



Clinical trial results:

Perioperative Analgesia for Knee Arthroplasty: A prospective randomised controlled trial

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-002439-10 |
| Trial protocol | GB |
| Global end of trial date | 30 November 2016 |

Results information

| | |
|-----------------------------------|----------------------------------|
| Result version number | v1 (current) |
| This version publication date | 22 September 2017 |
| First version publication date | 22 September 2017 |
| Summary attachment (see zip file) | PAKA study report (904.full.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | PAKA-33601-AS117013 |
|-----------------------|---------------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN60611146 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Warwick |
| Sponsor organisation address | Clifford Bridge Road, Coventry, United Kingdom, CV2 2DX |
| Public contact | PAKA Trial, University of Warwick Clifford Bridge Road Coventry, 02476 968629, |
| Scientific contact | PAKA Trial, University of Warwick Clifford Bridge Road Coventry, 02476 968629, |
| Sponsor organisation name | University Hospitals Coventry and Warwickshire |
| Sponsor organisation address | Clifford Bridge Road, Coventry , United Kingdom, CV2 2DX |
| Public contact | PAKA trial, UHCW, paka@warwick.ac.uk |
| Scientific contact | PAKA trial, UHCW, paka@warwick.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to determine if there a difference in patient reported pain prior to physiotherapy on the first post operative day between patients managed with local knee injections (peri-articular), compared to the standard treatment (femoral nerve block), following a total knee replacement.

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Authority. Patients received verbal and written information prior to consenting to the trial and had the time to consider their participation and opportunity to ask questions. Patient data were anonymised to ensure information was kept confidential. Identifiable information was kept separately in a secure location

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 262 |
| Worldwide total number of subjects | 262 |
| EEA total number of subjects | 262 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|-----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 74 |
| From 65 to 84 years | 181 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the University Hospitals Coventry and Warwickshire NHS trust, Hospital of St. Cross, Rugby from March 2014 to November 2015. All those undergoing primary unilateral TKA were eligible.

Pre-assignment

Screening details:

Participants listed for a unilateral knee replacement who attended a pre-op physiotherapy class at Rugby St Cross were screened for the study. Out of the 802 participants screened, 360 were excluded due to ineligibility, 234 were eligible but not recruited to the study, 264 recruited and 262 were randomised to the study.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind ^[1] |
| Roles blinded | Subject, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Due to the nature of the study it is not possible for the surgeon to be blinded to the treatment options. Both Groups will have a standardised dressing applied and for the peri-articular injection Group this will be part of normal standard of care. Outcome data will be collected by a research associate and an independent clinical physiotherapist that are blinded to the treatment options. Furthermore, the trial statistician will be blinded to the intervention groups throughout.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | FNB arm |

Arm description:

Femoral Nerve Block

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | 30 ml (75mg) of levobupivacaine hydrochloride 0.25%. |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection/infusion |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

Under aseptic conditions, the femoral artery will be palpated immediately below the inguinal ligament and nerve stimulation will be used to identify the femoral nerve just lateral to the artery. Once the femoral nerve has been identified the block may be performed in the routine manner using 30 ml (75mg) of levobupivacaine hydrochloride 0.25%. The precise technique used will be noted on trial documentation.

| | |
|------------------|--------|
| Arm title | PI arm |
|------------------|--------|

Arm description:

Periarticular injection

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | peri-articular infiltration |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

The peri-articular infiltration of multi-modal agents will involve the preparation of two 50ml syringes each containing 30ml (75mg) of levobupivacaine hydrochloride 0.25% injection, 0.5ml (5mg) morphine sulphate injection, 0.5ml (15mg) ketorolac trometamol injection and 0.25ml of 1:1000 adrenaline then diluted with 0.9% saline to make a mixture containing a total volume of 50ml. Adrenaline is added to the mixture to reduce blood loss after the operation. Each syringe will be prepared for immediate use and not stored.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: The Trial is patient and assessor blinded. It was not possible to blind the surgeons, as detailed in the Blinding implementation details section

| Number of subjects in period 1 | FNB arm | PI arm |
|---------------------------------------|--------------------|--------------------|
| Started | 131 | 131 |
| Primary outcome | 113 ^[2] | 117 ^[3] |
| Completed | 124 | 127 |
| Not completed | 7 | 4 |
| Adverse event, serious fatal | 1 | 1 |
| Consent withdrawn by subject | 1 | - |
| Lost to follow-up | 5 | 3 |

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects completed was the number of patients who received the TKR surgery and randomized to this group. However, due to reasons outlined in the reporting paper, the primary outcome was missed for a number of participants. These patients had not withdrawn, and many provided subsequent follow up data

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects completed was the number of patients who received the TKR surgery and randomized to this group. However, due to reasons outlined in the reporting paper, the primary outcome was missed for a number of participants. These patients had not withdrawn, and many provided subsequent follow up data

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | FNB arm |
| Reporting group description: Femoral Nerve Block | |
| Reporting group title | PI arm |
| Reporting group description: Periarticular injection | |

| Reporting group values | FNB arm | PI arm | Total |
|---|---------|--------|-------|
| Number of subjects | 131 | 131 | 262 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Participant age at baseline | | | |
| Units: years | | | |
| arithmetic mean | 68.2 | 68.7 | |
| standard deviation | ± 10 | ± 9.6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 80 | 77 | 157 |
| Male | 51 | 54 | 105 |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | FNB arm |
| Reporting group description: Femoral Nerve Block | |
| Reporting group title | PI arm |
| Reporting group description: Periarticular injection | |
| Subject analysis set title | FNB |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Femoral nerve block | |
| Subject analysis set title | PI |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Periarticular infiltration | |

Primary: Differences between allocation groups on the VAS pain score prephysiotherapy on the first day postoperatively

| | |
|--|---|
| End point title | Differences between allocation groups on the VAS pain score prephysiotherapy on the first day postoperatively |
| End point description: | |
| End point type | Primary |
| End point timeframe: Pre-physiotherapy on the first day postoperatively | |

| End point values | FNB arm | PI arm | | |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 113 | 117 | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | 44.1 (\pm 23) | 43.2 (\pm 24.6) | | |

Statistical analyses

| | |
|---|------------------|
| Statistical analysis title | Primary analysis |
| Statistical analysis description: The main analysis will investigate differences in the primary outcome measure, the VAS pain score pre-physiotherapy on the first day postoperatively, between the two treatment groups (single injection femoral nerve block and multimodal periarticular injection) on an intention-to-treat basis. | |
| Comparison groups | FNB arm v PI arm |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 230 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.77 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.3 |
| upper limit | 7.2 |

Notes:

[1] - A power calculation a priori detailed that 262 participants would be needed, based on a MCID of 12mm with a standard deviation of 30mm

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Six weeks from randomization (day of surgery)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | FNB arm |
|-----------------------|---------|

Reporting group description:

Femoral Nerve Block

| | |
|-----------------------|--------|
| Reporting group title | PI arm |
|-----------------------|--------|

Reporting group description:

Periarticular injection

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No AEs are reported as the number of AEs observed did not meet the 5% frequency reporting criterion.

| Serious adverse events | FNB arm | PI arm | |
|--|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 127 (20.47%) | 37 / 131 (28.24%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Surgical and medical procedures | | | |
| Admission to manage pain | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Admission to remove skin clips | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Knee instability undergoing revision | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|-----------------|--|
| Admission no cause found | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General malaise | Additional description: General malaise - No cause found | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chest infection | | | |
| subjects affected / exposed | 6 / 127 (4.72%) | 2 / 131 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Exacerbation of asthma | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| cement syndrome | Additional description: Cement syndrome (perioperative hypotension) | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Morphine overdose | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Death | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Nervous system disorders | | | |
| Foot drop | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Symptomatic anaemia requiring blood transfusion | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 3 / 131 (2.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Bleeding gastric ulcer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 131 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small bowel obstruction | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pressure sore | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superficial wound infection | | | |

| | | | |
|---|--|-----------------|--|
| subjects affected / exposed | 6 / 127 (4.72%) | 9 / 131 (6.87%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haematoma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | 6 / 131 (4.58%) | |
| occurrences causally related to treatment / all | 3 / 3 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 131 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 131 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reduced early ROM | Additional description: Reduced early ROM requiring manipulation | | |
| subjects affected / exposed | 2 / 127 (1.57%) | 2 / 131 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Deep wound infection undergoing revision | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | FNB arm | PI arm | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 131 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 26 August 2014 | Removal of temperature monitoring of trial drugs; inclusion of DN4 as a secondary outcome |
| 13 June 2015 | Addition of 12 month follow up point |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| The study involved only one centre in the NHS, although the trial included different surgeons and anaesthetists |
|---|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28663395>