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 (± 23)	43.2 (± 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