NSAIDs was not found to be significant for any variable. The numerical rating scale pain at T1 was higher compared with baseline, although statistically non-significant.

Conclusion No significant changes in inflammatory US features were seen in patients with erosive hand OA after withdrawal of NSAIDs for 2 weeks. This study suggests that an NSAID-free period is not necessary before assessing inflammatory disease activity in erosive hand OA.

Key words: osteoarthritis, ultrasonography, hand, inflammation

CLINICAL SCIENCE

Key messages

- Cessation of NSAIDs does increase the inflammatory sonographic features in erosive hand OA in the short term.
- However, the interaction term time*NSAIDs was not found to be significant for any variable.
- Interruption of NSAIDs before sonographic assessment of inflammatory activity in erosive hand OA is not necessary.

Introduction

Hand OA is a common musculoskeletal disorder mainly affecting post-menopausal women [1, 2]. A specific subtype, the erosive type of hand OA, is known for its severe inflammatory burden [3, 4] and substantial disability [5]. Currently, the pharmacological treatment of hand OA is restricted to symptomatic treatment [6]. For this purpose, NSAIDs are widely used agents in hand OA. Although useful for offering symptomatic relief and reducing inflammation, they do not prevent joint destruction or alter the course of the disease.

US is a useful and widely used imaging modality to assess inflammatory features in patients with hand OA [7–9]. Few studies have addressed the effect of NSAIDs on inflammatory US features. One study in knee OA

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showed a reduction of inflammatory US features, i.e. effusion and synovial proliferation, after treatment with celecoxib for 8 weeks [10]. In RA, it was demonstrated that intake of NSAIDs suppresses grey-scale and power Doppler signs despite ongoing disease activity [11]. Hence, these US findings seem to underestimate the patient's current disease state.

To date, it is unknown whether cessation or interruption of intake of NSAIDs is mandatory before assessing inflammatory disease activity in erosive hand OA.

The aim of the study was to examine whether intake of NSAIDs affects the inflammatory US features in erosive hand OA.

Methods

Patients and study design

Ninety-nine consecutive patients with erosive hand OA were enrolled in this prospective, non-randomized intervention trial. Patients with erosive hand OA, presenting to the outpatient clinic of the Rheumatology department of the Ghent University Hospital, were included.

All patients met the ACR criteria for hand OA [12] and were $\geq$45 years of age. Central radiographic erosions had to be present in at least two finger IP joints.

Exclusion criteria were as follows: trauma or surgery performed to the hands within 6 months before baseline, any IA injection of finger IP joints within 3 months before inclusion, intake of oral CSs 1 month before inclusion, positive RF and/or ACPA titres, carpal tunnel syndrome or any other inflammatory joint disease, such as RA, PsA or crystal arthropathy. The study was approved by the local ethics committee, and all procedures followed were in accordance with the Declaration of Helsinki. All patients gave oral and written informed consent.

Intervention and sonographic assessments

Regular intake of NSAIDs was registered. If patients reported taking on a regular base (i.e. $\geq$3 days a week) any NSAIDs at a therapeutic anti-inflammatory dose [13], they were allocated to the intervention (NSAID withdrawal) group. In the event of no regular intake of NSAIDs, the patient was allocated to the control (no NSAIDs) group. At baseline (T0), US examination of all 16 finger IP joints (i.e. PIP joints 2–5 and DIP joints 2–5 bilaterally) was performed. Patients taking NSAIDs at baseline were requested to discontinue any intake of NSAIDs for 2 weeks, after which another US was performed (T1). Patients in the control group also underwent US after 2 weeks, with the strict request not to take any NSAIDs in the meantime. Intake of paracetamol was not allowed in either group.

All US examinations were performed by the same sonographer (R.W.), who had $>$10 years of experience in musculoskeletal US [9], using an Esaote MyLab60 machine (Esaote, Genova, Italy) with a 12–18 MHz linear array transducer. Settings were optimized to obtain the best image. The sonographer was blinded to the clinical findings and allocation of the patient. All examinations were performed in the same conditions and at the same time of the day. The presence of synovial proliferation, effusion and power Doppler was recorded from the dorsal and palmar side. Synovial proliferation and effusion were scored according to the OMERACT atlas for hand OA from zero to three (zero: absent; one: minimal; two: mild; three: severe) [14]. Power Doppler settings were standardized with a pulse repetition frequency of 13.2 kHz and medium wall filter. Settings were adapted individually to reduce background noise.

Other assessments

At T0, demographic characteristics (age, disease duration and sex) were recorded. Patients were asked to indicate the level of pain experienced in the hands during the past 48 h on a numerical rating scale from 0 to 10 (0: no pain; 10: worst pain). Conventional radiographs of the hands were taken and scored for the presence of erosive features according to the anatomical phase scoring system [15]. Joints were categorized into non-erosive (including N, S and J phase) *vs* erosive phases (E, R, F).

Statistical analysis

Baseline demographics, radiographic features and US features were calculated (mean and SD. for continuous variables, and median and range for categorical variables) and groups were compared using Student's unpaired *t*-test and the Mann–Whitney *U*-test according to data distribution. Proportional statistics were assessed using the χ^2 test and Fisher's exact test.

Given that patients were not allocated randomly to either the control group (no NSAIDs) or the intervention group (NSAID withdrawal), models were adjusted for potential confounders of the association between group and US score. It was decided not to approach the US scores as nominal variables but to dichotomize (zero or one *vs* two or three) for synovial proliferation and effusion, because of a low prevalence of score three and potential over-interpretation of score one. For the power Doppler signal, zero *vs* greater than one was chosen, because of a low prevalence of power Doppler scores of two and three. Although anatomical phase was not considered as a confounder in exploratory analyses, potential phases were dichotomized, resulting in a more parsimonious model.

Binomial mixed models with a logit function were fitted for US scores of synovial proliferation (score greater than two), effusion (score greater than two) and power Doppler (score greater than one), with a random intercept for patient and with age (in years), sex (female *vs* male), duration of illness (in years), joint (PIP2 *vs* PIP3 *vs* PIP4 *vs* PIP5 *vs* DIP2 *vs* DIP3 *vs* DIP4 *vs* DIP5), side (left *vs* right), anatomical phase group (non-erosive *vs* erosive phases), NSAID group (NSAID withdrawal *vs* no NSAIDs), time (T1 *vs* T0) and a two-way interaction between NSAID group $\times$time as fixed factors. The regression coefficients from these models are subject-specific

parameters and should be interpreted given the subject-specific values of the random effects. The odds ratio (OR, 95% CI) of having an US score of at least two *vs* having an US score of at most one for synovial proliferation and effusion, and of having a US score of at least one *vs* zero for power Doppler is given.

Analyses were performed using IBM SPSS software v.25.0 (Armonk, NY, USA).

Results

Demographics

The NSAID withdrawal group consisted of 47 patients (77% female) and the no NSAIDs group of 52 patients (79% female). Except for age ($P = 0.005$), both groups were comparable for disease duration, numerical rating scale pain, BMI and number of radiographic affected joints (Table 1).

Baseline sonographic features

At baseline, for a given age, sex, duration of illness, joint, side and anatomical phase group, all inflammatory US features (i.e. synovial proliferation, effusion, and power Doppler) were comparable between the no NSAIDs and NSAID withdrawal group (Table 1).

Effect of time and NSAID withdrawal

Pain

At T1, the mean change in numerical rating scale pain compared with baseline increased more in the NSAID withdrawal group than in the no NSAID group, albeit statistically non-significant [0.53 (S.D. = 2.06) *vs* 0.29 (S.D. = 1.80), respectively, $P = 0.53$].

