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Effect of local anaesthetic infiltration on chronic postsurgical pain after total hip and knee replacement: the APEX randomised controlled trials

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Abstract
Total hip replacement (THR) and total knee replacement (TKR) are usually effective at relieving pain; however, 7% to 23% of patients experience chronic postsurgical pain. These trials aimed to investigate the effect of local anaesthetic wound infiltration on pain severity at 12 months after primary THR or TKR for osteoarthritis. Between November 2009 and February 2012, 322 patients listed for THR and 316 listed for TKR were recruited into a single-centre double-blind randomised controlled trial. Participants were randomly assigned (1:1) to receive local anaesthetic infiltration and standard care or standard care alone. Participants and outcomes assessors were masked to group allocation. The primary outcome was pain severity on the WOMAC Pain Scale at 12 months after surgery. Analyses were conducted using intention-to-treat and per-protocol approaches. In the hip trial, patients in the intervention group had significantly less pain at 12 months postoperative than patients in the standard care group (differences in means: 4.74; 95% confidence interval [CI]: 0.95-8.54; \( P = 0.015 \)), although the difference was not clinically significant. Post hoc analysis found that patients in the intervention group were more likely to have none to moderate pain than severe pain at 12 months than those in the standard care group (odds ratio: 10.19; 95% CI: 2.10-49.55; \( P = 0.004 \)). In the knee trial, there was no strong evidence that the intervention influenced pain severity at 12 months postoperative (difference in means: 3.83; 95% CI: \(-0.83 \) to 8.49; \( P = 0.107 \)). In conclusion, routine use of infiltration could be beneficial in improving long-term pain relief for some patients after THR.

Keywords: Hip, Knee, Arthroplasty, Pain, Randomised controlled trial

1. Introduction
Primary total hip replacement (THR) and primary total knee replacement (TKR) are 2 of the most commonly performed elective surgical procedures, with 76,448 THR operations and 76,497 TKR operations performed in England and Wales in 2012. Projections indicate increased demand in the coming decades. Joint replacement is usually performed to relieve pain and improve function related to osteoarthritis and is effective for the majority of patients. However, in the postoperative period, up to half of the patients report moderate or severe pain on the first postoperative day. In the longer-term, between 7% and 23% of patients with THR and between 10% and 34% of patients with TKR report an unfavourable pain outcome at 3 months to 5 years after surgery.

Given the prevalence and impact of chronic pain, it is important to investigate interventions to reduce chronic postsurgical pain after joint replacement. Evidence from several types of surgery indicates that severe acute postoperative pain is a risk factor for chronic postsurgical pain. This has been highlighted in joint replacement, breast surgery, inguinal hernia repair, and thoracic surgery. Mechanisms for the transition from acute to chronic postsurgical pain are likely to be multifactorial. It is probable that the large amount of noxious input induced by surgery contributes to this transition through hyperexcitability and sensitisation of neurones within the central nervous system, which can lead to long-lasting amplification of pain signalling within the spinal cord.

In orthopaedic surgery, local anaesthetic infiltration has been found to be effective at significantly reducing pain severity in the first 48 hours after surgery. However, because of a lack of trials with longer-term follow-up, it is not known whether benefits of local anaesthetic infiltration extend to reducing chronic postsurgical pain.

Studies on the trajectory of recovery after joint replacement illustrate that although much of the pain relief from surgery occurs in the first 3 months, improvements in pain continue throughout the first year.
The aim of these 2 double-blind randomized controlled trials (RCTs) with allocation concealment was to determine whether intraoperative local anaesthetic infiltration could significantly reduce pain at 12 months after THR or TKR.

2. Methods

2.1. Design overview

Two single-centre double-blind RCTs (the Arthroplasty Pain Experience [APEX] trials) were conducted: one with patients undergoing THR and the other with patients undergoing TKR. The design of the 2 trials was similar except for standard anaesthetic care, and these differences are described in more detail below. The protocol for these trials has been published previously. The APEX trials were approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94), and all participants provided informed written consent. The trials were registered as an International Standardised Randomised Controlled Trial (ISRCTN 0905682) and as a Clinical Trial of an Investigational Medicinal Product with the Medicine Healthcare and Regulatory Authority (18524/0215/001-0001) and EudraCT (2009-013817-93). Both trials were overseen by a Data Monitoring Committee and Trial Steering Committee, who regularly reviewed safety data and monitored trial conduct.

2.2. Setting and participants

Eligible patients were listed for a primary unilateral THR or TKR for osteoarthritis at a UK elective orthopaedic centre. Exclusion criteria were (1) medical comorbidity that precluded spinal anaesthesia, regional blocks, or strong analgesics postoperatively because inability to tolerate these pain relief strategies may have influenced the trial results; (2) severe dementia or psychiatric illness; (3) listing for simultaneous bilateral joint replacement; (4) previous participation in the trial; (5) inability to understand English. Patients were recruited at the preoperative assessment clinic by a research nurse and randomized before surgery by the trial administrator.

2.3. Randomization

Treatment allocation was conducted remotely through the Bristol Randomised Trials Collaboration to maintain allocation concealment. Patients were allocated on a 1:1 ratio to receive the intervention plus standard care or standard care alone using minimisation factors. The trial administrator informed the operating surgeon and anaesthetist of treatment allocation on the day of surgery. Participants and trial research nurses were blinded to treatment allocation.

2.4. Standard care and intervention treatment: total hip replacement

Standard anaesthetic care consisted of spinal anaesthesia with 3 mL of 0.5% plain bupivacaine placed at the L3/4 or L4/5 interspace. Intraoperatively, the patient was awake, sedated, or under light general anaesthetic depending on patient and anaesthetic factors. The intervention group received the same anaesthetic regime, plus an intraoperative local anaesthetic infiltration that consisted of 60 mL of 0.25% bupivacaine with 1 in 200,000 adrenaline. The local anaesthetic mixture was injected into the joint capsule and short external rotators (5 mL), fascia (20 mL), fat (15 mL), and subcutaneous tissue (20 mL) before closure of the wound.

2.5. Standard care and intervention treatment: total knee replacement

In line with evidence-based guidance from PROSPECT (procedure specific postoperative pain management), standard anaesthetic care consisted of a femoral nerve block and a spinal or general anaesthetic, depending on patient factors. The intervention group received the same anaesthetic regime, plus an intraoperative local anaesthetic infiltration that consisted of 60 mL of 0.25% bupivacaine with 1 in 200,000 adrenaline. The local anaesthetic mixture was injected directly into the posterior capsule (25 mL), medial and lateral capsule (10 mL), fascia and muscle (10 mL), and subcutaneous tissues (15 mL), before wound closure. Full details of treatment in both arms are described in the protocol.

2.6. Outcomes and follow-up

Baseline data, including sociodemographics, were collected preoperatively before randomization, and outcomes were assessed during the postoperative inpatient stay, and at 3, 6, and 12 months postoperatively.

2.6.1. Primary outcome

The primary outcome was the self-completion Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Scale score at 12 months postoperative. The 5-item WOMAC Pain Scale is a widely used and validated measure of joint pain severity when performing daily activities. Scores were transformed onto a 0-to-100 scale, with lower scores indicating more severe pain.

2.6.2. Secondary outcomes

Secondary outcomes were collected during the postoperative inpatient stay, and at 3, 6, and 12 months postoperative. Pain severity on admission to and discharge from the recovery ward was rated on a 4-point Likert-type scale (none to severe). Pain severity for the remainder of the day of surgery was rated every 4 hours on a 0-to-10 scale (best to worst). On postoperative days 1 to 3, patients rated the severity of night pain, pain on movement, and pain at rest on a 100-mm visual analogue scale. Satisfaction with pain relief and occurrence of nausea and vomiting was collected daily during the in-patient stay. Length of hospital stay and postoperative analgesia use were extracted from medical records. At 3, 6, and 12 months postoperative, patients completed the WOMAC Function, Pain, and Stiffness subscales and the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire. The painDETECT questionnaire, a measure of neuropathic pain, was completed at 12 months postoperatively. Details of medical and surgical adverse events were recorded throughout the trial through review of medical records, patient self-report, and assessment by a research nurse.

2.6.3. Effect modifiers

Measures of possible effect modifiers included: sociodemographic factors, Functional Comorbidity Index, Kellgren and Lawrence osteoarthritis grading scheme, Hospital Anxiety and Depression Scale, Pain Self-Efficacy questionnaire, Illness Perceptions Questionnaire-Revised, and Brief COPE.
2.7. Sample size
A sample size of 300 patients in each trial provided 90% power to detect a difference of 0.5 SDs on the WOMAC Pain Scale at 12 months postoperative with a 2-sided 1% significance level, allowing for a 20% dropout rate. Previous research suggests SDs of approximately 17 on the WOMAC Pain Scale before surgery. Hence, a difference between the trial arms of 0.5 SDs equates to a difference of approximately 8 to 9 units on the WOMAC Pain Scale, which represents a minimal perceptible clinical improvement.7

2.8. Statistical analysis
The hip and knee trials were analysed separately and all analyses were undertaken in Stata 13.1.

2.8.1. Primary analyses
Following a predefined analysis plan agreed with the Trial Steering Committee, linear regressions were used to estimate between-group difference in mean WOMAC Pain scores at 12 months postoperative, adjusted for preoperative WOMAC Pain scores and surgical approach. All patients in their originally assigned groups with available primary outcome data (281 THR patients and 273 TKR patients) were included in the primary analyses (intention-to-treat complete cases, ITT-CC).

2.8.2. Sensitivity analyses
Analyses were repeated on all randomized 322 THR patients and 316 TKR patients using multiple imputation technique by chained equations under a missing at random framework (20 imputations for the THR trial, 25 imputations for the TKR trial) stratified by randomization arm to handle missing outcomes (intention-to-treat imputed, ITT-imputed). The analyses were also conducted on a per-protocol basis (266 THR patients and 259 TKR patients) (per-protocol-complete cases, PP). Also as sensitivity analyses, any potential unbalance in patients’ baseline characteristics was controlled for in the ITT-CC, ITT-imputed, and PP analyses.

2.8.3. Post hoc analyses
Patient-reported outcome measures such as the WOMAC Pain score are bounded (0-100), limiting the ability of the questionnaire to detect improvement beyond the bounds of the scoring. The resulting ceiling or floor effect can generate a nonnormally distributed score, especially if a substantial proportion of the sample is affected. This can impact the robustness of the coefficient SE, confidence intervals, and P values obtained from a linear regression (through violations of the assumptions of homoscedasticity and normality). To explore the potential impact of the ceiling effect on the intervention effect, 2 further sensitivity analyses were conducted. First, transformations of WOMAC Pain scores using appropriate functions to obtain a continuous primary outcome that could be modelled with a linear regression were investigated. Second, the scores were modelled as an ordered categorical variable using published threshold definitions (severe [0-50], moderate [51-75], mild [76-99], no [100] pain). These categories relate to the original ordinal WOMAC Pain scale, eg, a patient who reports no pain for every item will score 100, a patient who reports mild pain on all the items will score 75 and so forth. A partial proportional-odds regression was used to model this new outcome. The model automatically generates logical and systematic groupings of the outcome categories: category 1 vs 2 to 4; 1 to 2 vs 3 to 4; 1 to 3 vs 4. It then performs a series of binary logistic regressions on those different grouping within a single analytical framework. In our context, the model explored the probability of having none, mild, or moderate vs severe pain; the probability of having no or mild pain vs moderate or severe pain; and finally the probability of having no or mild pain vs no or mild pain (mild, moderate, severe). The model produced the odds ratio associated with the intervention effect for each of the outcome category groupings adjusted for the preoperative WOMAC Pain scores and surgical approach.

2.8.4. Secondary analyses
A similar strategy was used to analyse the secondary outcomes and is described in more detail in Web appendix 1 (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

3. Results
3.1. Participants
Between November 2009 and February 2012, 630 eligible patients listed for THR and 585 patients listed for TKR were approached to take part in the trial. For the THR trial, 322 (51%) patients were recruited and randomized, 163 to the intervention arm and 159 to the standard care arm (Fig. 1A). For the TKR trial, 316 (54%) were recruited and randomized, 157 to the intervention arm and 159 to the standard care arm (Fig. 1B). Primary outcome data were collected from 281 (87%) patients with THR and 273 (86%) patients with TKR. Baseline demographic and clinical characteristics were generally well balanced between the arms in both trials (Tables 1 and 2). In the THR trial, some differences between trial arms in gender, living arrangement, and comorbidities were observed. In the TKR trial, slight imbalances between arms in working status, comorbidities, anxiety, and depression were observed.

3.2. Total hip replacement
3.2.1. Primary analysis
The majority of patients in both trial arms had excellent pain relief at 12 months after surgery, with a median WOMAC Pain score in the intervention arm of 100 (interquartile range [IQR]: 10) and in the standard care arm of 95 (IQR: 20) (Fig. 1A). For the THR trial, 316 (54%) patients were recruited and randomized, 157 to the intervention arm and 159 to the standard care arm (Fig. 1B). Primary outcome data were collected from 281 (87%) patients with THR and 273 (86%) patients with TKR. Baseline demographic and clinical characteristics were generally well balanced between the arms in both trials (Tables 1 and 2). In the THR trial, some differences between trial arms in gender, living arrangement, and comorbidities were observed. In the TKR trial, slight imbalances between arms in working status, comorbidities, anxiety, and depression were observed.

3.2.2. Sensitivity analyses
The effect of the intervention was stronger in the ITT-imputed analysis (difference in means: 5.35; 95% CI: 1.33-9.34; P = 0.009; Table 3) than in the PP analysis (P = 0.051; Table 3 and Fig. 2). The between-group difference in mean WOMAC Pain scores remained after further adjustments for baseline imbalances between groups (ITT-CC: P = 0.022; ITT-imputed: P = 0.028; Fig. 2).
Appendix 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42), although the differences were less apparent in the adjusted PP analyses (Fig. 2 Web appendix 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

### 3.2.3. Post hoc analysis of the primary outcome

An important ceiling effect was observed, with approximately 41% of the THR trial participants reporting no pain at 12 months after surgery. As a result, several key assumptions underlying the use of linear regression (homoscedasticity and normality), the a priori
primary analysis, were strongly violated and remained so with different continuous transformations of the WOMAC Pain scores. The modelling of the categorical version of the WOMAC Pain scores with partial proportional-odds regressions confirmed an effect of the intervention. Patients in the intervention group were more likely to have no, mild, or moderate pain than severe pain at 12 months postoperative than those in the standard care group (odds ratio: 10.19; 95% CI: 2.10-49.55; \( P = 0.004 \); Table 4).
However, the likelihood of having no or mild pain rather than moderate or severe pain and the likelihood of having no pain rather than any level of pain was not different between the 2 groups. Therefore, the intervention only affected the likelihood of having severe pain. These findings remained after further adjustments for imbalances between groups (Web appendix 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

Table 1
Baseline characteristics of participants by trial arm for the total hip replacement and total knee replacement trial.

|                  | Hip Intervention (n = 163) | Standard care (n = 159) | Knee Intervention (n = 157) | Standard care (n = 159) |
|------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Age              | 66.0 (11.4)                 | 66.4 (10.2)             | 69.5 (6.4)                  | 68.7 (7.9)              |
| Body mass index  | 28.9 (5.6)                  | 29.4 (5.4)              | 32.4 (6.5)                  | 32.8 (6.5)              |
| Self-efficacy    | 35.6 (13.7)                 | 34.2 (13.3)             | 36.0 (13.4)                 | 37.3 (12.0)             |
| WOMAC Pain†      | 43.4 (19.0)                 | 41.5 (17.9)             | 42.5 (17.3)                 | 42.4 (16.1)             |
| WOMAC Function†  | 43.7 (20.2)                 | 41.2 (17.2)             | 46.1 (17.7)                 | 46.0 (17.9)             |
| WOMAC Stiffness† | 47.4 (24.9)                 | 42.6 (20.7)             | 41.9 (21.0)                 | 41.1 (19.4)             |

Data shown as mean (SD).
* Pain Self-Efficacy questionnaire; scores range from 0 to 60 (worst to best).
† Scores range from 0 to 100 (worst to best).

Table 2
Baseline characteristics of participants by trial arm for the total hip replacement and total knee replacement trial.

|                  | Hip Intervention (n = 163) | Standard care (n = 159) | Knee Intervention (n = 157) | Standard care (n = 159) |
|------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Female sex       | 86 (53)                     | 103 (65)                | 81 (52)                     | 86 (54)                 |
| Living arrangement |                              |                         |                             |                         |
| Live with someone| 110 (68)                    | 123 (77)                | 112 (71)                    | 103 (65)                |
| Live alone       | 43 (26)                     | 32 (20)                 | 41 (26)                     | 44 (28)                 |
| Missing          | 10 (6)                      | 4 (3)                   | 4 (3)                       | 12 (7)                  |
| Working status   |                              |                         |                             |                         |
| Paid employment  | 47 (29)                     | 52 (33)                 | 41 (26)                     | 27 (17)                 |
| Retired          | 104 (64)                    | 104 (65)                | 111 (71)                    | 117 (74)                |
| Missing          | 12 (7)                      | 3 (2)                   | 5 (3)                       | 15 (9)                  |
| Education        |                              |                         |                             |                         |
| Compulsory age   | 98 (60)                     | 108 (68)                | 115 (73)                    | 109 (69)                |
| College          | 34 (21)                     | 30 (19)                 | 26 (17)                     | 25 (16)                 |
| University       | 20 (12)                     | 17 (11)                 | 9 (6)                       | 10 (6)                  |
| Missing          | 11 (7)                      | 4 (2)                   | 7 (4)                       | 15 (9)                  |
| Comorbidities*   |                              |                         |                             |                         |
| 0                | 3 (2)                       | 3 (2)                   | 4 (3)                       | 1 (1)                   |
| 1-3              | 127 (78)                    | 122 (77)                | 108 (69)                    | 104 (66)                |
| 4 or more        | 21 (13)                     | 28 (18)                 | 38 (24)                     | 43 (27)                 |
| Missing          | 12 (7)                      | 6 (4)                   | 7 (5)                       | 11 (7)                  |
| Anxiety†         |                              |                         |                             |                         |
| Definite         | 26 (16)                     | 31 (19)                 | 33 (21)                     | 18 (11)                 |
| Potential        | 26 (16)                     | 23 (15)                 | 24 (15)                     | 32 (20)                 |
| None             | 100 (61)                    | 100 (63)                | 93 (59)                     | 99 (62)                 |
| Missing          | 11 (7)                      | 5 (3)                   | 7 (5)                       | 10 (6)                  |
| Depression‡      |                              |                         |                             |                         |
| Definite         | 20 (12)                     | 25 (16)                 | 30 (19)                     | 16 (10)                 |
| Potential        | 25 (15)                     | 28 (15)                 | 29 (19)                     | 30 (19)                 |
| None             | 106 (63)                    | 101 (63)                | 91 (58)                     | 104 (65)                |
| Missing          | 12 (7)                      | 5 (3)                   | 7 (4)                       | 9 (6)                   |
| Surgical approach|                              |                         |                             |                         |
| Posterior        | 151 (93)                    | 147 (92)                | 122 (78)                    | 125 (79)                |
| Lateral          | 12 (7)                      | 12 (8)                  | 35 (22)                     | 34 (21)                 |
| Medical parapatellar |                      |                         |                             |                         |
| Subvastus         |                              |                         |                             |                         |
| Kellgren and Lawrence grade‡ |                  |                         |                             |                         |
| <3               | 4 (3)                       | 8 (4)                   | 1 (1)                       | 3 (2)                   |
| ≥3               | 136 (83)                    | 128 (81)                | 133 (84)                    | 133 (84)                |
| Noninterpretable | 12 (7)                      | 12 (8)                  | 1 (1)                       | 5 (3)                   |
| Missing          | 11 (7)                      | 11 (7)                  | 22 (14)                     | 17 (11)                 |

Data shown as n (%).
* Functional Comorbidity Index.
† Hospital Anxiety and Depression Scale. Scores of 0 to 7 = no anxiety or depression, 8 to 10 = potential anxiety or depression, >10 = definite anxiety or depression.
‡ Grades range from 0 to 4 (normal joint to severe osteoarthritis).
3.2.4. Secondary outcomes

There was no strong evidence of an effect of the intervention on any of the secondary outcomes (Web appendix 3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42), with the exception of neuropathic pain assessed by the painDETECT questionnaire. At 12 months postoperative, patients in the intervention arm reported significantly less neuropathic pain than patients in the standard care arm (ITT-CC relative risk: 0.17; 95% CI: 0.04-0.76; \( P = 0.021 \); Web Appendix 3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42, Table 12a). These findings were similar in the ITT-imputed and PP analyses, and after further adjustments for baseline imbalances between groups.

3.2.5. Safety data

Postsurgical superficial and deep wound infection rates were similar in the intervention group and standard care group (1.8% vs 1.9%; \( P = 1.000 \)). There were no differences in rates of serious adverse events between groups (Web appendix 4, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

3.3. Total knee replacement

3.3.1. Primary analyses

The majority of patients in both trial arms had good pain relief at 12 months after surgery, with a median WOMAC Pain score in the intervention group of 90 (IQR: 30) and in the standard care group of 85 (IQR: 35; Web appendix 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42, Table 12a). These findings were similar in the ITT-imputed and PP analyses, and after further adjustments for baseline imbalances between groups.

Table 3

|            | Hip | 95% CI          | P    | Knee | 95% CI          | P    |
|------------|-----|-----------------|------|------|-----------------|------|
| ITT-CC†    | 4.74| 0.95 to 8.54    | 0.015| 3.83 | −0.83 to 8.49   | 0.107|
| ITT-imputed‡§ | 5.35| 1.33 to 9.34    | 0.009| 3.33 | −1.21 to 7.88   | 0.150|
| PP‖        | 3.81| −0.02 to 7.63   | 0.051| 4.21 | −0.66 to 9.09   | 0.090|

Linear regression adjusted for preoperative pain score and surgical approach.

* \( n = 281 \).
† \( n = 273 \).
‡ \( n = 322 \).
§ \( n = 316 \).
‖ \( n = 266 \).
‡‡ \( n = 259 \).
CI, confidence interval; ITT-CC, intention-to-treat complete cases analysis; ITT-imputed, intention-to-treat with imputed information analysis; PP, per-protocol analysis.

| Figure 2. Mean difference and 95% confidence interval in WOMAC Pain score on a 0-to-100 scale for the effect of local anaesthetic wound infiltration in those randomized to treatment vs standard care. Three analytic models were used: (1) intention to treat with complete case (ITT-CC), (2) intention to treat with missing follow-up data imputed (ITT-imputed), and (3) a per-protocol approach (PP). The primary analysis (Primary) (solid lines) was adjusted for preoperative pain score and surgical approach, and further analyses (Adjusted) (dashed lines) were additionally adjusted for minor imbalances in baseline characteristics. \( P \) values are presented for analyses reaching nominal significance \( P < 0.05 \). |
Although they are effective in the management of chronic pain after THR and TKR, there was no strong evidence of an effect of the intervention on chronic pain after TKR (Table 3). There were no differences in rates of serious adverse events between groups (Web appendix 4, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

### 3.3.5. Safety data

Postsurgical superficial and deep wound infection rates were similar in the intervention group and standard care group (3.2% vs 1.9%; \( P = 0.500 \)). There were no differences in rates of serious adverse events between groups (Web appendix 4, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A42).

### 4. Discussion

This article reports the findings of the first large double-blind RCTs with allocation concealment designed to investigate the effectiveness of local anaesthetic infiltration at reducing chronic pain at 12 months after THR and TKR. These trials found some evidence that local anaesthetic wound infiltration can reduce pain severity at 12 months after THR, although the evidence was less clear for TKR. In the a priori analysis of the primary outcome, we found a 4 to 5 point difference in the mean WOMAC Pain score between patients in the intervention and standard care group of the THR trial and a 3- to 4-point difference in the TKR trial. The minimally clinically important difference on the 100-point WOMAC Pain scale is 8 to 9 points. Therefore, it could be argued that there is little evidence to support the use of infiltration for long-term pain relief, because although the results were statistically significant in the THR trial, the benefit will not be clinically meaningful. However, it is important to interpret these results in the context of outcomes after joint replacement. The majority of patients report little or no pain after joint replacement. Therefore, this intervention can only improve the outcome of the patients who would otherwise experience an unfavourable long-term pain outcome, which the literature suggests is approximately 10% of patients with THR and 20% of patients with TKR. Our post hoc analysis of the WOMAC Pain score highlighted the potential of local wound infiltration to reduce the number of patients with severe pain after THR.

The findings from these trials suggest that local anaesthetic infiltration could be beneficial in reducing long-term pain severity after THR for some patients. We also found evidence that the intervention reduces neuropathic pain at 12 months after THR, indicating that infiltration could benefit those patients who may otherwise experience the most severe long-term pain outcome, which the literature suggests is approximately 10% of patients with THR and 20% of patients with TKR. Our post hoc analysis of the WOMAC Pain score highlighted the potential of local wound infiltration to reduce the number of patients with severe pain after THR.

The lack of an effect of the intervention on chronic pain after TKR could be due to the use of femoral nerve block within the trial. Femoral nerve block is a well-established method of providing analgesia after TKR and in our centre is included in the multimodal anaesthesia regimen provided as part of standard care. Consistent with our findings, 2 small RCTs with short-term follow-up showed limited additional pain relief for local anaesthetic infiltration when used in conjunction with a femoral nerve block. Although they are effective in the management of chronic pain after THR, the benefits of femoral nerve block are limited due to the higher frequency of complications.
Future research should evaluate the long-term effectiveness of local anaesthetic infiltration vs femoral nerve blocks after TKR surgery.

Strengths of these trials include the long-term postoperative follow-up, use of robust and validated outcome measures, good rates of data collection for the primary outcome measure, and use of an independent allocation system and blinding to minimise bias. The sample is representative of the population undergoing THR and TKR, with a similar disease profile, gender mix and age range as reported by the National Joint Registry of England and Wales and other national registries, and thus we believe the results to be generalisable. However, it is also important to acknowledge the limitations of these trials when interpreting the results. A large number of patients in both trials reported no pain on the WOMAC Pain Scale at 12 months postoperative; the resulting skewness of the data violated the assumptions of our a priori linear regression, and therefore we conducted post hoc analysis of the primary outcome using a categorical version of the WOMAC Pain scores. In this analysis, the number of patients with severe chronic pain was small, and the wide 95% confidence intervals for the odds ratios highlight that the results should be interpreted with caution. It is also important to acknowledge that the trials were not powered for the analyses of the primary outcome as categorical variables or to detect differences in the treatment effect for the secondary outcomes.

For many patients, THR and TKR is an effective treatment for painful osteoarthritis, and additional interventions to improve pain relief are not required. However, a sizeable proportion of people report chronic postsurgical pain. Preoperative identification of patients at high risk of a poor outcome has proved challenging, and until better predictive models can be developed, it is unfeasible to target interventions at high-risk patients. Easily implementable and cost-effective interventions that can be administered to all patients undergoing joint replacement are needed to reduce the number of patients with chronic pain after surgery. Findings of our trials suggest that local anaesthetic infiltration is beneficial for decreasing long-term pain in patients with THR, although further research is required to determine whether the intervention is also beneficial for patients undergoing TKR. Given that approximately 80,000 THR operations are performed annually in England and Wales, and 7% to 23% of patients are likely to develop severe chronic postsurgical pain, our findings suggest that routine use of local anaesthetic infiltration has the potential to improve pain outcomes for between 4600 and 15,300 patients every year. A full economic evaluation of the cost-effectiveness of this intervention within the APEX trials will be reported in a future publication.

In conclusion, these trials provide evidence that local anaesthetic infiltration reduces chronic pain at 1 year after THR, suggesting that the routine use of infiltration could improve long-term pain relief.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A42.

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