Ultrasound detected synovial change and pain response following intra-articular injection of corticosteroid and a placebo in symptomatic osteoarthritic knees: a pilot study

Michelle Hall[1, 2], Sally Doherty[1], Philip Courtney[3], Khalid Latief[3], Weiya Zhang[1], Michael Doherty[1]

[1]Academic Rheumatology, University of Nottingham, UK
[2]School of Health Sciences, University of Nottingham, UK
[3]Nottingham University Hospitals NHS Trust, UK

Correspondence to Dr Michelle Hall, School of Health Sciences, Clinical Sciences Building, Hucknall Rd, Nottingham NG5 1PB UK; michelle.hall@nottingham.ac.uk
Telephone: +44 (0)115 823 1756. Fax: +44 (0) 115 8231757

Copyright BMJ Publishing group Ltd

Citation: Hall, M., Doherty, S., Courtney, P., Latief, K., Zhang, W., Doherty, M. . (2014). "Ultrasound detected synovial change and pain response following intra-articular injection of corticosteroid and a placebo in symptomatic osteoarthritic knees: a pilot study." Annals of the Rheumatic Diseases **73**(8): 1590-1591.

http://ard.bmj.com/content/73/8/1590.short

Intra-articular injection (IAI) of steroid is a safe and effective treatment for painful knee osteoarthritis (OA).[1] The mechanism of action is thought to be partly mediated by an anti-inflammatory effect on the synovium which may be detected by changes observed on ultrasound (US) examination.[2] Placebo IAI of saline can also significantly reduce pain though the mechanisms are not generally thought to associate with a peripheral effect.[3-5] This pilot study aimed to investigate whether improved knee pain correlated with improved US measures following IAI of a corticosteroid or a placebo in OA knees.

Twenty-five participants with painful knee OA (Kellgren & Lawrence grade $\geq$2) were randomised to one of two treatment sequences (IAI of methylprednisolone (40mg in 1 ml) followed by IAI of saline placebo (1ml, 0.9%), or vice versa) to their most painful knee. 1 ml of synovial fluid (equal to the volume injected) was aspirated from the knee joint. No participant had inflammatory arthritis or had IAI of steroid within the previous 3 months. The 2nd injection was delivered after knee pain returned to its pre-injection level. Pain was assessed using a 100mm visual analogue scale (VAS) and Western Ontario and McMaster Osteoarthritis Knee Index (WOMAC).[6] US examination was carried out by a blinded assessor immediately prior to and 1 week following each injection, using a Toshiba Aplio SSA-770A machine with a multi-frequency (7-12 MHz) linear array transducer. A standardised protocol reflecting EULAR and OMERACT definitions was used.[7,8] Maximal depth of effusion, synovial hypertrophy and popliteal cysts were measured in millimeters (mm).

Ten men and fifteen women (mean age, 72 years (SD 7.8)) were enrolled and completed the study. All baseline characteristics were balanced for both sequence groups ($p<0.05$). Independent t-tests showed no order effect for pain response following the steroid injection ($p=0.87$) or placebo injection ($p=0.72$) and there was no significant difference in the mean time (days) between injections (steroid first = 95 (SD 65); placebo first = 81 (SD 47); $p=0.81$).

As expected, significant improvements in pain VAS were observed following both injections (mean difference: steroid -17.4mm SD (26.8), $p=0.003$; placebo -13.44mm SD (22.44), $p=0.006$) (table 1, figure 1A). Maximal depth of synovial hypertrophy was significantly reduced following the steroid injection (mean difference -0.94mm SD

(2.18), p=0.04) and was non-significantly reduced following the placebo injection (mean difference -0.98mm SD (3.65) p=0.91) (table 1, figure 1B). No change in effusions (table 1, figure 1C) or popliteal cysts were observed following either injection (table 1). We found no correlation between change in pain VAS and change in US measures following either injection though this may be related to the small sample size.

The observed improvement in synovial hypertrophy following IAI of steroid accords with a recent MRI study which reported a significant reduction in mean synovial volume following IAI of steroid.[9] However, we also observed a reduction in synovial hypertrophy following the placebo injection which mirrored the changes following the steroid. The analgesic effects of a placebo are considered to occur through expectancy-induced descending inhibitory mechanisms such as release of endogenous opioid but it has also been suggested that a reduction of local inflammation may arise through activation of the hypothalamic-pituitary-adrenal (HPA) axis as part of expectancy-induced descending inhibition of pain.[10] We believe that this may be the first study to show a possible peripheral ("anti-inflammatory") effect of IAI of placebo on the synovium, whilst acknowledging that our observations may partly reflect natural variances in synovial hypertrophy. Properly powered studies are needed to confirm these findings.

Contributors MH, PC, KL, WZ and MD conceived the study. SD performed the US examination. MH and WZ analysed the data. MH, WZ and MD drafted the manuscript, PC and KL contributed to revising the manuscript.

Funding We are grateful to Arthritis Research UK for funding this work (AHP Training Fellowship Grant no. 18861).
Competing interests None.
Ethics approval Derbyshire Research Ethic Committee approved this study.
Patient consent Obtained.
Provenance and peer review Not commissioned; externally peer-reviewed.

Table 1 Pain and ultrasound measures at baseline and change at 1 week following intra-articular cortico-steroid and placebo injection.

	Baseline			Change at 1 week				
	Placebo N=25	Steroid N=25	†P value	Placebo N=25	‡P value (for placebo)	Steroid N=25	‡P value (for steroid)	†P value
Pain VAS (mm)	61.8(20.5)	61.4(22.2)	0.95	-13.4 (22.4)	0.006	-17.4 (26.8)	0.003	0.59
WOMAC								
Pain (0-20)	9.2 (3.5)	9.4 (2.7)	0.82	-0.8 (2.4)	0.11	-2.0 (2.7)	0.001	0.13
Stiffness (0-8)	3.9 (1.7)	3.9 (1.2)	1.00	-0.3 (1.3)	0.30	-0.6 (1.5)	0.30	0.43
Function (0-58)	33.4(11.2)	32.3(10.3)	0.70	-1.4 (6.6)	0.30	-2.6 (8.4)	0.14	0.61
US Features (mm)								
Effusion	7.3 (3.6)	7.0 (3.9)	0.76	-0.6 (2.5)	0.28	-0.1 (2.5)	0.91	0.40
Synovial hypertrophy	7.7 (4.5)	6.9 (3.6)	0.50	-1.0 (3.7)	0.19	-0.9 (2.2)	0.04	0.91
Popliteal cyst median (range)	0 (0-10.8)	0 (0-14.20)	0.70	0 (-3.1, 6.1)	0.69	0 (-9.8, 4.4)	0.11	0.12

VAS, Visual analogue scale; WOMAC, Western Ontario and McMaster Osteoarthritis Knee Index; US Ultrasound.

Data are presented as mean (SD) where normally distributed and as the median (range) where non-normally distributed.

†P values represent paired tests for differences between placebo and steroid injections

‡P values represent paired tests for change from baseline to 1 week

REFERENCES

1. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16(2):137-62.
2. Keen HI, Mease PJ, Bingham CO, et al. Systematic Review of MRI, Ultrasound, and Scintigraphy as Outcome Measures for Structural Pathology in Interventional Therapeutic Studies of Knee Arthritis: Focus on Responsiveness. *The Journal of Rheumatology* 2011;38(1):142-54.
3. Zhang W, Robertson J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann. Rheum. Dis.* 2008;67(12):1716-23.
4. Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. *Osteoarthritis and Cartilage* 2013;21(9):1229-35.
5. Benedetti F, Amanzio M. Mechanisms of the placebo response. *Pulmonary Pharmacology & Therapeutics* 2013;26(5):520-23.
6. Bellamy N, Buchanan W, Goldsmith C, et al. Validation study of WOMAC: a health status instrument for measuring clinically-important patient-relevant outcome following total hip or knee arthroplasty in osteoarthritis. *Journal of Orthopaedic Rheumatology* 1988;1:95-108.
7. D'Agostino MA, Conaghan P, Le Bars M, et al. EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis. *Ann. Rheum. Dis.* 2005;64(12):1703-9.
8. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *The Journal of Rheumatology* 2005;32(12):2485-87.
9. O'Neill TW, Forsythe LM, Parkes MJ, et al. Change in MRI synovitis correlates with change in pain following intra-articular steroid injection. *Osteoarthritis and Cartilage* 2013;21, Supplement(0):S300.
10. Guess HA, Kleinman A, Kusek JW, et al., editors. *The Science of Placebo: Toward an interdisciplinary research agenda*. London: BMJ Books, 2002.