



Clinical trial results:

A Randomised Study to Investigate the Effectiveness of Acupuncture for the Relief of Dyspnoea in Patients with Non-Small Cell Lung Cancer and mesothelioma

Summary

EudraCT number	2006-000810-18
Trial protocol	GB
Global end of trial date	21 July 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2020
First version publication date	24 July 2020
Summary attachment (see zip file)	Accupuncture Abstract June 2014 (End of Trial Report.pdf) ACCUPUNCTURE EJC 2016 REPORT (EJC 2016.pdf)

Trial information

Trial identification

Sponsor protocol code	REC 06/Q0801/27
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Additional study identifiers

ISRCTN number	ISRCTN34841555
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Royal Marsden NHS Foundation Trust
Sponsor organisation address	Fulham Road, London, United Kingdom, SW3 6JJ
Public contact	The Royal Marsden NHS Foundation Trust, The Royal Marsden NHS Foundation Trust, 44 2086426011, mary.obrien@rmh.nhs.uk
Scientific contact	The Royal Marsden NHS Foundation Trust, The Royal Marsden NHS Foundation Trust, 44 2086425011, mary.obrien@rmh.nhs.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	26 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2014
Global end of trial reached?	Yes
Global end of trial date	21 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether use of acupuncture in lung cancer-related breathlessness improves symptoms when compared with use of morphine

Protection of trial subjects:

There were regular meetings to review adverse events and progress of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 173
Worldwide total number of subjects	173
EEA total number of subjects	173

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)	40
From 65 to 84 years	124
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

First patient was recruited to the study on 04/07/2006. Recruitment of subjects continued until the last patient recruited to the study on 10/06/2014.

Pre-assignment

Screening details:

175 patients were randomised, but 2 patients failed inclusion criteria with only 173 patients being eligible for the study.

Pre-assignment period milestones

Number of subjects started	175 ^[1]
Number of subjects completed	173

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Diagnosis of SCLC, hence not eligible: 2
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 175 patients enrolled, 173 completed, 2 were withdrawn due to diagnosis

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Acupuncture (Arm A)

Arm description:

Acupuncture alone

Arm type	Experimental
Investigational medicinal product name	Acupuncture
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal system
Routes of administration	Transdermal use

Dosage and administration details:

Acupuncture was administered to two upper sternal midline points, five paraspinal points from T1 to T5, two to three trigger points in the trapezius muscle bilaterally and LI4 (acupuncture point near the base of thumb) bilaterally. Thirty-millimetre-long 36-gauge stainless steel acupuncture needles (Seirin) were inserted and left in situ for 10 min. At sternal points, needles were inserted to the level of the periosteum and gently 'pecked' twice.

After needle removal, stainless steel press needle studs (Seirin/Acumedic) were inserted in the upper 6 cm of the midline sternum to 0.6 mm and covered with a dressing. Treatments were given between 12 and 2 pm to avoid diurnal variation. Patients were instructed to massage studs for 1 to 2 minutes when symptomatic or prior to exercise whilst documenting in a diary. All studs were removed and the area healed before any chemotherapy was given.

Arm title	Morphine (Arm M)
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Arm description:

Morphine alone

Arm type	Active comparator
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Investigational medicinal product name	Oramorph
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients will be prescribed a fixed dose of oral morphine solution (Oramorph; 10mg in 5ml) 2.5mg 4 hourly.

Patients will be instructed to take their dose of morphine at 4-hour intervals, with breakthrough doses as required - not less than 1 hour after previous dose - and omission of doses if not required.

Patients were given a daily diary card to document this.

Patients were allowed to increase or decrease their dose of morphine if required.

Arm title	Acupuncture + Morphine (Arm AM)
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Arm description:

Combination of Acupuncture and Morphine

Arm type	Experimental
Investigational medicinal product name	Acupuncture + Morphine (Oramorph)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

In arm AM, patients received 2.5mg dose of morphine (same as for arm M) 20 mins before acupuncture (as for arm A).

Patients were instructed to massage studs and take further doses of morphine if breathlessness persists. Daily diary cards were provided for documentation. All studs were removed and the area healed before any chemotherapy was given.

