Final Study Report

Hyperbaric oxygen (HBO) in the treatment of radiation-induced xerostomia
A randomized, prospective multicenter study)

(Hyperbarer Sauerstoff (HBO) in der Behandlung der radiogenen Xerostomie
Eine randomisierte, prospektive Multizenter-Studie)

HBO-Study

Investigational Medicinal Products:
Hyperbaric oxygen - HBO (oxygen for medical purposes)

Indication: Radiation-induced Xerostomia

Phase of the clinical trial: Phase II

EudraCT-Number: 2007-002384-27

KKSH-037

Version Date: 18.08.2020
Version: V02F

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Sponsor
Martin-Luther -University Halle-Wittenberg,
represented by the chancellor, represented by the Dean of the Faculty of Medicine,
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Study Start (FPI): 28-05-2008
End of Study (LPO): 24-03-2011

Signatures

I agree with the content of the final study report in its final version. The reported clinical trial was conducted in accordance with the current version of the Declaration of Helsinki, ICHGCP Guideline (International Conference on Harmonization - Good Clinical Practice) and applicable national laws and regulatory requirements.

Author and Coordinating Investigator, Representative of the Sponsor	Prof. Thomas Kuhnt	31.08.2020 Date
Statistician	Apl. Prof. Andreas Wienke	31.8.2020 Date

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1. Name of the Sponsor

Martin-Luther-University Halle-Wittenberg, represented by the chancellor, represented by the Dean of the Faculty of Medicine.

2 Finished Products	3 Active Substances
Oxygen for medical purposes 100% (gas for inhalation)	Oxygen

4 Individual Study Chart

Not applicable

5 Study Title

Hyperbaric oxygen (HBO) in the treatment of radiation-induced xerostomia - A randomized, prospective multicenter study (HBO-Study)

- Protocol-Version: Final 02 (18 February 2008) was the first version approved by the EC on 20-03.2008 and by the CA on 12-03-2008. Version Final 01 (05 November 2007) was not approved neither by the EC nor by the CA. Version Final 02 was also the last valid version of the protocol.

6 Investigators	7 Study Trial Sites
Prof. Dr. med. Thomas Kuhnt	01: Universitätsklinikum Halle (Saale), Klinik und Poliklinik für Strahlentherapie, Ernst-Grube-Str. 40, 06097 Halle (Saale)
Dr. med. Christian Heiden	02: Klinikum Traunstein, Institut für kontrollierte hyperbare Sauerstoffbehandlung und Tauchmedizin, 83278 Traunstein

8 Publikationen

Not applicable

9 Study Period (years)

Date of first enrolment: 28-05.2008
Date of last patient last visit: 03-09-2010

Before achieving the required sample size, recruitment was terminated early on 24th March, 2011, because of inadequate recruitment. The last patient completed study therapy September 2010 and study follow-up in May 2017.

Both from an ethical and economic point of view, the continuation of the study was no longer feasible due to poor patient enrolment. A further delay of the final evaluation was not reasonable from a scientific point of view.

10 Phase of Development

Phase II.

The investigational medicinal product used in this trial had already a marketing authorization in the member state concerned.

11 Objectives

The aim of the study was to clarify whether a radiation-induced xerostomia can be effectively treated by standard HBO. For this purpose, the percentage change in total salivation was to be compared at rest and after provocation in the treatment and control groups. Secondary objectives were the investigator-dependent xerostomy graduation, the subjective xerostomia symptoms and quality of life as well as the safety of HBO therapy with regard to side effects and complications.

12 Methodology

This trial was designed as open label, two-arm, multicenter phase II study.

Initial examinations: 30 to 7 days before the start of therapy (screening) and 7 to 1 days before the start of therapy (Baseline)

Study treatment: HBO group: 40 HBO treatments TS 240/90, on 5 weekdays, 2.4 ATA, 100% O_2 (10-15 minutes compression with air, 90 minutes oxygen breathing with 2 air-pauses for 10 min after each 30 min oxygen breathing and 10 minutes decompression with oxygen). The treatments were to be performed in a multi-person pressure chamber using tightly fitting full face masks with demand system or head tents, whereby the increase in tissue oxygenation in the pressure chamber was to be controlled by means of a transcutaneous oxygen partial pressure measurement on the subclavicular skin.

Treatment in the control group: no further specific treatment, no (sham) compression.

Follow-up: 3 months

Interim evaluation: No interim evaluation planned and carried out

About 3-4 trial sites were planned to take part in this study. Actually, two sites were initiated and enrolled patients (see Section 6 and 7).

The IMP in this study was a authorized substance with a comprehensive safety data profile. Therefore the establishment of a DMC for this study was assessed as not necessary by the coordinating investigator. The EC was informed about that decision.

13 Number of Patients

See also flow chart appendix 21.1.

Planned number of cases: 100 (50 per group) / enrolled patients: 14 (7 per group) / registered patients: 14 (7 per group) / drop-outs/lost to follow up: 1 patient

13.1 Treatment exposure and dose reduction

In the HBO group, two patients did not receive the planned 40 HBO treatments but only 29 and 30, respectively; these two patients and one patient in the control group did not reach the regular end of the study (Section 21.1, Figure 5).

13.2 Demographic and Other Baseline Characteristics

The ITT/Safety evaluation data set included 14 patients, 7 per group. The gender distribution was equal in both groups with 4 men and 3 women. The mean age ± standard deviation was 64.4 ± 7.3 years in the HBO group and 63.6 ± 6.8 years in the control group (Table 1).

Table 1 Age, ITT/Safety n=14

Age [yr]	HBO n=7	Control n=7	Total n=14
N	7	7	14
MW	64.4	63.6	64.0
STD	7.3	6.8	6.7
Min	56	55	55
Q1	56.0	58.0	58.0
Median	64.0	64.0	64.0
Q3	73.0	71.0	71.0
Max	74	72	74

All patients had a complete tumor remission and the tumor therapy was completed. In 2 patients in the HBO group and one in the control group there were measures to remedy the xerostomia. In the HBO group there were 2 ex-smokers and no smoker, in the control group one smoker and one ex-smoker. The total salivation at rest (Table 2) was 0.021 ± 0.028 and 0.034 ± 0.069 ml/min in the HBO and control groups, respectively; after provocation 0.531 ± 1.180 and 0.494 ± 0.787 ml/min (Table 3).

Table 2 Total salivation at rest (fasting), ITT/Safety n=14

Baseline Total Salivation at rest (fasting) [ml/min]	HBO n=7	Control n=7	Total n=14
N	6	5	11
Missing	1	2	3
MW	0.0213	0.0343	0.0272
STD	0.0278	0.0689	0.0483
Min	0.000	0.000	0.000
Q1	0.0000	0.0012	0.0000
Median	0.0080	0.0060	0.0060
Q3	0.0500	0.0070	0.0500
Max	0.062	0.157	0.157

Table 3 Total salivation after provocation, ITT/Safety n=14

Baseline Total salivation after Provocation [ml/min]	HBO n=7	Control n=7	Total n=14
N	6	6	12
Missing	1	1	2
MW	0.5308	0.4940	0.5124
STD	1.1793	0.7873	0.9562
Min	0.000	0.007	0.000
Q1	0.0000	0.0200	0.0037
Median	0.0060	0.1025	0.0325
Q3	0.2430	0.7316	0.4873
Max	2.930	2.000	2.930

Two and five patients in the HBO group suffered from grade 2 and 3 xerostomia; all seven patients in the control group suffered from grade 3 xerostomia. Both the subjectively perceived dry mouth and the burden of dry mouth were rated on a scale of 0 (not at all) to 10 (intolerable) with a median of 9.0, i.e. quite intolerable, in both groups (Table 4 and Table 5).

Table 4 Dry mouth, ITT/Safety n=14

Baseline Dry mouth*	HBO n=7	Control n=7	Total n=14
N	7	7	14
MW	8.6	8.0	8.3
STD	1.8	1.8	1.8
Min	5	5	5
Q1	8.0	6.0	8.0
Median	9.0	9.0	9.0
Q3	10.0	9.0	10.0
Max	10	10	10

* How dry is your mouth today? 0 (not at all) to 10 (intolerable)

Table 5 Burden from dry mouth, ITT/Safety n=14

Baseline Burden from dry mouth*	HBO n=7	Control n=7	Total n=14
N	7	7	14
MW	8.3	7.6	7.9
STD	2.1	2.9	2.4
Min	5	3	3
Q1	6.0	5.0	6.0
Median	9.0	9.0	9.0
Q3	10.0	10.0	10.0
Max	10	10	10

* How much does your dry mouth stress you today? 0 (not at all) to 10 (intolerable)

13.3 Discontinuation / Drop-out / Protocol Violators

In three patients (1 HBO group, 2 Control) the evaluation of the exclusion criterion "Known incompatibility of Wrigley's Freident ®" was missing. These patients were not excluded. No other inclusion or exclusion criteria were violated.

14 Diagnosis and main inclusion criteria

Diagnosis: Radiation-induced Xerostomia

Inclusion criteria:

- complaints of xerostomia (visual analogue scale)
- at least 6 months after radiotherapy of the head and neck region including all salivary glands with at least 50 Gy
- objective hyposalivation / xerostomia (at rest < 0,25 ml saliva per minute, stimulated < 0,1 ml saliva per minute)
- patient must have given written informed consent

Exclusion criteria:

- prior radiotherapy was an intensity modulated radiotherapy
- prior hyperbaric oxygen therapy after radiotherapy
- conditions which might be an additional risk for the treatment with hyperbaric oxygen such as spontaneous pneumothorax within the last two years, surgery of the eardrum or the middle ear, acute infection of the upper airways, not adequately treated epilepsy, concurrent radio- or chemotherapy, hereditary spherocytosis, psychosis, lung emphysema, asthma, severe COPD, prior surgery of the thorax, pace maker
- myocardial infarction within the last 6 months
- drug therapy which might induce xerostomia
- known intolerance or hypersensitivity to Wrigley's Freident®
- pregnancy or breast-feeding women (for women aged less than 60 years a pregnancy test was mandatory)
- women of childbearing potential with unclear contraception. The following contraceptive methods are recommended: combined oral contraceptives or progesterone-only pill, hormone-dispensing or copper intra-uterine system, hormone patches, long-acting injections, vaginal ring
- treatment with other investigational drugs or participation in another clinical trial within 30 days prior to enrollment
- refusal of cooperation or consent

15 Investigational medicinal products, dose, mode of administration

Hyperbaric oxygen (HBO) (Medical oxygen), site dependent brand from hospital stock was used

Dose: 40 treatments with hyperbaric oxygen once per day, five days per week, 2.4 ATA, 100 % oxygen (10-15 minutes compression with air, 90 min of oxygen breathing - two 10 minutes break for breathing air after each 30 minutes of oxygen, 10 minutes decompression with oxygen

Route of administration: Respiratory Use (Noncurrent)

Formulation: Inhalation gas

16 Duration of treatment

For the patients of the HBO group, 40 HBO treatments TS 240/90, once daily, five times weekly, 2.4 ATA, 100 % O2 (10-15 min compression with air, 90 min oxygen breathing with 1 air break for 10 min after each 45 min oxygen breathing and 10 min decompression with oxygen) were planned.

The treatment was carried out in the multi-person pressure chamber using head tents with demand system. Treatment duration thus 8 weeks (according to treatment scheme)

17 Test product, dose, mode of administration

Not applicable

18 Criteria for evaluation

18.1 Efficiency

The primary parameter to determine efficacy is the percentage change in total salivation on day 28 (4 weeks HBO), day 56 (8 weeks HBO) and day 146 (3 months after HBO) compared

to the baseline (before treatment) at rest and after provocation. However, the absolute change in total salivation instead of the percentage change was evaluated, since in some patients salivation at baseline was 0ml/min. Due to the low number of cases (14 instead of 100 patients) and the high number of incorrect values, no statistical tests were used for the analysis of the secondary endpoints. The improvement of quality of life by means of QLQ-H&N35 could not be determined because only very few questionnaire data were available.

18.2 Safety

The safety analyses were performed with the ITT/ safety evaluation data set (all 14 patients).

The adverse events (AE) were coded with the Medical Dictionary for Activities in the Context of Drug Regulatory Affairs (MedDRA® version 16.1, English) and grouped by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA system. The frequency of AEs was determined overall, by degree and in relation to HBO treatment.

19 Statistical methods

SAS 9.1 (English) was used for the statistical evaluation. The primary analyses of the respective changes in total salivation between the HBO and control groups were performed with two-sided T-tests (significance level alpha=5%) without adjustment of the p-values for multiple testing. The secondary target criteria were evaluated descriptively, the planned T and Chi-square tests were not applied due to the data available. The improvement of the QoL situation could not be evaluated. However, the scores from the few available QoL questionnaires were listed on a patient-by-patient basis.

20 Summary / Conclusions

20.1 Efficiency Results

The **primary endpoint** was the respective changes of the total salivation compared to baseline. No statistically significant difference between HBO and control group could be shown at any time. The results of the two-sided T-tests are shown in the Table 6 with the p-values not adjusted for multiple testing.

Table 6: T-tests- change in total salivation [ml/min] compared to baseline, ITT n=14

a. at rest

Change of total salivation at rest [ml/min]	HBO		Control		Difference (HBO - Control)		T-Test		
	N	NMISS	N	NMISS	MW	[95% CI]	t	DF	p
Visit 3 (Day 28)	4	3	5	2	-0.003	[-0.1027,0.0970]	-0.07	7	0.948
Visit 4 (Day 56)	6	1	5	2	-0.029	[-0.1275,0.0699]	-0.61	5.21	0.565
Visit 5 (Day 146)	6	1	4	3	0.286	[-0.6655,1.2379]	0.86	5.38	0.428

b. after provocation

Change of total salivation after provocation [ml/min]	HBO		Control		Difference (HBO - Control)		T-Test		
	N	NMISS	N	NMISS	MW	[95% CI]	t	DF	p
Visit 3 (Day 28)	4	3	6	1	-0.359	[-0.9862,0.2673]	-1.32	8	0.223
Visit 4 (Day 56)	6	1	6	1	-0.631	[-1.8179,0.5567]	-1.18	10	0.264
Visit 5 (Day 146)	6	1	4	3	0.019	[-1.8639,1.9010]	0.03	5.08	0.978

The course of the total salivation at rest and after provocation was graphically displayed in spaghetti plots (Figure 1 and 2).