Synovial proliferation

Within the no NSAID group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds for having a US score of at least two at T1 was 1.30 times the odds at baseline (= 30% higher odds at T1 compared with baseline; OR = 1.304; 95% CI, 0.958, 1.775; $P = 0.091$). Within the NSAID withdrawal group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds of having a US score of at least two at T1 was significantly

Table 1 Demographic and radiographic data (patient level) and T0 and T1 sonographic data (joint level)

	NSAID withdrawal (n = 47 patients)		No NSAIDs (n = 52 patients)		P-value*
Demographic data					
Female, *n* (%)	36 (77)		41 (79)		0.788
Age, mean (S.D.), years	59 (6.3)		63 (8.5)		0.005
Disease duration, mean (S.D.), years	11 (6.8)		14 (8.3)		0.066
NRS pain, mean (S.D.)	4.7 (2.3)		3.9 (2.4)		0.139
BMI, mean (S.D.), kg/m^2	25 (3.6)		25 (3.8)		0.672
Radiographic data					
Number of erosive/remodelled joints[a], median (range)	5 (4–8)		6 (4–7)		0.228
Sonographic scores					
	NSAID withdrawal (n = 751 joints)[b]		No NSAIDs (n = 822 joints)[c]		OR (95% CI) (P-value)
Synovial proliferation, *n* (%)	T0	T1	T0	T1	
Grade 0	445 (59)	393 (52)	443 (54)	390 (48)	0.584 (0.328, 0.038) (0.067)
Grade 1	239 (32)	265 (35)	268 (32)	298 (36)	
Grade 2	61 (8)	90 (12)	89 (11)	124 (15)	
Grade 3	6 (<1)	3 (<1)	22 (3)	10 (1)	
Effusion, *n* (%)					
Grade 0	335 (45)	297 (40)	396 (48)	391 (48)	1.364 (0.811, 2.293) (0.242)
Grade 1	282 (38)	306 (41)	315 (38)	317 (38)	
Grade 2	124 (17)	129 (17)	105 (13)	101 (12)	
Grade 3	10 (1)	19 (2)	6 (1)	13 (2)	
Power Doppler signal, *n* (%)					
Grade 0	683 (91)	659 (88)	747 (92)	745 (91)	0.846 (0.508, 1.409) (0.520)
Grade 1	49 (7)	64 (8)	55 (7)	45 (5)	
Grade 2	17(2)	27 (3)	18 (2)	29 (4)	
Grade 3	2 (<1)	1 (<1)	2 (<1)	3 (<1)	

[a]Defined by anatomical phase score, including E, R and F. [b]One joint missing owing to amputation. [c]Ten joints missing from three patients [one joint from two patients owing to amputation; total left hand (eight joints) missing in one patient owing to amputation]. **P*-value reflects comparison between NSAID withdrawal *vs* no NSAIDs. NRS: numerical rating scale; OR: odds ratio.

Table 2 Change in US scores: unadjusted (crude) and adjusted analyses

Variable	Group	Crude OR	95% CI	*P*-value	Adjusted OR[a]	95% CI	*P*-value
Synovial proliferation	No NSAIDs	1.263	0.949, 1.681	0.109	1.304	0.958, 1.775	0.091
	NSAID withdrawal	**1.475**	**1.048, 2.075**	**0.026**	**1.552**	**1.079, 2.232**	**0.018**
	Interaction term time*NSAIDs	–	–	0.496	–	–	0.470
Effusion	No NSAIDs	1.022	0.764, 1.367	0.883	1.027	0.761, 1.387	0.860
	NSAID withdrawal	1.150	0.872, 1.517	0.324	1.164	0.872, 1.554	0.303
	Interaction term time*NSAIDs	–	–	0.566	–	–	0.562
Power Doppler signal	No NSAIDs	1.226	0.777, 1.936	0.381	1.016	0.715, 1.444	0.929
	NSAID withdrawal	1.194	0.739, 1.928	0.469	**1.480**	**1.036, 2.116**	**0.031**
	Interaction term time*NSAIDs			0.936	–	–	0.14

[a]OR in generalized linear model with adjustment for age, BMI, disease duration and anatomical phase. OR: odds ratio. Statistically significant changes in bold.

higher compared with baseline (OR = 1.552; 95% CI, 1.079, 2.232; $P = 0.018$; Table 2).

Effusion

At T1, within the no NSAID group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds of having a US score of at least two was 1.02 times the odds at baseline (OR = 1.027; 95% CI, 0.761, 1.387; $P = 0.860$). Within the NSAID withdrawal group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds for having a US score of at least two at T1 were not significantly different compared with baseline (OR = 1.164; 95% CI, 0.872, 1.554; $P = 0.303$; Table 2).

Power Doppler signal

At T1, within the no NSAIDs group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds for having a US score of greater than one was 1.01 times the odds at baseline (OR = 1.016; 95% CI, 0.715, 1.444; $P = 0.929$). Within the NSAID withdrawal group, for a given age, sex, duration of illness, joint, side and anatomical phase group, the odds of having a US score of greater than one at T1 was significantly higher compared with baseline (OR = 1.480; 95% CI, 1.036, 2.116; $P = 0.03$; Table 2).

*Interaction term NSAIDs*time*

The interaction term NSAIDs*time was not found to be statistically significant for synovial proliferation, effusion or power Doppler, implying that there was no indication that the change in odds between T0 and T1 was different for the no NSAID group and the NSAID withdrawal group ($P = 0.47$, 0.56 and 0.14, respectively; Table 2).

Discussion

To our knowledge, these results are the first to suggest that withdrawal of NSAID intake does not affect the presence of inflammatory sonographic findings in erosive hand OA. This accounts for synovial proliferation, joint effusion and the power Doppler signal. These results are in line with previous results in hand OA showing that parenteral CSs could not suppress synovial hypertrophy or the power Doppler signal, although a significant reduction of pain was seen [16]. Our results contrast with knee OA results, where celecoxib was able to suppress US inflammation after 8 weeks [10]. Pharmacological therapy in hand OA has hitherto been limited to symptomatic treatment, such as paracetamol and NSAIDs [6]. In clinical trials, NSAIDs are often discontinued temporarily or permanently in order not to influence the assessment of disease activity, either clinically or by US. Our results suggest that there is no need to interrupt treatment and expose our patients unnecessarily to more symptoms of pain and/or inflammation.

The effect of NSAIDs on structural lesions was not studied here, because the interval between the two US assessments was too short.

Few studies have reported on the sensitivity to change of US in hand OA, and they were not able to demonstrate changes [6, 16], in contrast to rheumatic disorders such as RA and gout, where US was found to be responsive [17–20]. Therefore, it remains unknown whether US is, in fact, capable of detecting inflammatory changes in hand OA.

Although this was not a randomized trial, baseline data, clinical and US features were comparable between both groups. It could be hypothesized that patients regularly taking NSAIDs experience higher level of pain and inflammation, but this was not the case. The type of NSAID intake was heterogeneous, but patients were allocated to the NSAID group when a regular intake of a standard anti-inflammatory dose was reported (i.e. $\geq$3 days per week), and it can be assumed that the anti-inflammatory effect of NSAIDs is comparable among several compounds [13].

The study has several limitations. Only one sonographer performed all the US examinations; however, this sonographer has >10 years of experience in US and has proven good inter- and intra-reader reliability in previous research [9]. Also,

the intake of NSAIDs was monitored by the patients, but no external control was available. Although explicitly insisted, it could be possible that unauthorized intake of NSAIDs happened during the interval period of withdrawal.

Ideally, a randomized prospective study with standard NSAID intake, one dose regimen, controlled washout and greater sample sizes is needed to confirm the absence of causality between NSAIDs and US inflammation in erosive hand OA.

In conclusion, our study suggests that NSAIDs do not influence the sonographic features of inflammation in patients with hand OA; hence, discontinuation is not necessary before US assessment.

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