Number of subjects in period 1	Acupuncture (Arm A)	Morphine (Arm M)	Acupuncture + Morphine (Arm AM)
Started	57	60	56
Completed	57	60	56

Period 2

Period 2 title	VAS Dyspnoea response at 4 hours
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Acupuncture (Arm A)
Arm description: Acupuncture alone	
Arm type	Experimental
Investigational medicinal product name	Acupuncture
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal system
Routes of administration	Transdermal use
Dosage and administration details:	
<p>Acupuncture was administered to two upper sternal midline points, five paraspinal points from T1 to T5, two to three trigger points in the trapezius muscle bilaterally and LI4 (acupuncture point near the base of thumb) bilaterally. Thirty-millimetre-long 36-gauge stainless steel acupuncture needles (Seirin) were inserted and left in situ for 10 min. At sternal points, needles were inserted to the level of the periosteum and gently 'pecked' twice.</p> <p>After needle removal, stainless steel press needle studs (Seirin/Acumedic) were inserted in the upper 6 cm of the midline sternum to 0.6 mm and covered with a dressing. Treatments were given between 12 and 2 pm to avoid diurnal variation. Patients were instructed to massage studs for 1 to 2 minutes when symptomatic or prior to exercise whilst documenting in a diary. All studs were removed and the area healed before any chemotherapy was given.</p>	

Arm title	Morphine (Arm M)
Arm description: Morphine alone	
Arm type	Active comparator
Investigational medicinal product name	Oramorph
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
<p>Patients will be prescribed a fixed dose of oral morphine solution (Oramorph; 10mg in 5ml) 2.5mg 4 hourly.</p> <p>Patients will be instructed to take their dose of morphine at 4-hour intervals, with breakthrough doses as required - not less than 1 hour after previous dose - and omission of doses if not required.</p> <p>Patients were given a daily diary card to document this.</p> <p>Patients were allowed to increase or decrease their dose of morphine if required.</p>	

Arm title	Acupuncture + Morphine (Arm AM)
Arm description: Combination of Acupuncture and Morphine	
Arm type	Experimental
Investigational medicinal product name	Acupuncture + Morphine (Oramorph)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
<p>In arm AM, patients received 2.5mg dose of morphine (same as for arm M) 20 mins before acupuncture (as for arm A).</p> <p>Patients were instructed to massage studs and take further doses of morphine if breathlessness persists. Daily diary cards were provided for documentation. All studs were removed and the area healed before any chemotherapy was given.</p>	

Number of subjects in period 2	Acupuncture (Arm A)	Morphine (Arm M)	Acupuncture + Morphine (Arm AM)
Started	57	60	56
Completed	57	55	56
Not completed	0	5	0
Other	-	2	-
Not received treatment	-	3	-

Baseline characteristics

Reporting groups

Reporting group title	Acupuncture (Arm A)
Reporting group description:	
Acupuncture alone	
Reporting group title	Morphine (Arm M)
Reporting group description:	
Morphine alone	
Reporting group title	Acupuncture + Morphine (Arm AM)
Reporting group description:	
Combination of Acupuncture and Morphine	

Reporting group values	Acupuncture (Arm A)	Morphine (Arm M)	Acupuncture + Morphine (Arm AM)
Number of subjects	57	60	56
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median	74	75	70
inter-quartile range (Q1-Q3)	50 to 88	42 to 87	49 to 88
Gender categorical			
Units: Subjects			
Female	17	24	18
Male	40	36	38
Pathology			
Units: Subjects			
NSCLC	46	46	45
Mesothelioma	11	14	11
ECOG Performance Status			
ECOG Performance Status: 0-3			
Units: Subjects			
0/1	27	30	24
02	23	22	24
03	7	8	8
Dyspnoea VAS			
Visual analogue scale (VAS) for breathlessness measured on a 10cm scale			
Units: 0cm to 10cm scale			

median	6.3	6.7	6.4
inter-quartile range (Q1-Q3)	4.0 to 9.0	4.0 to 8.6	4.1 to 8.6
Relaxation VAS			
Visual analogue scale (VAS) for relaxation measured on a 10cm scale			
Units: 0cm to 10cm scale			
median	4.3	2.4	4.4
inter-quartile range (Q1-Q3)	0.1 to 9.4	0.0 to 7.1	0.0 to 8.6
FEV1 - Lung Function			
Forced Expiratory Volume which calculates the amount of air that a person can force out of their lungs in 1 second			
Units: Litres			
median	1.4	1.2	1.4
inter-quartile range (Q1-Q3)	0.4 to 3.5	0.4 to 2.8	0.5 to 2.5
PEFR - Lung Function			
Peak Expiratory Flow Rate			
Units: Liters per minute (L/min)			
median	204	171	204
inter-quartile range (Q1-Q3)	24 to 504	48 to 471	78 to 510

Reporting group values	Total		
Number of subjects	173		
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			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	59		
Male	114		
Pathology			
Units: Subjects			
NSCLC	137		
Mesothelioma	36		
ECOG Performance Status			
ECOG Performance Status: 0-3			
Units: Subjects			
0/1	81		
02	69		
03	23		

Dyspnoea VAS			
Visual analogue scale (VAS) for breathlessness measured on a 10cm scale			
Units: 0cm to 10cm scale			
median			
inter-quartile range (Q1-Q3)	-		
Relaxation VAS			
Visual analogue scale (VAS) for relaxation measured on a 10cm scale			
Units: 0cm to 10cm scale			
median			
inter-quartile range (Q1-Q3)	-		
FEV1 - Lung Function			
Forced Expiratory Volume which calculates the amount of air that a person can force out of their lungs in 1 second			
Units: Litres			
median			
inter-quartile range (Q1-Q3)	-		
PEFR - Lung Function			
Peak Expiratory Flow Rate			
Units: Liters per minute (L/min)			
median			
inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Acupuncture (Arm A)
Reporting group description:	
Acupuncture alone	
Reporting group title	Morphine (Arm M)
Reporting group description:	
Morphine alone	
Reporting group title	Acupuncture + Morphine (Arm AM)
Reporting group description:	
Combination of Acupuncture and Morphine	
Reporting group title	Acupuncture (Arm A)
Reporting group description:	
Acupuncture alone	
Reporting group title	Morphine (Arm M)
Reporting group description:	
Morphine alone	
Reporting group title	Acupuncture + Morphine (Arm AM)
Reporting group description:	
Combination of Acupuncture and Morphine	
Subject analysis set title	Total
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
VAS Dyspnoea response at 4 hours	

Primary: VAS dyspnoea response at 4 hours after baseline

End point title	VAS dyspnoea response at 4 hours after baseline
End point description:	
<p>The primary endpoint of the study is dyspnoea response at 4 hours. A patient is considered to have had a dyspnoea response if they record a 1.5 or greater point reduction in the VAS for dyspnoea at 4 hours compared to baseline.</p> <p>Patients withdrawn before the 4 hour assessment are considered to be non-responders.</p> <p>Primary endpoint analysed as per intention-to-treat (ITT) population i.e. all randomised patients fulfilling the eligibility criteria (173 total).</p>	
End point type	Primary
End point timeframe:	
VAS dyspnoea response at 4 hours after baseline	

End point values	Acupuncture (Arm A)	Morphine (Arm M)	Acupuncture + Morphine (Arm AM)	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	60	56	173
Units: Proportion				
Responders	42	36	37	115
Non-Responders	15	24	19	58
Response rate (%)	74	60	66	66

Statistical analyses

Statistical analysis title	VAS Dyspnoea response at 4 hours after treatment
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Statistical analysis description:

Proportion of responders and non-responders compared between Arm A vs. Arm M, and comparison between Arm AM vs. Arm M. Response is defined as 1.5 points (or more) reduction in VAS dyspnoea at 4 hours compared to baseline assessment. Two interim analyses were performed in 2009 & 2012. Protocol specified that trial would stop if there was sufficient evidence of a treatment effect ($\alpha = 0.01$). As there was no significant difference in the response rate between arms, recruitment continued to 173

Comparison groups	Acupuncture (Arm A) v Morphine (Arm M) v Acupuncture + Morphine (Arm AM)
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 ^[1]
Method	Chi-squared

Notes:

[1] - p-value = 0.12 for comparison between Arm A vs. Arm M

p-value = 0.50 for comparison between Arm (A+M) vs. Arm M

There was no significant difference between the treatment comparisons.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events including SAEs were reported from the time of informed consent and for a minimum of 28 days after stopping study medication.

Toxicity data were available for 123 patients. Side-effects were in line with morphine's toxicity profile.

Adverse event reporting additional description:

In arm M, 39% of patients reported toxicity (G1) such as constipation, nausea and drowsiness. One patient withdrew due to morphine intolerance. In arm AM, 35% of patients reported toxicity, constipation (G1) being the most common (33%). One patient died of progressive lung cancer. In arm A, 1% reported toxicity (G1-2).

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	3

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

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: This is not applicable for this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2009	The protocol was approved in 2006 with a sample size of 141 patients (47 per treatment arm). Early clinical impression was that patients were getting a higher level of dyspnoea relief than expected; in order to allow for early termination of the study in the event of one treatment arm being ineffective, an amendment was passed in 2009 to allow for 2 interim analyses, in particular an interim analysis would allow the study to be terminated early if there is sufficient evidence of a treatment benefit from acupuncture. The sample size was increased up to a maximum of 174 patients (58 per treatment arm) in order to maintain the power of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported