Clinical trial results:
Hyperbaric oxygen treatment of mandibular osteoradionecrosis. A randomized clinical trial.

Summary

EudraCT number	2007-007842-36
Trial protocol	DK SE GB
Global end of trial date	31 December 2018

Results information

Result version number	v1 (current)
This version publication date	28 January 2020
First version publication date	28 January 2020

Trial information

Trial identification

Sponsor protocol code	DAHANCA-21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00760682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Copenhagen University Hospital
Sponsor organisation address	Blegdamsvej 9, Copenhagen , Denmark, DK-2100 Copenhagen
Public contact	Lone Forner , Copenhagen University Hospital , +45 26396440, loneforner@outlook.dk
Scientific contact	Lone Forner , Copenhagen University Hospital , +45 26396440, loneforner@outlook.dk

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	01 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of hyperbaric oxygen treatment on mandibular osteoradionecrosis and secondary endpoints xerostomia, hypersalivation, trismus, dysphagia, pain, BMI and quality of life. Only primary endpoints have been finally analyzed.
An important information about the trial is the inclusion of data of a separate Dutch study. The Dutch participants are not recruited in the DAHANCA-21 trial, but in the Dutch trial NWHHT 2009-1. Due to slow recruitment in both trials, it was decided to share the data after termination of the studies. It must therefore be emphasized that no Dutch participants were recruited into DAHANCA-21, but the pooled data are presented in this report.

Protection of trial subjects:

Following measures were made to minimise pain and distress: Thorough information prior to giving consent and thorough care taken to ensure that participants were comfortable with participation throughout the study. Patients were informed that they were entitled to leave the study without giving any reason for this. The treatment they were assigned to was not painful but potentially stressful because it took place in a closed compartment, the hyperbaric chamber. Participants were informed that a hyperbaric tender would be able to get into the chamber within 20 seconds. It was possible to speak to the tenders surveilling the chamber from outside. Participants were informed that there would at all times be a tender outside the chamber to watch what was going on inside the chamber. Participants were encouraged to share experiences and adress treatment-related stress to assigned doctors and to the investigator.
Annual safety reports were submitted to the national regulatory authorities

Background therapy:

Hyperbaric oxygen is 100% oxygen delivered in a mask or a hood while decompressing the hyperbaric chamber to approximately 2.4 ATA, corresponding to diving at 14-15 meters. Decompression lead to a greater delivery of the oxygen into the body. There is currently insufficient evidence of an effect of hyperbaric oxygen on osteoradionecrosis (radiotherapy-induced bone tissue necrosis)

Evidence for comparator: -

Actual start date of recruitment	01 June 2008
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	Netherlands: 20
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Denmark: 51
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	70
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment periods from June 1st, 2008 to August 1st, 2017.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	97
Number of subjects completed	97

Period 1

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

Blinding implementation details:

This is an open-label due to the different schedules of treatment administration

Arms

Are arms mutually exclusive?	Yes
Arm title	Hyperbaric oxygen and surgery

Arm description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

30 preoperative and 10 postoperative exposures at 2.4 ATA pressurisation

Arm title	Surgery

Arm description:

Surgical removal of necrotic mandibular bone

Arm type	Standard care, comparator

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Hyperbaric oxygen and surgery	Surgery
Started	46	51
Completed	46	51

Period 2	
Period 2 title	Therapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial is open labelled

Arms

Are arms mutually exclusive?	Yes
Arm title	Hyperbaric oxygen and surgery

Arm description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

30 preoperative and 10 postoperative exposures at 2.4 ATA pressurisation

Arm title	Surgery

Arm description:

Surgical removal of necrotic mandibular bone

Arm type	Standard care, comparator

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Hyperbaric oxygen and surgery	Surgery
Started	46	51
Completed	36	40
Not completed	10	11
Consent withdrawn by subject	6	5
Cancer recurrence	2	1

Death	-	1
Surgery not needed	-	1
Lost to follow-up	2	3

Period 3

Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial is open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Hyperbaric oxygen and surgery

Arm description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

30 preoperative and 10 postoperative exposures at 2.4 ATA pressurisation

Arm title	Surgery

Arm description:

Surgical removal of necrotic mandibular bone

Arm type	Standard care, comparator

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Hyperbaric oxygen and surgery	Surgery
Started	36	40
Completed	26	34
Not completed	10	6
Cancer recurrence	-	2
Death	4	2
Ear problems in HBO chamber	1	-

Surgery not needed	1	-
Lost to follow-up	2	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Hyperbaric oxygen and surgery
Reporting group description:	
In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone	
Reporting group title	Surgery
Reporting group description:	
Surgical removal of necrotic mandibular bone	

Reporting group values	Hyperbaric oxygen and surgery	Surgery	Total
Number of subjects	46	51	97
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)	32	38	70
From 65-84 years	14	13	27
85 years and over	0	0	0
Adults (>17 years)	0	0	0
Age continuous Units: years			
median	59	60	
full range (min-max)	48 to 78	49 to 80	-
Gender categorical Units: Subjects			
Female	9	10	19
Male	37	41	78

Subject analysis sets	
Subject analysis set title	Analysis of the effect of hyperbaric oxygen on ORN
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
While DAHANCA-21 was ongoing, recruitment was slow. At the time of initiation of DAHANCA-21, a similar trial was initiated in the Netherlands, the NWHHT 2009-1 trial. It was considered to join these trials from the beginning, but because both trials were ready to start at this time, it was decided to keep in touch and exchange experiences. After a few years, it became clear that recruitment was slow, and it was decided to include the Dutch data material in DAHANCA-21. Overall, 20 Dutch participants were included. 10 completed their participation, and further one participant was included in the intention-to-treat analysis. 60 participants completed the study, while another five were considered eligible for the intention-to-treat analysis. Of these 65, only 54 was from the DAHANCA-21 recruitment group, while the remaining 11 were Dutch.	

Reporting group values	Analysis of the effect of hyperbaric oxygen on ORN		
Number of subjects	60		
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)	70		
From 65-84 years	27		
85 years and over	0		
Adults (>17 years)	0		
Age continuous Units: years			
median	60		
full range (min-max)	48 to 80		
Gender categorical Units: Subjects			
Female	10		
Male	55		

End points

End points reporting groups

Reporting group title	Hyperbaric oxygen and surgery

Reporting group description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Reporting group title	Surgery

Reporting group description:

Surgical removal of necrotic mandibular bone

Reporting group title	Hyperbaric oxygen and surgery

Reporting group description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Reporting group title	Surgery

Reporting group description:

Surgical removal of necrotic mandibular bone

Reporting group title	Hyperbaric oxygen and surgery

Reporting group description:

In Arm 1, participants were allocated to 30 preoperative and 10 postoperative exposures to hyperbaric oxygen consisting of inhaling 100% oxygen from a hood while decompressed to 2.4 ATA. Surgical procedure includes surgical removal of necrotic mandibular bone

Reporting group title	Surgery

Reporting group description:

Surgical removal of necrotic mandibular bone

Subject analysis set title	Analysis of the effect of hyperbaric oxygen on ORN
Subject analysis set type	Intention-to-treat

Subject analysis set description:

While DAHANCA-21 was ongoing, recruitment was slow. At the time of initiation of DAHANCA-21, a similar trial was initiated in the Netherlands, the NWHHT 2009-1 trial. It was considered to join these trials from the beginning, but because both trials were ready to start at this time, it was decided to keep in touch and exchange experiences. After a few years, it became clear that recruitment was slow, and it was decided to include the Dutch data material in DAHANCA-21. Overall, 20 Dutch participants were included. 10 completed their participation, and further one participant was included in the intention-to-treat analysis. 60 participants completed the study, while another five were considered eligible for the intention-to-treat analysis. Of these 65, only 54 was from the DAHANCA-21 recruitment group, while the remaining 11 were Dutch.

Primary: Osteoradionecrosis

End point title	Osteoradionecrosis

End point description:

Osteoradionecrosis was evaluated on a scale from 0-4 based on the grading system Common Toxicity Criteria of Adverse Event version 3.0

End point type	Primary

End point timeframe:

1 year

End point values	Hyperbaric oxygen and surgery	Surgery	Hyperbaric oxygen and surgery	Surgery
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	34	26	34
Units: Osteoradionecrosis disease grades 0-4	26	34	26	34

End point values	Hyperbaric oxygen and surgery	Surgery	Analysis of the effect of hyperbaric oxygen on ORN	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	34	60	
Units: Osteoradionecrosis disease grades 0-4	26	34	60	

Statistical analyses

Statistical analysis title	Osteoradionecrosis at 1 year follow-up
Statistical analysis description: Multivariate analysis	
Comparison groups	Hyperbaric oxygen and surgery v Surgery
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 [1]
Method	Multivariate analysis
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	0.6
upper limit	6.3

Notes:

[1] - No statistically significant difference was found in the intent-to-treat analysis between ORN patients having received either HBO+surgery or HBO alone

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events could be assessed at any time point with in the study period of 1 year

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	HBO + standard care
Reporting group description: -	
Reporting group title	Standard care

Reporting group description: -

Serious adverse events	HBO + standard care	Standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 46 (4.35%)	2 / 51 (3.92%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head hitting hyperbaric chamber door			
subjects affected / exposed	1 / 46 (2.17%)	0 / 51 (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			
Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected hematoma of lower limb			

subjects affected / exposed	1 / 46 (2.17%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected reconstruction plate leading to sinuitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 51 (1.96%)	
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: 1 %

Non-serious adverse events	HBO + standard care	Standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	0 / 51 (0.00%)	
Ear and labyrinth disorders			
Ear problems during pressurization i hyperbaric chamber			
subjects affected / exposed	1 / 46 (2.17%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2010	Addition of centres in Bradford and Cardiff. Changes to monitoring plan. Investigator of Aarhus centre was changed.
06 March 2011	Addition of centres in Stockholm, Chichester/Portsmouth, Gdansk and Valencia. Exclusion of centre in Rome. Extension of approval date until April 30, 2015.
29 November 2012	Addition: Possibility for adding airbreaks to the protocol treatment for individual hyperbaric units
26 February 2014	Extension of approval date
06 May 2015	Addition of Midlands as centre
21 April 2016	Addition of Leeds, London and Hull as centres. Extension of approval date

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 planned number of 114 observations was not achieved.

Notes: