



Clinical trial results:

The use of Ketamine as an anaesthetic during electroconvulsive therapy (ECT) for depression: does it improve treatment outcome?

Summary

EudraCT number	2011-000396-14
Trial protocol	GB
Global end of trial date	18 February 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2018
First version publication date	29 July 2018
Summary attachment (see zip file)	Ketamine as the anaesthetic for electroconvulsive therapy: The KANECT randomised controlled trial (Fernie et al (2017) Ketamine as the anaesthetic.pdf)

Trial information

Trial identification

Sponsor protocol code	3/006/11
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01306760
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen/NHS-Grampian
Sponsor organisation address	Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB
Public contact	Research Governance Office, University of Aberdeen/NHS-Grampian, 44 (0) 1224 551123, researchgovernance@abdn.ac.uk
Scientific contact	Research Governance Office, University of Aberdeen/NHS-Grampian, 44 (0) 1224 551123, researchgovernance@abdn.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	22 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2014
Global end of trial reached?	Yes
Global end of trial date	18 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main research question is whether the use of ketamine as the anaesthetic for ECT treatment for depression improves the treatment outcome with respect to speed of response and reduction in side effects when compared to conventional anaesthesia.

Protection of trial subjects:

An unblinding procedure was specified should the medical need arise.

An independent Trial Steering Committee was in place and met approximately every 6 months while recruitment was open.

Background therapy:

We placed no restrictions on concomitant medication prescribing during the course of the trial except that benzodiazepines were withdrawn prior to ECT. No restrictions were placed on any rescue medications.

Evidence for comparator:

The active comparator, propofol, was used in 88.2% of ECT treatments in Scotland at the time the trial took place.

Reference: Scottish ECT Accreditation Network. Scottish ECT Accreditation Network Annual Report 2015: A summary of ECT in Scotland for 2014. Edinburgh, Scotland: ISD Scotland Publications; 2015.

Actual start date of recruitment	01 November 2011
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	35
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were receiving ECT for major depression on an informal basis at the Royal Cornhill Hospital, Aberdeen, Scotland between November 2011 and December 2013. The final assessment of the final patient was completed in February 2014. The ethnicity of all patients was White British. All participants provided informed consent.

Pre-assignment

Screening details:

Eligible if receiving ECT on an informal basis (i.e. not detained), considered fit by an anaesthetist (American Society of Anaesthesiologists physical status classification system score of 1 or 2), had no comorbid psychiatric diagnoses recorded by the treating psychiatrist & were between the ages of 18-75. Exclusion criteria applied.

Period 1

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

Blinding implementation details:

Randomisation recorded in medical notes as Drug A or B by the Principal Investigator or ECT nurses. Patients were first assessed before randomisation. All post-ECT assessments were conducted by researchers blinded to the anaesthetic assignment.

All analyses were conducted by a researcher blind to the group assignment.

The decision on management of the ECT course was taken by the patients' treating clinicians, who were blind to anaesthetic assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ketamine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ketamine
Investigational medicinal product code	
Other name	Ketalar
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

An intravenous cannula was inserted in the non-isolated arm. The patients in the ketamine group were administered a hypnotic dose of ketamine of up to 2 mg/kg followed by limb isolation and subsequent administration of the muscle relaxant suxamethonium (0.5-1 mg/kg).

Arm title	Propofol
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	Diprivan 1%
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

A hypnotic dose of propofol up to 2.5 mg/kg followed by limb isolation and administration of

suxamethonium (0.5-1 mg/kg).

Heart rate, 3 lead ECG, Oxygen Saturation (SpO₂), fractional inspired oxygen (FiO₂), and end-tidal CO₂ (EtCO₂) were monitored continuously during the procedure. All participants received positive pressure ventilation with 100% oxygen during the procedure until spontaneous respiration resumed. Non-invasive blood pressure was measured before the administration of the anaesthetic, immediately post seizure and repeated if necessary. In the recovery room patients received oxygen-enriched air via a facemask, while non-invasive blood pressure and SpO₂ were monitored.

Number of subjects in period 1	Ketamine	Propofol
Started	20	20
Completed post-ECT4 assessments	14	17
Completed post-ECT assessment	16	17
Completed 1-month post-ECT assessments	13	13
Completed	13	13
Not completed	7	7
Consent withdrawn by subject	1	-
Physician decision	3	1
Maintenance ECT within follow-up period	1	1
withdrawn due to exposure to legal high	-	1
Lost to follow-up	2	3
Prescribed another course of ECT within follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Ketamine
Reporting group description: -	
Reporting group title	Propofol
Reporting group description: -	

Reporting group values	Ketamine	Propofol	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	17	35
From 65-84 years	2	3	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.76	49.88	
standard deviation	± 9.97	± 12.53	-
Gender categorical Units: Subjects			
Female	11	11	22
Male	9	9	18

End points

End points reporting groups

Reporting group title	Ketamine
Reporting group description: -	
Reporting group title	Propofol
Reporting group description: -	

Primary: Number of ECT treatments

End point title	Number of ECT treatments
End point description: The decision to end the ECT course was taken by the participant's treating clinician who was blind to anaesthetic assignment.	
End point type	Primary
End point timeframe: Number of ECT treatments in the ECT course. Includes 2 of 16 participants in the ketamine group and 2 of 19 in the propofol group who received 4 ECTs or less. Please refer to Table on page 5 or CONSORT flow diagram in results paper for more info.	

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 ^[1]	19 ^[2]		
Units: ECT treatments				
arithmetic mean (standard deviation)	7.88 (± 3.18)	7.26 (± 2.23)		

Notes:

[1] - Completed post-ECT assessment

[2] - Completed post-ECT assessment

Statistical analyses

Statistical analysis title	t-test
Statistical analysis description: The number of ECT treatments received by patients in each group was compared using an independent samples t-test.	
Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 ^[3]
Method	t-test, 2-sided

Notes:

[3] - $t(33) < 1.0$, $p > .05$, $d = 0.23$.

Primary: Hamilton Depression Rating Scale (HDRS) - Acute analysis

End point title	Hamilton Depression Rating Scale (HDRS) - Acute analysis
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End point description:

An acute effects analysis, Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared (η^2) provided an estimate of effect size with 95% confidence intervals (95% CI)

End point type	Primary
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End point timeframe:

compared outcomes pre-ECT with post-ECT4.

Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper:
<https://doi.org/10.1192/bjp.bp.116.189134>

Consult Table on page 5 for number of subjects in analyses

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 ^[4]	19 ^[5]		
Units: HDRS score				
arithmetic mean (standard deviation)	17.25 (\pm 6.88)	13.58 (\pm 5.71)		

Notes:

[4] - Completed post-ECT 4 assessment

[5] - Completed post-ECT 4 assessment

Statistical analyses

Statistical analysis title	ANCOVA - acute HDRS
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Statistical analysis description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[6]
Method	ANCOVA

Notes:

[6] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Primary: Montgomery-Asberg Depression Rating Scale (MADRS) - Acute analysis

End point title	Montgomery-Asberg Depression Rating Scale (MADRS) - Acute analysis
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End point description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared (η^2) provided an estimate of effect size with 95% confidence intervals (95% CI)

End point type	Primary
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End point timeframe:

pre-ECT compared with with post-ECT4.

Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper:
<https://doi.org/10.1192/bjp.bp.116.189134>

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: MADRS score				
arithmetic mean (standard deviation)	23.81 (± 11.2)	18.74 (± 9.44)		

Statistical analyses

Statistical analysis title	ANCOVA - acute MADRS
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Statistical analysis description:

analysis of covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[7]
Method	ANCOVA

Notes:

[7] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Primary: Hamilton Depression Rating Scale (HDRS) - Treatment effects analysis

End point title	Hamilton Depression Rating Scale (HDRS) - Treatment effects analysis
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End point description:

In a treatment effects analysis, linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT and 1-month assessments.

End point type	Primary
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End point timeframe:

pre-ECT compared with those at post-final ECT and 1-month assessments.

Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: <https://doi.org/10.1192/bjp.bp.116.189134>

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: HDRS scores				
arithmetic mean (standard deviation)	13.50 (± 9.32)	8.41 (± 4.70)		

Statistical analyses

Statistical analysis title	Linear mixed model
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Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month

assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	> 0.05 ^[9]
Method	Mixed models analysis

Notes:

[8] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

[9] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Primary: Montgomery Asberg Depression Rating Scale (MADRS) - Treatment effects analysis

End point title	Montgomery Asberg Depression Rating Scale (MADRS) - Treatment effects analysis
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End point description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

End point type	Primary
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End point timeframe:

Pre-ECT compared to post-ECT and 1-month post-ECT

Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: <https://doi.org/10.1192/bjp.bp.116.189134>

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: MADRS score				
arithmetic mean (standard deviation)	18.69 (± 16.48)	8.18 (± 6.27)		

Statistical analyses

Statistical analysis title	Linear mixed model - MADRS treatment effects
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Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

Comparison groups	Ketamine v Propofol
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Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	> 0.05 ^[11]
Method	Linear Mixed model

Notes:

[10] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

[11] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Secondary: Spatial Recognition Memory (SRM) - Acute analysis

End point title	Spatial Recognition Memory (SRM) - Acute analysis
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End point description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared (η^2) provided an estimate of effect size with 95% confidence intervals (95% CI)

End point type	Secondary
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End point timeframe:

compared outcomes pre-ECT to post-ECT4

Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper: <https://doi.org/10.1192/bjp.bp.116.189134>

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: Proportion correct				
arithmetic mean (standard deviation)	0.60 (\pm 0.12)	0.63 (\pm 0.10)		

Statistical analyses

Statistical analysis title	ANCOVA - acute SRM
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Statistical analysis description:

analysis of covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[12]
Method	ANCOVA

Notes:

[12] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Secondary: Spatial Recognition Memory (SRM) - Treatment effects analysis

End point title	Spatial Recognition Memory (SRM) - Treatment effects analysis
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End point description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

End point type	Secondary
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End point timeframe:

Pre-ECT compared with post-ECT and 1-month post-ECT.

Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: <https://doi.org/10.1192/bjp.bp.116.189134>

End point values	Ketamine	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: SRM proportion correct				
arithmetic mean (standard deviation)	.60 (± .16)	.64 (± .11)		

Statistical analyses

Statistical analysis title	Linear mixed model - SRM treatment effects
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Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

Comparison groups	Ketamine v Propofol
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	> 0.05 ^[14]
Method	Linear Mixed model

Notes:

[13] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

[14] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

up to 30 days after the participant completed or discontinued the study.

Adverse event reporting additional description:

The CI and sponsor informed within 24 hours of serious adverse events or reactions and follow up with a formal written report.

If a SUSAR is life threatening then the MHRA and REC will be notified within 7 days of the event occurring; if the SUSAR is not life threatening, then it will be reported within 15 days of the event occurring.

Assessment type	Systematic
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Dictionary used

Dictionary name	No dictionary
Dictionary version	00

Reporting groups

Reporting group title	Ketamine
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Reporting group description: -

Reporting group title	Propofol
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Reporting group description: -

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 non-serious adverse events were recorded during the course of the trial.

Serious adverse events	Ketamine	Propofol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
prolonged hospital admission	Additional description: a participant developed an elevated mood following their ECT course		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ketamine	Propofol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2011	Increase in time data held from 10 to 15 years from end of study.
08 August 2013	<p>Change in definition of the sample from which participants can be recruited to add "We will also recruit in-patients who subsequently leave the hospital "on pass" between treatments (after appropriate medical assessment by their treating teams), and return to the hospital for ECT before going home on the same day."</p> <p>Due to good recruitment (N = 35) with 9 months of recruitment remaining a change to target sample size from 40 to 50 was made.</p> <p>A non-substantial amendment was later made in May 2014 reducing the target sample size back to 40.</p>

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 limitations of the EUdract system and the support provided mean that accurately representing the results within it was difficult. Readers are advised to read the open-access paper linked to this record for a full description of the analysis.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28254962>