Clinical trial results:
A double-blind, randomised placebo-controlled trial to determine whether low-dose intravenous ketamine peri-operatively can prevent chronic post-surgical pain, in patients undergoing thoracotomy or video assisted thoracic surgery (VATS).

Summary

EudraCT number	2011-000506-21
Trial protocol	GB
Global end of trial date	09 July 2015

Results information

Result version number	v1 (current)
This version publication date	14 September 2016
First version publication date	14 September 2016
Summary attachment (see zip file)	Final report (Chumbley1 Final Report (3).doc)

Trial information

Trial identification

Sponsor protocol code	Chumbley1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Imperial College Healthcare NHS Trust
Sponsor organisation address	Praed Street, London, United Kingdom, W2 1NY
Public contact	Rebecca Ward, Research Governance Manager, Imperial College Healthcare NHS Trust, 0044 2075949459, becky.ward@imperial.ac.uk
Scientific contact	Rebecca Ward, Research Governance Manager, Imperial College Healthcare NHS Trust, 0044 2075949459, becky.ward@imperial.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	31 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2015
Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this research is to question whether a low-dose ketamine infusion given for 96 hours during and after surgery, will reduce the incidence of chronic post-surgical pain, 6 weeks after surgery, in patients undergoing thoracotomy and video assisted thoracic surgery (VATS). The study is primarily two studies, one for patients undergoing thoracotomy and the other for patients undergoing VATS. There were to be 72 patient in the thoracotomy trial and 72 patient in the VATS trial. We were unable to complete the VATS trial due to a lack of subjects. These patients were in the advanced stages of cancer and did not want to participate.

Protection of trial subjects:

The study was investigating pain. All patients received their normal pain management, but the study group received an extra infusion of ketamine or placebo. If the patients were still experiencing pain at the first follow-up session the GP was contacted and a regimen suggested to treat persistent pain after surgery.

Background therapy:

All patient received their normal pain relief, which was agreed on discussion with the patient and their anaesthetist. This consisted of either an epidural infusion or patient-controlled analgesia, plus or minus a paravertebral infusion for those patients have a thoracotomy. For patients having VATS surgery, they received patient-controlled analgesia, plus or minus a paravertebral infusion.

Evidence for comparator:

The comparator was saline placebo.

Actual start date of recruitment	10 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	45
From 65 to 84 years	58
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Adult patients aged 18 years and over, who were booked for either a thoracotomy or VATS procedure at Imperial College Healthcare NHS Trust were invited to participate in the study. They had to be able to read and speak English in order to answer the detailed pain questionnaires.

Pre-assignment

Screening details:

Patients were excluded if they refusal to participate, if they had previous chronic thoracic pain, neuropathic pain existing at time of recruitment or were taking the one of the following medications: strong opioids (step 3 analgesics), tricyclic antidepressants, venlaflaxine, gabapentin, pregabalin

Pre-assignment period milestones

Number of subjects started	104
Number of subjects completed	

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients were blinded to whether they received an infusion of ketamine or a saline placebo, both bags looked and were labelled the same. The infusion bags were made up in the aseptic infusion department in pharmacy. The investigators were blind to the type of infusion that the patients received and the blinding remained unbroken until all of the participants had completed their 12 month follow up.

Arms

Are arms mutually exclusive?	Yes
Arm title	ketamine

Arm description:

Patients who received ketamine

Arm type	Experimental
Investigational medicinal product name	Ketamine
Investigational medicinal product code	PL 00057/0530
Other name	Ketelar
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 0.1mg/kg/hour intravenous infusion running for 96 hours

Arm title	Saline Placebo

Arm description:

Patients received a saline placebo

Arm type	Placebo
Investigational medicinal product name	O.9% sodium chloride
Investigational medicinal product code	
Other name	saline
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
Infusion run at same rate as ketamine

Number of subjects in period 1	ketamine	Saline Placebo
Started	52	52
6 week follow-up	47	52
12 months follow-up	36	38
Completed	36	38
Not completed	16	14
Patient died of cancer	7	7
Consent withdrawn by subject	1	-
Lost to follow-up	8	7

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	104	104	
Age categorical Units: Subjects			
Adults (18-64 years)	45	45	
From 65-84 years	58	58	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	57.84		
standard deviation	± 15.7	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	61	61	
Pain score on moving			
Pain score on moving, 0 (no pain), 10 (worst pain			
Units: numerical			
arithmetic mean	0.5		
full range (min-max)	0 to 7	-	
Worst pain in previous 24 hours			
Worst pain in previous 24 hours, 0(no pain) to 10 (worst pain)			
Units: numerical			
arithmetic mean	0.93		
full range (min-max)	0 to 8	-	
SLANSS			
Short form of the Leeds Assessment of Neuropathic Signs and Symptoms (0 to 24 score). Score over 12 is considered to be neuropathic pain			
Units: numerical			
arithmetic mean	0.7		
full range (min-max)	0 to 14	-	

End points

End points reporting groups	
Reporting group title	ketamine
Reporting group description: Patients who received ketamine	
Reporting group title	Saline Placebo
Reporting group description: Patients received a saline placebo	

Primary: Pain on moving at 6 weeks	
End point title	Pain on moving at 6 weeks
End point description: Pain scores on moving at 6 weeks	
End point type	Primary
End point timeframe: Pain on moving at 6 weeks	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: numerical				
arithmetic mean (standard deviation)	2.02 (± 2.27)	1.4 (± 2.06)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description: Mann-Whitney U test to compare the ketamine and placebo groups	
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	99
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Mann-Whitney
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	10
Variability estimate	Standard deviation

Primary: Worst pain score at 6 weeks	
End point title	Worst pain score at 6 weeks
End point description:	
Worst pain score in past 24 hours measured at 6 weeks.	
End point type	Primary
End point timeframe:	
Worst pain score in past 24 hours measured at 6 weeks.	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: numerial				
arithmetic mean (standard deviation)	2.82 (± 2.595)	2.21 (± 2.531)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description:	
Comparing means of worst pain at 6 weeks in ketamine and placebo group	
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	99
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	10
Variability estimate	Standard deviation

Primary: S-Lanns pain score at 6 weeks	
End point title	S-Lanns pain score at 6 weeks
End point description:	
S-Lanns pain score measured at 6 weeks	
End point type	Primary
End point timeframe:	
S-Lanns pain score measured at 6 weeks	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: numerical				
arithmetic mean (standard deviation)	5.83 (± 6.709)	4.02 (± 5.949)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	99
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	24
Variability estimate	Standard deviation

Secondary: Pain on moving at 12 months	
End point title	Pain on moving at 12 months
End point description: Pain score on Moving at 12 months	
End point type	Secondary
End point timeframe: Pain score on moving at 12 months	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: numerical				
arithmetic mean (standard deviation)	0.39 (± 1.695)	0.34 (± 1.047)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	10
Variability estimate	Standard deviation

Secondary: Worst pain score at 12 months	
End point title	Worst pain score at 12 months
End point description: Worst pain score on moving at 12 months.	
End point type	Secondary
End point timeframe: Worst pain score on moving at 12 months.	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: numerical				
arithmetic mean (standard deviation)	0.58 (± 1.779)	0.53 (± 1.72)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)

Confidence interval	
sides	2-sided
lower limit	0
upper limit	10
Variability estimate	Standard deviation

Secondary: S-Lanns pain score at 12 months

End point title	S-Lanns pain score at 12 months
End point description: S-Lanns pain score at 12 months	
End point type	Secondary
End point timeframe: S-Lanns pain score at 12 months	

End point values	ketamine	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: numerical				
arithmetic mean (standard deviation)	2.17 (± 5.107)	1.32 (± 4.237)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	ketamine v Saline Placebo
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	24
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of ketamine infusion, which ran for 96 hours to discharge from hospital	
Adverse event reporting additional description: Patients were visited daily whilst in hospital by the researchers	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	ketamine
Reporting group description: Patients who received ketamine	
Reporting group title	Saline Placebo
Reporting group description: Patients received a saline placebo	

Serious adverse events	ketamine	Saline Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 52 (21.15%)	11 / 52 (21.15%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotensive episode following theatre		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Hallucination, visual	Additional description: Hallucinations experienced post operatively, mostly thought to be due to opioids		
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea infectious	Additional description: Clostridium difficile confirmed		
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress	Additional description: Patient developed respiratory distress post thoracotomy, re-intubated and ventilated.		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung hypoinflation	Additional description: Lung collapse following thoracotomy for cancer, unable to oxygenate. Death due to respiratory failure.		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis	Additional description: injury post thoracotomy intubation, causing hoarse voice		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal failure	Additional description: Patient developed renal failure 13 days after starting trial. Renal biopsy showed undetected myeloma		
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion postoperative			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation postoperative			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	ketamine	Saline Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 52 (76.92%)	34 / 52 (65.38%)	
Nervous system disorders			
Dizziness	Additional description: Patients who felt lightheaded post-surgery		
subjects affected / exposed	21 / 52 (40.38%)	8 / 52 (15.38%)	
occurrences (all)	21	8	
Nightmare	Additional description: vivid dreams experienced post-surgery		
subjects affected / exposed	19 / 52 (36.54%)	5 / 52 (9.62%)	
occurrences (all)	19	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	25 / 52 (48.08%)	22 / 52 (42.31%)	
occurrences (all)	25	22	
Vomiting	Additional description: post operative vomiting		

subjects affected / exposed occurrences (all)	14 / 52 (26.92%) 14	11 / 52 (21.15%) 11	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 16 / 52 (30.77%) 16	 16 / 52 (30.77%) 16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2013	Changes made to the wording in the patient information sheet, patient contact letter and protocol on the request of the surgeon after a patient complained about the term 'chronic' pain
07 January 2014	Study documents and protocol changed to allow a second study site at St George's Hospital. Recruitment to the VATS study was slow and it was thought that a second site would improve recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported