Hand **O**steoarthritis: investigating **P**ain **E**ffects in a randomised placebo-controlled feasibility study of **e**strogen-containing therapy

Lay Summary of Results from the HOPE-e Study

Background

Hand osteoarthritis (OA) affects 2 million people in the UK, causing pain and functional difficulties. There are few treatments except pain relief and exercise, which are often inadequate. Hand OA is more common in women, especially around menopause, when levels of the hormone estrogen fall. Hormone replacement therapy or 'HRT' (containing estrogen) appears to protect people with hip OA from joint replacement. However, there had never been randomised trials testing HRT for painful hand OA. The HOPE-e study aimed to test whether this type of study could be successfully run, whether it was acceptable to take this type of treatment for hand OA, and the best ways of collecting information, to help plan a full-size trial.

Methods

We did this by running a small clinical trial of a tablet HRT, 'conjugated estrogens-bazedoxifene'. Women who met entry criteria had a 50% chance of being given the HRT medication or placebo (dummy) tablets. They took these once daily for 24 weeks, then gradually stopped over 4 weeks. We recorded how many people were a) interested in taking part in the study, b) met its entry criteria, c) agreed to take part, d) took any medication and e) stayed on medication. We collected information that would be used to test how well the treatment worked in a full-size trial, including; hand pain, hand function, hand appearance, grip strength, joint pain, quality of life and menopause symptom questions. Hand pain was measured in two ways, 1) daily rating 14 days before each study visit (daily average hand pain), and 2) at each study visit, recall average hand pain over the past 14 days as a single value (recall average hand pain). We recorded side effects and held two focus groups to learn from the participants' experiences, particularly how acceptable various aspects of the study were.

Results

Was it feasible to recruit people to this type of study?

Over 15 months from 2019-2020, we received 434 enquiries/referrals. People who took part in the study heard about HOPE-e from several different sources. The most successful source was presence on online websites, followed by text messages sent by GP practices.

Of 96 screenings, 35 people appeared to fulfil entry criteria. 33 gave their consent to take part and 28 went on to receive medication (6.5% of all enquiries, 80% of those appearing eligible). All 28 people completed the study. Of the 406 who did not enter the study, 250 (62%) did not fulfil entry criteria, 101 (25%) did not respond to further contact, and 55 (14%) chose not to take part.

The study met its goal of recruiting at least 22 people to join the study.

Who joined the study?

The average age of the 28 participants was 58 years with an average of 6 years since menopause. Most participants were white (96%), were in full-time or part-time work (79%), and had painful hand OA in both finger and base-of-thumb joints (68%).

- **Did people who joined the study stay in the study?**

All 28 participants completed all study visits and there was very high completeness of data collection. Most people took their study tablets regularly throughout (100% in HRT group, 93% in the placebo group), suggesting that the study medication was broadly acceptable.

- **How did two different methods for collecting hand pain data compare?**

People's pain over time looked similar in both treatment groups, between the two methods. However, the data collected for recalled average hand pain (at the visit) had more variation compared to daily average hand pain reported by text message and was also higher on average at each time point. Most people were happy to record daily average hand pain by text message (92% agreed or strongly agreed). In a full-size trial we would choose this type of daily rating over recalled pain.

- **What effects did taking part in the study have on hand pain?**

There was slightly higher average hand pain in the HRT group compared with those on placebo at baseline (the visit before starting medication). By both methods (daily and recall), the average hand pain decreased from baseline to week 24 in both groups. The two methods agreed that there was no evidence of a difference between HRT and placebo. However, this study was a feasibility study and was never designed to recruit enough participants to answer the question as to whether this treatment was effective. From these results, we now know that about 10 times as many people would need to be recruited in a full-size trial to answer this question.

- **What happened to hand pain when people stopped taking study medication?**

Participants were asked to taper their study medication from week 24 to week 28. The average hand pain reported at week 28 was higher in the HRT group compared to the placebo group. 46% in HRT arm reported worsening hand pain at week 28 compared with 17% who stopped placebo tablets. This indicates a possible effect of the medication.

- **What effects did taking part in the study have on other hand measures?**

There was no evidence of an effect on grip strength or hand function. There was some evidence that the treatment improved the left-hand (mostly non-dominant) appearance, although the study was not designed to detect this and this could have happened by chance.

- **What effects did taking part in the study have on quality of life and menopause symptoms?**

The study compared two menopause symptom questionnaires. The shorter (Greene) questionnaire had a higher percentage of the answers completed and was found easier to understand and complete and would be chosen for a future full-size trial.

The results suggested that HRT improved quality of life and menopause symptoms over the course of the study. Although these improvements could have occurred by chance; these are expected findings from published data on HRT.

- **Was the study medication safe and well-tolerated?**

Overall the study medication was safe and well-tolerated. There were 69 adverse events (potential side effects) recorded in the study in 25 of 28 participants. These were similar in the HRT and placebo groups, suggesting there was not a strong effect of the study medication. This was a similar rate to large trials of HRT. 13 of the 69 adverse events at the time were recorded as possibly HRT related, affecting 9 participants (5 of whom were on placebo).

3 people stopping the medication because of side effects were all on placebo. There were no side effects considered to be medically serious (e.g. life-threatening) reported during the study.

- **Did participants and study staff guess which treatment they were taking?**

Participants and the study doctor were overall 'well blinded' to the study treatment (not being able to guess what they were taking). There was no evidence of either participants or the study doctor guessing their treatment correctly beyond chance in either of the groups.

- **Were people satisfied about their participant in the study?**

People were generally satisfied with taking part in the study. 92% of participants would recommend taking part to others with hand OA. Many found the flexibility offered by a combination of remote and face to face visits (due to the pandemic) attractive. There was an even distribution of satisfaction and dissatisfaction with the medication amongst participants in both treatment groups. Participants on HRT and placebo were all satisfied with the ease of use of the medication.

- **What were the key findings from the focus groups?**

Two online focus groups (ten participants in total) were held. From analysis of the transcripts, three main categories and 16 areas of recommendation for improvements for a full-size trial were developed. These areas included considering hand stiffness as well as pain, considering a single-hand rating of pain (rather than an average of both hands) on a daily basis, recognising taking photographs of hands could be upsetting or uncomfortable for people with hand OA, reducing the overall number of questionnaires or questions, standardising and including hand exercises and other pieces of advice at the start of the study, and considering a longer follow-up period after stopping the medication.

- **Future full-size trial**

Using data collected from this study we estimate we would need to enrol 296 participants to assess whether HRT reduces hand pain for post-menopausal women with painful hand OA. Based on our recruitment rates, this would require 21 GP/hospital sites to recruit participants for 21 months.

Conclusions

This study told us that running a clinical trial of a form of HRT in post-menopausal women with painful hand OA is feasible and acceptable to those taking part. This information is crucial given the often-contentious nature of HRT and its safety considerations, both real and perceived. The study was not designed to test how well HRT worked or its safety in this population (which would both need bigger numbers of participants). The study's findings do not change practice. However, for the first time it has provided feasibility and proof-of-concept data for the use of a type of HRT in women with moderate-to-high symptoms of hand OA. We now aim to run (or encourage the running by others) of a full-size trial to test whether HRT is effective at improving hand OA symptoms after menopause.

Publication

The full study results are published in the The Lancet Rheumatology Journal. This article is free and accessible for all to read. Please scan the QR code or enter the web address below to access the full article where further details on what has been summarised above can be found.

https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913(22)00218-1.pdf

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