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A pragmatic randomised controlled trial comparing the efficacy of a femoral nerve block and periarticular infiltration for early pain relief following total knee arthroplasty

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Aims

The aim of this study was to compare the effectiveness of a femoral nerve block and a periarticular infiltration in the management of early post-operative pain after total knee arthroplasty (TKA).

Patients and Methods

A pragmatic, single centre, two arm parallel group, patient blinded, randomised controlled trial was undertaken. All patients due for TKA were eligible. Exclusion criteria included contraindications to the medications involved in the study and patients with a neurological abnormality of the lower limb. Patients received either a femoral nerve block with 75 mg of 0.25% levobupivacaine hydrochloride around the nerve, or periarticular infiltration with 150 mg of 0.25% levobupivacaine hydrochloride, 10 mg morphine sulphate, 30 mg ketorolac trometamol and 0.25 mg of adrenaline all diluted with 0.9% saline to make a volume of 150 ml.

Results

A total of 264 patients were recruited and data from 230 (88%) were available for the primary analysis. Intention-to-treat analysis of the primary outcome measure of a visual analogue score for pain on the first post-operative day, prior to physiotherapy, was similar in both groups. The mean difference was -0.7 (95% confidence interval (CI) -5.9 to 4.5; p = 0.834). The periarticular group used less morphine in the first post-operative day compared with the femoral nerve block group (74%, 95% CI 55 to 99). The femoral nerve block group reported 39 adverse events, of which 27 were serious, in 31 patients and the periarticular group reported 51 adverse events, of which 38 were serious, in 42 patients up to six weeks post-operatively. None of the adverse events were directly attributed to either of the interventions under investigation.

Conclusion

Periarticular infiltration is a viable and safe alternative to femoral nerve block for the early post-operative relief of pain following TKA.

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About 93 000 total knee arthroplasties (TKAs) were performed by surgeons in the NHS in the United Kingdom in 2014; a 200% increase since 2004.[1] There may be severe pain in the early post-operative period after this operation.[2] A femoral nerve block, as a single routine peri-operative infiltration of local anaesthetic, improves the control of pain and reduces the need for systemic analgesics such as opiates.[2,3] However, it does not provide analgesic effects to the posterior aspect of the knee joint, which is supplied by the sciatic nerve, and so pain relief is often incomplete. A femoral nerve block may occasionally be associated with serious complications, including damage to the adjacent major blood vessels and to the nerve itself.[2] It also temporally impairs quadriceps muscle function leading to limited extension of the knee and falls post-operatively.[2,4] Alternative analgesic regimes include an adductor canal block, but this also does not provide analgesic effects to the back of the knee.[5]

A popular alternative approach is the intra-operative periarticular infiltration of analgesic agents including local anaesthetics, opiates and non-steroidal anti-inflammatory drugs, which may be delivered directly to the sources of pain, reducing the risk of systemic side effects.[6] Periarticular infiltration can be administered by the operating surgeon without specialist equipment, compared with a femoral nerve block which requires ultrasound or a nerve stimulator or both to be administered safely.

Periarticular infiltration does not inhibit quadriceps function and can provide analgesia to the whole of the knee joint.[2] However, there is little evidence to support its routine use in the management of early post-operative pain.[2,7,8]

We report a randomised controlled trial (RCT) comparing the use of a femoral nerve block and periarticular infiltration in patients undergoing TKA to establish the most effective management of early post-operative pain.

Patients and Methods

This was a single centre, two arm parallel group RCT undertaken at the University Hospitals Coventry and Warwickshire NHS Trust, Hospital of St. Cross, Rugby. Patients were recruited between December 2013 and October 2015. All those undergoing primary unilateral TKA were eligible. Exclusion criteria were:

- concomitant medical or psychiatric problems which would interfere with treatment or follow-up;
- a neurological abnormality in the ipsilateral leg, e.g. history of stroke, neurogenic pain or previous nerve pain;
- a specific contraindication to the analgesic agents used;
- participation in a clinical trial involving a pharmaceutical product during the previous 90 days;
- previous entry in the present trial;
- an inability to adhere to any procedure involved in the trial.

Patients were allocated to treatment by a remote telephone 1:1 randomisation service using a computer-generated schedule with randomised blocks and stratified by type of anaesthetic (general or spinal). The sizes of the blocks were randomly chosen to ensure concealment. Randomisation was undertaken by an independent member of the operating theatre staff on the day of surgery after a spinal anaesthetic with sedation or a general anaesthetic had been administered.

All patients attended a routine pre-operative TKA education class. Unless contraindicated, they were given gabapentin as premedication and received either a spinal anaesthetic with sedation or a general anaesthetic. After randomisation, they were allocated to receive either femoral nerve block or periarticular infiltration. The femoral nerve block technique involved identification of the femoral nerve below the inguinal ligament using nerve stimulation and/or ultrasound, according to the anaesthetist's normal practice, and infiltration of 75 mg of 0.25% levobupivacaine hydrochloride around the nerve. Periarticular infiltration involved 150 mg of 0.25% levobupivacaine hydrochloride, 10 mg morphine sulphate, 30 mg ketorolac trometamol and 0.25 mg of adrenaline, all diluted with 0.9% saline to make a volume of 150 ml. This was infiltrated into the skin and soft tissues of the knee by the surgeon. The zones of infiltration included the medial, lateral, suprapatellar and posterior soft tissues. Surgeons were advised to infiltrate roughly equal quantities to all four zones.

The remainder of the operation was performed according to the surgeons' routine practice. All patients followed the same routine post-operative pathway unless they had specific contraindications. All received regular paracetamol, ibuprofen and gabapentin and morphine sulphate sustained release. Oramorph was administered as required. Routine thromboprophylaxis included intermittent positive pressure calf compression until mobile and subcutaneous low molecular heparin for 14 days post-operatively.

The fidelity with which both interventions were delivered was reviewed by an independent clinician (TC). The results were relayed to those delivering the interventions in order to maintain compliance with the protocol.

The primary outcome measure was a 100 visual analogue score (VAS) of pain reported by the patient on the first day post-operatively and before the start of physiotherapy, with 0 being no pain and 100 being the worst pain. This has been validated for the assessment of pain after TKA.[8] The primary endpoint was chosen after feedback from the patient indicating adequate pain relief on the first post-operative day prior to physiotherapy, and was of principal importance to the study population; this is consistent with other smaller RCTs which have also used this time point.[9-11]

The secondary outcome measures are described below. Pain after physiotherapy on the first post-operative day and pain before and after physiotherapy on the second post-operative day, was assessed using the same VAS as the primary outcome. Functional assessment was carried out by a physiotherapist using straight leg raise and range of movement of the knee, and the ability to transfer from bed to chair and the time taken to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down (timed up and go).[12] Total opiate, paracetamol, ibuprofen and gabapentin analgesia used up to 24 and 48 hours post-operatively were recorded. All opiates were converted to a morphine equivalent dose using a multiplication conversion factor of 0.1 for codeine and tramadol, as outlined in the British National Formulary.[13] The Oxford Knee Score (OKS),[14] EuroQol (EQ-5D-5L),[15-17] and Douleur Neuropathic Pain (DN2) score[18,19] were taken six weeks post-operatively. The OKS is a validated self-administered outcome measure.[14] The EQ-5D-5L is a validated measure of health-related quality of life, consisting of five dimensions and a separate VAS.[15,16] The values were calculated using the 3L crosswalk value sets.[17] The DN2 assesses neuropathic pain using two questions.[18,19] Adverse events (AEs) up to six weeks post-operatively were recorded. An AE was defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with the treatment. They were further classified into serious adverse events (SAEs) if they fulfilled any of the following criteria: were immediately life-threatening, required hospitalisation or prolongation of the existing hospitalisation, resulted in persistent or significant disability or incapacity or were regarded by the study team as an important medical condition.

Although not reported in this study, patients were followed up at up to 12 months with OKS, EQ-5D-5L, DN2

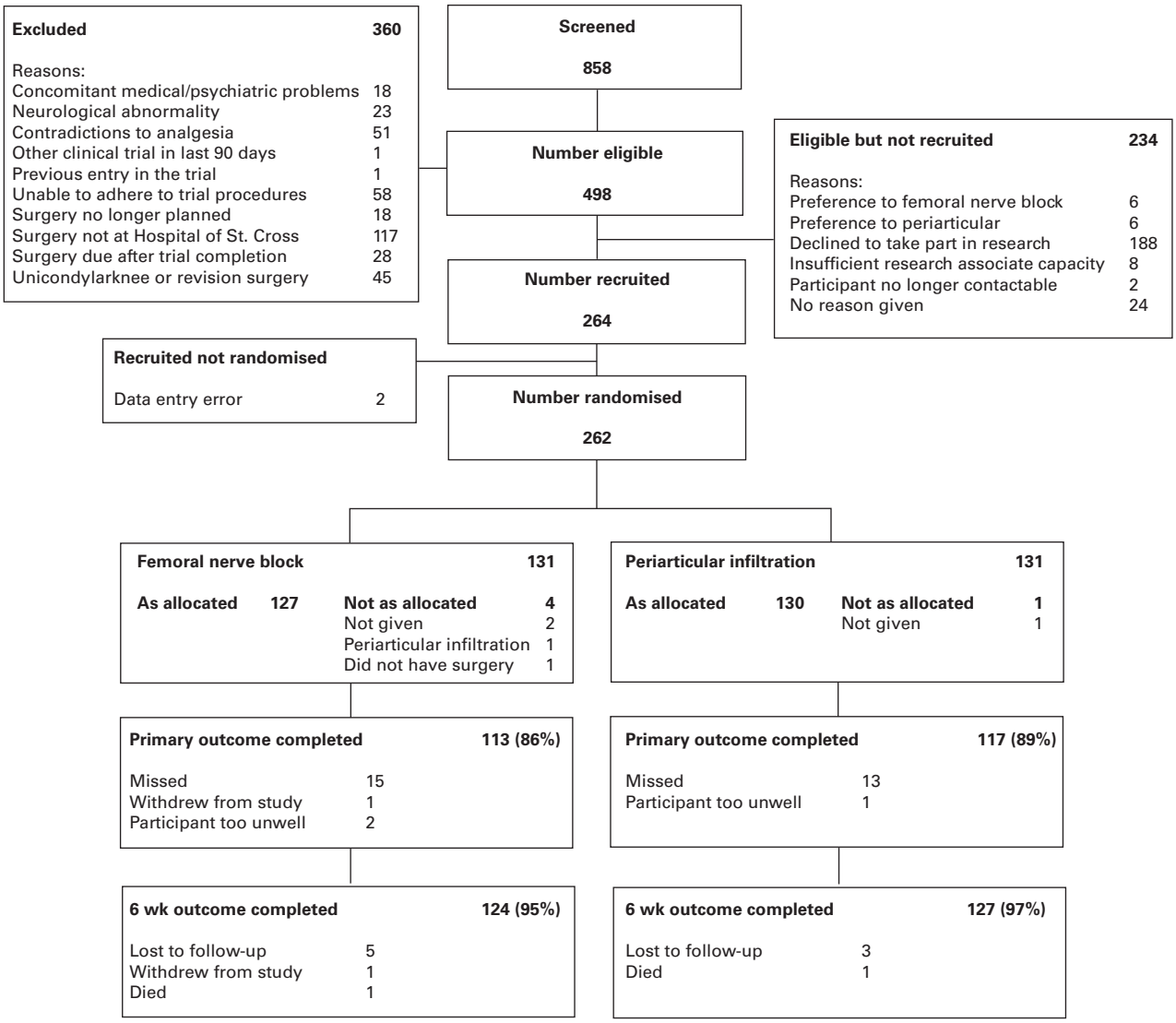

Fig. 1

Overall flow of patients within the trial.

and AEs being recorded.[20] These additional data are being used to help inform the design of a further trial examining chronic pain after TKA.

Patients were blind to the intervention to which they were allocated. Concealment was maintained by ensuring randomisation was performed after spinal anaesthesia and sedation or general anaesthesia and then administered within a sterile zone with drapes to prevent the patients from seeing which intervention they received. In addition, in order to ensure post-operative concealment, all patients had a standard dressing applied to the area where a femoral nerve block is usually performed. It was not possible to blind the surgeon and anaesthetist delivering the interventions to the treatment options. Outcome data were collected by independent physiotherapists who were blinded to the allocation of treatment.

The protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines[21] and published *a priori*.[19] Statutory NHS research and ethical approval was obtained on 23 September 2013, reference 13/WM/0316. The trial was conducted in accordance with the Medicines for Human use (Clinical Trials) Regulations 2004, the International Conference on Harmonisation Good Clinical Practice and reported in line with the Consolidated Standards of Reporting Trials statement.[22]

Patients were consulted during their routine clinical appointments to determine if the research question was important to them and those in a successful pilot trial were asked to provide feedback on the processes of the trial.[21] A small number of those in the pilot trial helped to develop the full proposal including the choice of primary outcome measure. One of the patients who was in the trial steering

Table I. The baseline characteristics of the patients

Patient characteristic	Femoral nerve block (n = 131)	Periarticular (n = 131)
Gender, male, n (%)	51 (*38.9*)	54 (*41.2*)
Age (yrs), mean (SD)	68.2 (10.0)	68.7 (9.6)
Weight (kg), mean (SD)	82.0 (17.2)	83.2 (17.6)
Smoker, yes, n (%)	13 (*10.2*)	10 (*7.8*)
Oxford Knee Score, mean (SD)	23.0 (6.8)	23.5 (7.9)
EuroQol-5D-5L, mean (SD)	0.5 (0.2)	0.5 (0.2)
Received spinal anaesthetic (remainder received general anaesthetic), n (%)	78 (*48*)	86 (*52*)

SD, standard deviation

Table II. Main outcomes (excluding analgesia use and adverse events)

Outcome		FNB	PI	Valid responses FNB	Valid responses PI	p-value	Treatment difference (95% CI)
Pain score day 1 pre-physio		44.1 (23.0)	43.2 (24.9)	113	117	0.770	-0.9 (-5.3 to 7.2)
Pain score day 1 pre-physio; per protocol		43.7 (23.5)	43.7 (24.6)	112	116	0.990	0.04 (-6.2 to 6.3)
Pain score day 1 after physio		49.0 (22.4)	51.7 (22.0)	108	111	0.371	-2.7 (-8.6 to 3.2)
Pain score day 2 before physio		40.8 (26.4)	38.1 (24.3)	107	102	0.435	2.7 (-4.2 to 9.7)
Pain score day 2 after physio		43.3 (24.1)	41.5 (22.6)	100	98	0.591	1.8 (-4.8 to 8.3)
Able to straight leg raise day 1, n (%)		50 (*42.4*)	61 (*51.7*)	118	118	0.192	-9.3 (-22.8 to 4.2)
Able to straight leg raise day 2, n (%)		44 (*41.1*)	53 (*50.5*)	100	105	0.219	-9.4 (-0.23.7 to 4.9)
Knee ROM day 1	Extension (°)	-5.4° (7.4°)	-3.5° (12.9°)	118	117	0.174	-1.7 (-4.6 to 0.8)
	Flexion (°)	67.4° (18.2°)	72.8° (40.9°)	118	117	0.197	-5.4 (-13.5 to 2.8)
Knee ROM day 2	Extension (°)	-4.6° (6.4°)	-4.8° (5.6°)	111	103	0.848	0.1 (-1.4 to 1.8)
	Flexion (°)	73.6° (14.2°)	79.0° (13.6°)	110	103	0.005*	-5.4 (-9.1 to -1.6)
Ability to transfer day 1	No. independent (%)	44 (*36.1*)	51 (*43.6*)	122	117	0.069	-7.5 (-20.7 to 5.7)
	No. assistance of 1 (%)	42 (*34.4*)	47 (*40.2*)				-5.8 (-18.8 to 7.3)
	No. assistance of 2 (%)	15 (*12.3*)	5 (*4.3*)				8.0 (0.3 to 15.7)
	No. unable (%)	21 (*17.2*)	14 (*12.0*)				5.2 (-4.5 to 15.0)
Ability to transfer day 2	No. independent (%)	69 (*62.7*)	76 (*72.4*)	110	105	0.254†	-9.7 (-23.0 to 3.7)
	No. assistance of 1 (%)	30 (*27.3*)	19 (*18.1*)				9.2 (-2.9 to 21.2)
	No. assistance of 2 (%)	6 (*5.5*)	6 (*5.7*)				-0.2 (-6.7 to 6.1)
	No. unable (%)	5 (*4.5*)	4 (*3.8*)				1.6 (-5.3 to 6.8)
Timed up and go day 1	Time of those able in seconds	99.3 (51.8)	92.8 (41.8)	61	70	0.436	6.5 (-10.0 to 22.9)
	No. unable (%)	53 (*46.5*)	40 (*36.4*)	114	110	0.161	10.1 (-3.6 to 23.9)
Timed up and go day 2	Time of those able in seconds	89.8 (65.8)	73.3 (41.3)	85	90	0.051	16.4 (-0.1 to 33.0)
	No. unable (%)	20 (*19.0*)	14 (*13.3*)	105	105	0.349	-13.1 (-5.2 to 16.6)
OKS at 6 wks		31.0 (7.2)	31.4 (8.2)	120	125	0.673	-0.4 (-2.4 to 1.5)
EQ-5D-5L at 6 wks		0.8 (0.2)	0.8 (0.2)	122	123	0.670	-0.01 (-0.06 to 0.04)
DN2 at 6 wks		2.0 (1.6)	1.7 (1.4)	102	108	0.118	0.4 (-0.04 to 0.77)

*< 0.05 therefore reached significance
†to conduct chi-squared test, due to small cell counts "assistance of 2" and "unable" responses have been combined. For continuous outcomes, means (standard deviations) are reported and were compared using *t*-tests. For count outcomes, number (percentage valid) are reported and were compared using chi-squared tests. Analyses are intention-to-treat unless stated
FNB, femoral nerve block; PI, periarticular infiltration; CI, confidence interval; physio, physiotherapy; ROM, range of movement; OKS, Oxford Knee Score; EQ-5D-5L, EuroQol-5D-5L; DN2, Douleur Neuropathic Pain score

group was active in overseeing the running of the trial and the ways of disseminating the results.

Sample size and analysis plan. The available literature suggested a difference in the VAS for pain between the groups of 12 mm (95% confidence interval (CI) 9 to 15) to be the minimum clinically important difference (MCID).[23] Based on pilot data, the standard deviation (SD) for VAS for pain was 30 mm.[24] Therefore, to test the null hypothesis of equality of the means of the treatment groups, assuming approximate normality for the VAS, primary outcome data for 264 patients (132 in each arm) were required for 90% power and 5% significance.

Initial analysis investigated differences in the primary outcome scores on an intention-to-treat basis using an independent samples *t*-test. This was augmented with linear regression analysis that adjusted for age, gender and type of anaesthetic. Tests were two-sided and considered to provide evidence for a significant difference at $p < 0.05$. Estimates of treatment effects were presented with 95% CIs. For continuous approximately normally distributed secondary outcome measures (e.g. OKS, EQ-5D-5L), data were analysed in a similar manner to the primary outcome. In hospital medication variables were log transformed prior to testing in order to improve the approximation of the normal distribution. Data, such as adverse events, were compared between groups using chi-squared tests.

Some data were not available due to the voluntary withdrawal of patients, lack of completion of individual items or loss to follow-up. Where possible, the reasons for missing data were determined and reported. All analysis pre-

Table III. Analgesic use up to 24 and 48 hours (log transformed treatment difference)

Analgesia type and timing		FNB (n = 125)	PI (n = 120)	p-value (transformed *t*-test)	Treatment difference, % of FNB (95% CI)
Paracetamol (mg), mean (SD)	Up to 24 hrs	3524 (689.4)	3533 (620.8)	0.338	82 (50 to 122)
	24 to 48 hrs	3720 (929.8)	3791 (818.9)	0.817	94 (55 to 149)
Ibuprofen (mg), mean (SD)	Up to 24 hrs	332 (492.7)	265 (436.3)	0.285	67 (30 to 103)
	24 to 48 hrs	340.6 (531.8)	301.7 (520.5)	0.309	67 (55 to 103)
Morphine equivalent dose (mg), mean (SD)	Up to 24 hrs	62.7 (39.7)	54.8 (39.8)	0.042*	74 (55 to 99)
	24 to 48 hrs	40.0 (44.4)	32.5 (28.1)	0.203	82 (55 to 111)
Gabapentin (mg), mean (SD)	Up to 24 hrs	492 (354.3)	522 (397.3)	0.835	106 (61 to 182)
	24 to 48 hrs	522.2 (384.7)	580.0 (419.2)	0.671	110 (61 to 201)

*p < 0.05
FNB, femoral nerve block; PI, periarticular infiltration; CI, confidence interval; SD, standard deviation

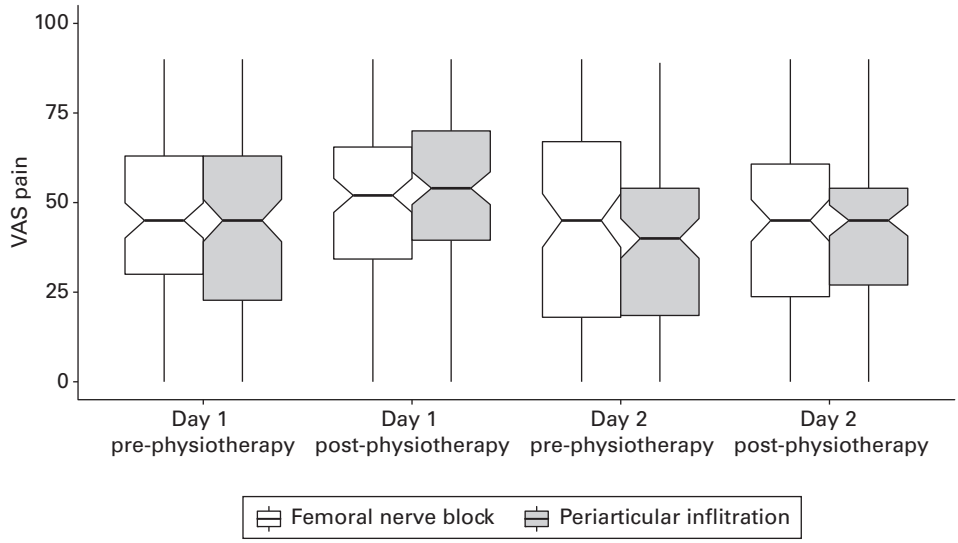

Fig. 2

Box plots of visual analogue pain scores (VAS) on day 1 and 2.

sented are based on complete cases. The analysis was implemented using the software package R (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 264 patients were recruited between March 2014 and November 2015 and, of these, 262 were randomised. Two patients were not randomised due to an error of data entry. Figure 1 shows the flow of patients through the trial. Baseline characteristics including age, gender, OKS and EQ-5D-5L were similar in both groups (Table I).

A total of 59 anaesthetists performed the femoral nerve blocks (median, three per anaesthetist, interquartile range (IQR) 1 to 7; three operation notes did not name the anaesthetist) and 33 surgeons performed the periarticular infiltrations (median, four per surgeon, IQR 2 to 11).

The main outcomes are shown in Table II.

On an intention-to-treat primary analysis, the mean difference between groups was not statistically significant; -0.9 (p = 0.770, 95% CI -5.3 to 7.2). Using multiple linear regression analysis to adjust for age, gender and type of anaesthetic, the mean difference between groups was not statistically significant: -0.7 (p = 0.834, 95% CI -5.9 to 4.5).

The results of the secondary analysis are shown in Tables II and III.

On the first post-operative day, after physiotherapy, the mean pain scores increased in both groups, (femoral nerve block group, 49; periarticular group, 52), however, there was no statistically significant difference between groups; -2.7 (p = 0.371, 95% CI -8.6 to 3.2). The mean differences in pain scores on the second post-operative day, both before and after physiotherapy, were also not statistically different between the groups, 2.7 (p = 0.435, 95% CI -4.2 to 9.7) and 1.8 (p = 0.591, 95% CI -4.8 to 8.3), respectively. Figure 2 shows the pain scores on the first and second post-operative days as box plots.

The proportion of patients able to transfer from bed to chair independently on the first post-operative day (treatment difference -7.5%; p = 0.069, 95% CI -20.7 to 5.7) and the mean time in seconds to get up and go on the second

Table IV. Reported adverse events within six weeks of surgery

Adverse event within 6 wks	FNB	PI	Odds ratio of adverse events (95% CI)*	p-value†
Death	1	1	1 (0.0 to 79.0)	1
Cement syndrome (peri-operative hypotension)	0	1	-	-
Deep wound infection undergoing revision	0	1	-	-
Superficial wound infection	6	9	0.7 (0.2 to 2.1)	0.596
Leaking wound no infection	0	1	-	-
Knee instability undergoing revision	0	1	-	-
Wound haematoma	0	1	-	-
Reduced early ROM (physio only)	1	1	1 (0.0 to 79.0)	1
Reduced early ROM (requiring manipulation)	2	2	1 (0.1 to 14.0)	1
Leg paraesthesia	1	1	1 (0.0 to 79.0)	1
Foot drop	0	1	-	-
Morphine overdose	1	3	0.3 (0.006 to 4.2)	0.622
Acute kidney injury	3	6	0.5 (0.1 to 2.4)	0.500
Chest Infection	6	2	3.1 (0.5 to 31.8)	0.281
Leg swelling (no deep vein thrombosis)	2	2	1 (0.1 to 14.0)	1
Pulmonary embolism	1	0	-	-
Atrial fibrillation	1	0	-	-
Symptomatic anaemia requiring blood transfusion	1	3	0.3 (0.0 to 4.2)	0.622
Bleeding gastric ulcer	1	1	-	-
Vomiting	1	0	-	-
Gastroenteritis	0	1	-	-
Urinary tract infection	1	0	-	-
Urinary retention	1	2	0.5 (0.0 to 9.7)	1
Small bowel obstruction	0	1	-	-
Exacerbation of asthma	1	0	-	-
Leg rash	2	2	1 (0.1 to 14.0)	1
Shingles	1	0	-	-
Leg skin tear	1	0	-	-
Pressure sore	1	0	-	-
Dehydration	1	0	-	-
Admission to manage pain	1	1	1 (0.0 to 79.0)	1
Admission to remove skin clips	0	1	-	-
Admission no cause found	0	1	-	-
General malaise (no cause found)	1	3	0.3 (0.0 to 4.2)	0.622
Back pain	1	0	-	-
Total	**39**	**51**	**0.7 (0.4 to 1.1)**	**0.152**
Classified as serious adverse event	**27**	**38**	**0.6 (0.3 to 1.2)**	**0.152**

*if only one adverse event, odds ratio not calculated
†Fisher's exact test
FNB, femoral nerve block; PI, periarticular infiltration; CI, confidence interval; ROM, range of movement

post-operative day (treatment difference 16.4 seconds; p = 0.051, 95% CI -0.1 to 33.0), were both marginally in favour of periarticular infiltration and had borderline statistical significance. The mean flexion of the knee on the second post-operative day was better in the periarticular group, however the difference between the groups was small at -5.4° (p = 0.005, 95% CI -9.1 to -1.6). Amongst the remaining functional outcomes on the first and second post-operative days, there was no significant difference between groups: the ability to straight leg raise (day 1 p = 0.192 and day 2 p = 0.219), the ability to transfer independently (day 1 p = 0.069 and day 2 p = 0.254) and timed up and go (day 1 p = 0.161 and day 2 p = 0.349).

There was no statistically significant difference in the total use of analgesia up to 24 and 48 hours post-operatively for paracetamol (p = 0.338 and 0.817, respectively), ibuprofen (p = 0.285 and 0.309, respectively) or gabapentin (p = 0.835 and 0.671, respectively) which were given routinely. However, the requirement for morphine, which was administered according to requirement, was less up to 24 hours post-operatively in those receiving periarticular infiltration (74% of the total dose given in the femoral nerve block group, p = 0.042, 95% CI 55 to 99). At 48 hours there was no statistically significant difference in the equivalent dose of morphine (p = 0.203) (Table III).

At six weeks post-operatively, there was no statistically significant differences in mean OKS (-0.4, p = 0.673, 95% CI -2.4 to 1.5), EQ-5D-5L (-0.01, p = 0.670, 95% CI -0.06 to 0.04) or DN2 scores (0.4, p = 0.118, 95% CI -0.04 to 0.77).

There were two deaths during the trial. One patient who had been allocated to and received periarticular infiltration died of a myocardial infarction (Table IV). One patient who had been allocated to and received a femoral nerve block died of sepsis. There were 39 AEs, of which 27 were SAE, amongst 31 patients in the femoral nerve block group, and

51 AEs, of which 38 were SAEs, amongst 42 patients in the periarticular infiltration group (Table IV). The most frequent AEs were: superficial wound infection (15), acute renal failure (nine) and chest infection (eight). None were related to the type of anaesthetic under investigation.

Following the primary analysis, we did a *post hoc* per protocol analysis for equivalence of outcome. This also revealed that the mean difference between the groups was not statistically significant 0.04 (95%CI -6.2 to 6.3, p = 0.990).

Discussion

This trial shows that pain scores on the day after TKA are the same in patients who have had a femoral nerve block and those who have had periarticular infiltration of local anaesthetic. It was not designed to show equivalence in outcomes; however, the 95% CIs for the difference between the groups in the per protocol analysis were only just over half of the pre-specified MCID. We can, therefore be confident that we have excluded a clinically important difference in pain scores on the first post-operative day between the two interventions.

Although the pain scores were similar in the two groups, the use of morphine up to 24 hours post-operatively was less in the periarticular group. Although morphine is an effective supplementary analgesic for post-operative pain, dose dependent systemic side effects, including nausea, vomiting, respiratory depression, pruritus, reduced gut mobility and urinary retention mean that lower doses are preferable.[25]

Two other early functional secondary outcomes had borderline significant differences between the groups (the ability to transfer independently on day 1 and the flexion of the knee on day 2) and both were in favour of periarticular infiltration. Although caution is needed in interpreting the relevance of the secondary observations, these and the primary outcome findings support the suggestion that periarticular infiltration is a good alternative to femoral nerve block. Both are designed to provide early analgesia and by six weeks we found no difference in PROMs between the groups.

None of the AEs were directly attributed to either of the interventions and the frequency of AEs was similar in both treatment groups, and were comparable with those reported in the literature, suggesting that periarticular infiltration does not pose an additional risk to the patients.[26-28]

Periarticular infiltration has previously been compared with femoral nerve block for early pain relief following TKA in three small RCTs including, in total, 181 patients.[9-11] However, meta-analyses by Marques et al[8] and Albrecht et al[29] and a Cochrane Review by Chan et al[2] of these RCTs have been unable to draw firm conclusions about the comparative effectiveness of these interventions, largely because of a lack of statistical power and moderate quality (GRADE)[30] evidence. Our results now show that periarticular infiltration offers comparable early pain relief, and safety. Patients and clinicians should therefore consider other factors including the availability of specialist equipment such as a nerve stimulator or ultrasound for administering the femoral nerve block, and any specific contraindications when making a preference for either intervention.

The main strengths of this trial are the blinded assessment of outcome and its pragmatic design. It followed a published protocol and included an intention-to-treat primary analysis, meaning that the findings should be applicable to routine clinical practice.

The main weakness is that it involved only one NHS centre. Although, it included many different surgeons and anaesthetists, the study should be repeated in other healthcare settings. We tested only one regime of periarticular infiltration, but there are others with different types and doses of local anaesthetic. However, the regime that we chose and tested was representative of our region and many hospitals in the United Kingdom. An error of data entry resulted in the final sample for primary analysis being two less than anticipated. However, the evaluated treatment difference of -0.9 was less than the MCID of 1.2, and smaller than the anticipated SD; we are therefore confident that the study was not underpowered and that there is no clinical difference between the two treatment arms.

In conclusion, we did not find a clinically meaningful difference in the perception of pain on the day after TKA between patients who have a femoral nerve block and those having a periarticular infiltration of local anaesthetic. Periarticular infiltration, which can be administered without the need for specialist additional equipment and reduces post-operative morphine requirements, should be considered as a viable and safe alternative to femoral nerve block for early pain relief following TKA.

Take home message:

- Periarticular infiltration is a good alternative to femoral nerve block for managing post-operative pain following TKA.
- Periarticular infiltration may reduce a patients' requirements for additional morphine following TKA.
- Within the limits of the trial, periarticular infiltration was a safe alternative to femoral nerve block.

Author contributions:

P. D. H. Wall: Took over as Chief Investigator for the trial after A. P. Sprowson died, Provided trial management, Contributed to the writing of the manuscript, Will act as guarantor for the manuscript.

A. P. Sprowson†: Was the original Chief Investigator and grant holder for the study, Provided trial management, Developed the trial protocol, Contributed to the writing of the manuscript.

N. R. Parsons: Developed the trial protocol, Analysed the results, Contributed to the writing of the manuscript.

H. Parsons: Developed the trial protocol, Analysed the results, Contributed to the writing of the manuscript.

J. Achten: Developed the trial protocol, Contributed to the writing of the manuscript.

S. Balasubramanian: Developed the trial protocol, Contributed to the writing of the manuscript.

P. Thompson: Developed the trial protocol, Contributed to the writing of the manuscript.

M. L. Costa: Provided trial management, Developed the trial protocol, Contributed to the writing of the manuscript, Chief Investigator for the pilot study.

†Andrew P. Sprowson died unexpectedly on 13 March 2015. He was the Chief Investigator and main grant holder for this trial. Andrew was an academic orthopaedic surgeon who was dedicated to improving evidence-based care in his field. He was an exceptionally enthusiastic researcher and surgeon and will be greatly missed by both his academic and clinical colleagues.

*For the Perioperative Analgesia for Knee Arthroplasty (PAKA) Study Group.

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Please note since publication Figure 1 has been corrected.

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