Home based exercise for osteoarthritis

We read with interest the report by Ravaud et al.¹ This largest ever study of exercise in osteoarthritis (OA) (2957 people followed up for 24 weeks) examined the effect of patient self assessment and the adjunct of a booklet and videotape to encourage unsupervised exercise. They found significant reductions in pain and disability in all groups including controls, but no between-group differences, thus concluding a “true negative” result.

There is convincing evidence that exercise reduces pain and disability from knee and hip OA.² The authors suggest that small numbers and lack of attention control in previous studies and the unsupervised nature of their own programme may explain this discrepancy. Yet one UK study not cited by the authors recruited 796 subjects with knee pain (47% with radiographic OA) from three general practices and employed a minimally supervised exercise programme with attention control, demonstrating a clear benefit over 2 years.³ Several caveats of the Ravaud study warrant emphasis:

- All patients received rofecoxib, with paracetamol as escape analgesia, decreasing baseline pain and reducing the maximum possible effect of exercise. This regimen is contrary to EULAR recommendations,⁴ which advocate paracetamol⁵ followed by topical agents for knee OA, then non-steroidal anti-inflammatory drugs/cokibs,⁶,⁷ and opioids for refractory pain.⁸
- Adherence is a major predictor of outcome to exercise⁹ and adherence to the exercise regimen was very low (less than one third of the patients).
- The rationale for “self assessment tools” is unclear. That patient self assessment itself might influence outcome is interesting. However, self assessment was used to guide adjustment of pharmacotherapy by the physician. Whatever the rationale, an alternative design incorporating assessment and adjustment for “response shift” (alteration over time in patient perception of symptom severity)¹⁰ would have been preferable.
- Controls received “usual care” from their rheumatologist. What guidance the rheumatologists received is unclear. However, although only 70% of controls recalled receiving muscle strengthening advice, one would expect rheumatologists to deliver optimum care, including exercise advice. Therefore controls received an expert management package not “attention control.” “Usual care” might equate to attention control in general practice where care is suboptimal but is an important strategy for specialist delivery. Although unstated, “usual care” presumably was given to all groups. Differences in exercise levels between groups are only presumed because exercise undertaken by controls was not assessed.

- Over 800 rheumatologists recruited only four patients each, making treatment standardisation almost impossible. Previous studies have recruited large numbers from very few centres.¹² Presumably the number of recruiting rheumatologists and rofecoxib use reflects industry sponsorship rather than study requirement.

Reassuringly, their study has not diminished the authors’ enthusiasm for exercise for OA. They conclude that for specialist care the addition of a booklet and videotape to encourage exercise is of no benefit. However, we believe the study was inadequately designed to examine effectiveness of unsupervised exercise over 6 months and is a “false negative” trial for exercise.

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References

Author’s reply

We thank Dr Roddy and coauthors for their interest in our report. Obviously, we had some communication problems in the published manuscript because several points have been misunderstood:

- Clinical efficacy versus clinical relevance

There is no doubt that exercises have shown clinical efficacy (improvement in symptoms) in sophisticated clinical trials, but the observed treatment effect was small and deserved to be evaluated in conditions of daily practice.

- Potential caveats of our study

- The protocol clearly mentioned that all the patients justified non-steroidal anti-inflammatory drug (NSAID) treatment. Moreover, it has to be noticed that after the EULAR recommendations were published, two studies have recently suggested that (a) patients do prefer NSAIDs rather than analgesics in crossover design trials; (b) the effect of paracetamol treatment is questionable in knee osteoarthritis (OA).¹²

- We do agree that adherence (compliance) is a major problem in OA. The question remaining is how to improve it. Our main objective was to check whether a simple route of administration of exercises (booklets, video) resulted in the same treatment effect as the sophisticated procedures previously used in clinical trials.

- The design used in the study was a 2 x 2 factorial design, which is appropriate when two different, but potentially related, treatment modalities are evaluated. Such a design allows evaluation of each treatment separately and checking as to whether there is an additive or synergistic effect between the two treatments.
The fact that our “control” group was usual care is considered a potential caveat by Dr Roddy and as a sign of quality by us. Again, we do recognise the demonstrated symptomatic effect of exercises in OA. However, we considered that this effect has been demonstrated in sophisticated and quite artificial situations. To check whether such treatment is indicated for improvement in pain we conducted this study considering the control group as patients receiving the current usual care.

This rationale explains why we did not conduct a conventional (but artificial) clinical trial in a few centres recruiting patients who are referred to this research centre. Instead we asked physicians who are in charge of patients with painful knee OA to participate.

To conclude, as for a drug development, we do believe that for non-pharmacological treatments, after a treatment effect has been shown in sophisticated clinical trials, a demonstration of its benefit has to be obtained through clinical trials conducted in conditions of daily practice. This was the rationale and the intrinsic quality of the study we reported. We do hope that such methodology will be further adopted for any non-pharmacological treatment.

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Which dose regimen for glucocorticoid pulse therapy in patients with severe refractory RA?

Very recently Durez et al convincingly demonstrated that tumour necrosis factor blockade is, in comparison with glucocorticoid pulse therapy, promising, improving not only clinical measures of disease activity but also biological inflammatory indices in a subset of patients with severe refractory rheumatoid arthritis (RA).1 We would like to comment on the small effect that was seen with intravenous pulse methylprednisolone (MP) in this study.

We recently suggested that glucocorticoid pulse therapy should be defined as treatment with >=250 mg prednisone equivalent per day for one or a few days.2 According to this proposed nomenclature pulse therapy was indeed applied. However, the data obtained for this subset of patients with severe refractory RA show only small, if any, effects on the Ritchie score, Health Assessment Questionnaire, morning stiffness, or serum C reactive protein (CRP). These results are surprising at first glance. But what can we conclude by trying to interpret these interesting data?

Firstly, a single glucocorticoid application even at a high dose may have a strong but only short lived effect. We assume that 1 g MP produces 100% saturation of cytosolic glucocorticoid receptors with 100% of genotoxic effects exerted. This is therapeutically helpful and probably the patient will feel better—but only for a short period because receptor occupation rapidly reverts to the original value unless a new dose is given. The same consideration applies to exerted genomic effects, which fade away fairly rapidly unless repeated doses are given.2,3 These may be the reasons why a single application of a high dose does not produce therapeutic effects that are still measurable after 2 or more weeks. Figure 1 shows what we consider to be the duration of effect of MP (and infliximab) for this study.

We further conclude from the presented data that either a very high dose of a glucocorticoid needs to be given for more than just 1 day or monthly repeated infusions are required. Those therapeutic regimens have been successfully established in several different rheumatic diseases.4 Durez et al state in their article (p 1071) that “the absence of a significant effect of MP pulse therapy contrasts with some previously published studies”. Indeed, reported data show significantly greater effects of pulse therapy than this study demonstrated.

For instance in some of the Utrecht studies on aspects of MP pulse therapy data on efficacy are available,5,6 but in these studies MP was always given three times intravenously at a dosage of 1 g on alternate days (days 1, 3, and 5).

One study compared the efficacy of placebo and MP during the start of oral methotrexate treatment in patients with active RA. All measures evaluated (joint scores, erythrocyte sedimentation rate (ESR), CRP) improved significantly with intravenous pulse therapy compared with placebo at 6 weeks, and after 18 weeks most differences were still significant.4

Another study evaluating the effect of MP also showed that the Ritchie score, ESR, and CRP were significantly decreased after 1 week; these effects were weaker after 3 and 6 weeks.5

In yet another study looking at the short term effects of MP on disease activity and wellbeing in 66 patients with active RA after 1 week, ESR decreased from 68 to 38 mm/1st h, CRP from 57 to 16 mg/L, morning stiffness from 126 to 34 minutes. Grip strength increased from 8 to 15 kg, while mobility, self care, improvement in pain and depressed mood increased significantly as well.6 These data are in line with published reports, reviewed by Weusten et al.7

Finally, we would like to emphasise that these comments are meant to enhance the work by Durez et al, which was an excellent paper. We would be unable to debate these issues without the availability of the data they obtained from this very carefully conducted study.8 In summary we assume that the glucocorticoid regimen used in the study of Durez et al might have been too weak to reach adequate efficacy and that comparison with tumour necrosis factor α blockade is perhaps limited in this respect.

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Authors’ reply

We sincerely thank Drs Buttgereit, Burmester, and Bijlsma for their stimulating comments on our study. They suggest that our decision to administer one intravenous pulse of 1 g of methylprednisolone (MP)—instead of a series of three infusions—explains the tin effect seen in our patients with rheumatoid arthritis (RA). Although we agree with the pharmacological arguments soundly put forward by Buttgereit, Burmester, and Bijlsma, it should be emphasised that, to the best of our knowledge, a direct comparison of the clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis 2004;63:1069–74.


References


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