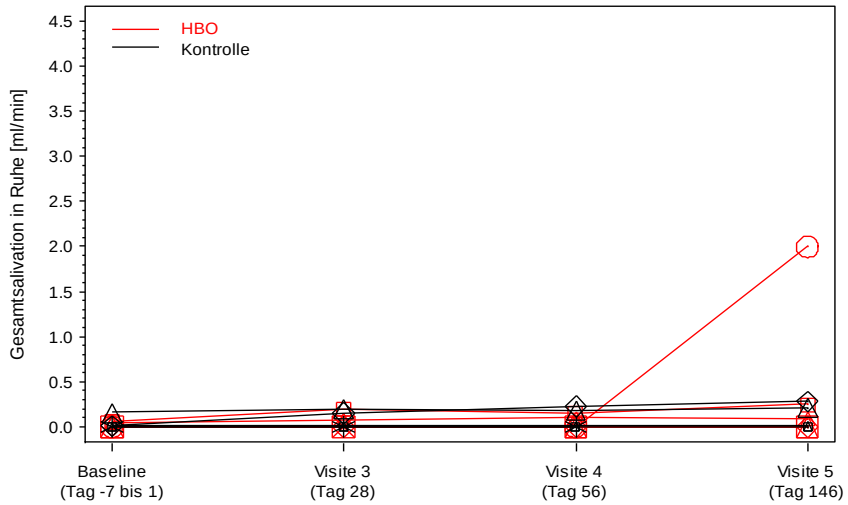

Figure 1 Total salivation at rest over time

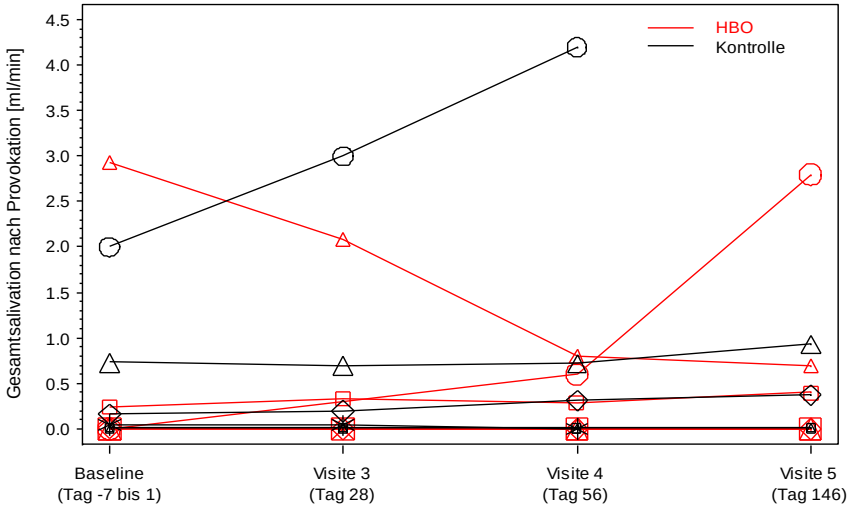

Figure 2 Total salivation after provocation over time

Secondary efficacy endpoints were

- Improvement of the xerostomy score (change in the degree of xerostomia as well as improvement of the overall salivation at rest and after provocation)
- Improvement of the subjectively perceived dry mouth and the stress caused by dry mouth
- Improvement of the QoL situation (Module EORTC QLQ-H&N35)

compared to baseline in each case respectively.

The secondary endpoints were only evaluated descriptively due to the data available. The degree of xerostomia did not change in most patients compared to baseline (Table 7).

Table 7 Change in the degree of xerostomia compared to baseline, ITT n=14

Change Grade of Xerostomia		HBO n=7 N	Control n=7 N	Total n=14 N
Visit 3	Missing	2	.	2
	-1	.	1	1
	0	5	6	11
Visit 4	Missing	1	.	1
	-2	.	1	1
	-1	2	1	3
	0	4	5	9
Visit 5	Missing	.	1	1
	-1	1	2	3
	0	6	4	10

The improvement of the total salivation compared to baseline both at rest and after provocation was similarly distributed in both groups (Table 8).

Table 8 Improvement of total salivation compared to baseline, ITT n=14

Total salivation compared to baseline		HBO n=7	Control n=7	Total n=14	HBO n=7	Control n=7	Total n=14
		at rest			after provocation		
Visit 3	Missing	3	2	5	3	1	4
	excellent	1	1	2	0	1	1
	good	1	1	2	0	0	0
	bad	2	3	5	4	5	9
Visit 4	Missing	1	2	3	1	1	2
	excellent	2	1	3	1	1	2
	good	0	1	1	0	1	1
	bad	4	3	7	5	4	9
Visit 5	Missing	1	3	4	1	3	4
	excellent	2	2	4	1	1	2
	good	1	0	1	1	1	2
	bad	3	2	5	4	2	6

On average, the subjectively perceived dry mouth decreased slightly more in the HBO group than in the control group in rounds 4 and 5 compared to the baseline (Table 9).

Table 9 Change in dry mouth compared to baseline, ITT n=14

	Change of dry mouth	N	NMiss	MW	STD	Min	Q1	Median	Q3	Max
HBO n=7	Visit 3	5	2	-0.4	0.5	-1	-1.0	0.0	0.0	0
	Visit 4	6	1	-2.0	1.4	-4	-3.0	-2.0	-1.0	0
	Visit 5	7	0	-2.0	1.6	-4	-4.0	-1.0	-1.0	0
Control n=7	Visit 3	6	1	-0.7	1.6	-4	0.0	0.0	0.0	0
	Visit 4	6	1	-0.3	0.8	-2	0.0	0.0	0.0	0
	Visit 5	6	1	-0.2	0.4	-1	0.0	0.0	0.0	0

	Change of dry mouth	N	NMiss	MW	STD	Min	Q1	Median	Q3	Max
Total	Visit 3	11	3	-0.5	1.2	-4	-1.0	0.0	0.0	0
	Visit 4	12	2	-1.2	1.4	-4	-2.0	-0.5	0.0	0
	Visit 5	13	1	-1.2	1.5	-4	-1.0	-1.0	0.0	0

The same was true for the subjectively perceived burden of dry mouth during all three visits (Table 10).

Table 10 Change in the burden of dry mouth compared to baseline, ITT n=14

	Change in the burden of dry mouth	N	NMiss	MW	STD	Min	Q1	Median	Q3	Max
HBO n=7	Visit 3	5	2	-0.8	0.8	-2	-1.0	-1.0	0.0	0
	Visit 4	6	1	-1.7	1.4	-4	-2.0	-1.5	-1.0	0
	Visit 5	7	0	-1.1	1.8	-4	-3.0	-1.0	0.0	1
Control n=7	Visit 3	6	1	-0.2	0.8	-1	-1.0	0.0	0.0	1
	Visit 4	6	1	0.2	1.5	-1	-1.0	0.0	0.0	3
	Visit 5	6	1	-0.5	0.5	-1	-1.0	-0.5	0.0	0
Total	Visit 3	11	3	-0.5	0.8	-2	-1.0	0.0	0.0	1
	Visit 4	12	2	-0.8	1.7	-4	-1.5	-1.0	0.0	3
	Visit 5	13	1	-0.8	1.3	-4	-1.0	-1.0	0.0	1

The time course with regard to dry mouth can be seen in Figure 3 and 4.

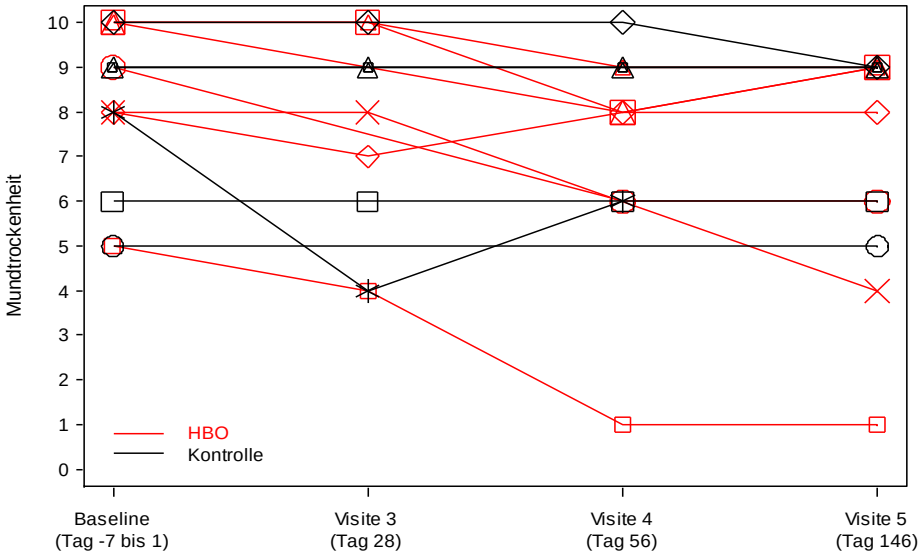

Figure 3 Subjectively perceived burden of dry mouth over time

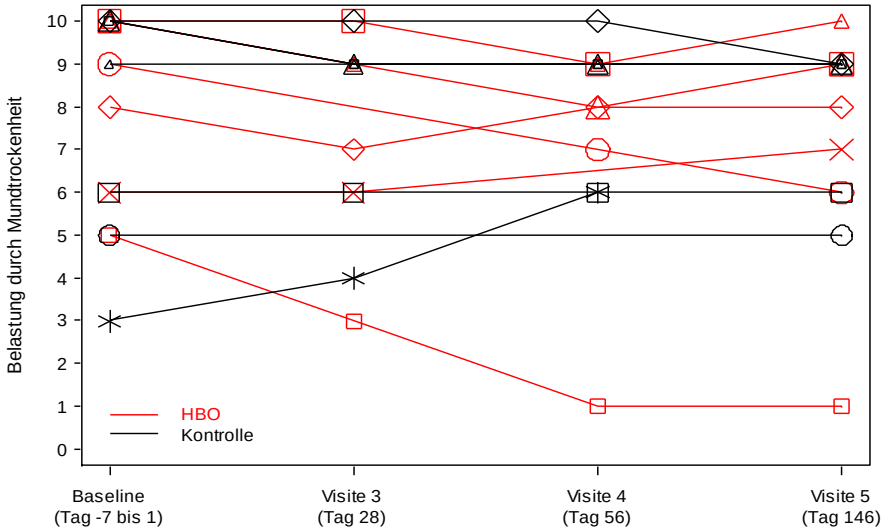

Figure 4 Subjectively perceived burden of dry mouth over time

The improvement in quality of life could not be conclusively assessed, as the associated QoL questionnaires were only partially completed. However, the scores for the available data were calculated according to the QLQ-C30 Scoring Manual of EORTC and presented patient by patient (Table 11 and 12).

Table 11 EORTC QLQ-H&N35 Scores (0=no complaints to 100=severe complaints), ITT n=14 a. Scales of symptoms: pain, dysphagia, odour/taste disorders, speaking problems, eating in company, social environment, sexual problems; individual items: teeth, mouth opening

Arm	PATID	Visit	Day	HN PAIN	HN SWALLOW.	HN SENSES	HN SPEECH	HN SOCIAL EATING	HN SOCIAL CONTACT	HN SEXUAL.	HN TEETH	HN OPENING MOUTH
HBO	01-001	Baseline	.	67	42	67	0	33	0	33	33	67
		Visit 5	161	17	33	0	0	17	0	33	33	0
	01-003	Visit 5	204	0	25	33	44	92	40	100	67	100
	01-007	Visit 4	.	25	75	67	44	75	0	0	0	67
	02-002	Visit 4	.	8	25	17	56	42	33	0	0	0
	02-004	Baseline	.	.	.	.	.	.	.	.	.	.
	02-005	Baseline	.	.	.	.	.	.	.	.	.	.
	02-010	Baseline	.	.	.	.	.	.	.	.	.	.
Contr.	01-002	Baseline	.	.	.	.	.	.	.	.	.	.
	01-002	Visit 5	162	0	17	17	11	17	0	0	67	33
	01-005	Visit 5	150	58	25	67	22	25	20	.	100	67
	02-001	Baseline	.	.	.	.	.	.	.	.	.	.
	02-003	Baseline	.	0	0	50	33	83	13	100	0	.
	02-008	Baseline	.	.	.	.	.	.	.	.	.	.
	02-011	Baseline	.	.	.	.	.	.	.	.	.	.
	02-012	Baseline	.	.	.	.	.	.	.	.	.	.

Table 12 b. Continuation of single items: dry mouth, tough saliva, cough, feeling ill, analgesics, dietary supplement, feeding tube, weight loss, weight increase.

Arm	PATID	Visit	Tag	HN DRY MOUTH	HN STICKY SALIVA	HN COUGHED	HN FELT ILL	HN PAIN KILLERS	HN NUTRIT. SUPP	HN FEED. TUBE	HN WEIGHT LOSS	HN WEIGHT GAIN
HBO	01-001	Baseline	.	100	100	33	0	0	0	0	0	100
		Visit 5	161	100	100	33	0	0	0	0	0	100
	01-003	Visit 5	204	100	0	0	0	100	100	100	100	.
	01-007	Visit 4	.	100	0	100	0	0	100	0	100	0
	02-002	Visit 4	.	100	100	33	0	100	100	100	100	100
	02-004	Baseline	.	.	.	.	.	.	.	.	.	.
	02-005	Baseline	.	.	.	.	.	.	.	.	.	.
	02-010	Baseline	.	.	.	.	.	.	.	.	.	.

Arm	PATID	Visit	Tag	HN DRY MOUTH	HN STICKY SALIVA	HN COUGHED	HN FELT ILL	HN PAIN KILLERS	HN NUTRIT. SUPP	HN FEED. TUBE	HN WEIGHT LOSS	HN WEIGHT GAIN
Contr	01-002	Visit 5	162	33	33	0	0	0	0	0	0	0
	01-005	Visit 5	150	67	33	67	100	0	0	0	0	100
	02-001	Baseline	.	.	.	.	.	.	.	.	.	.
	02-003	Baseline	.	100	67	0	67	0	0	100	0	100
	02-008	Baseline	.	.	.	.	.	.	.	.	.	.
	02-011	Baseline	.	.	.	.	.	.	.	.	.	.
	02-012	Baseline	.	.	.	.	.	.	.	.	.	.

20.2 Safety Results

Analysis of adverse events:

Table 13 AEs by SOC, PT and degree, Safety n=14 N: Number of patients, N AE: Number of AEsprovides an overview of the AEs recorded. For 2 out of 7 patients in the HBO group AEs were recorded, while in the control group there was one AE in one of 7 patients. Only AEs of severity 1 and 2 occurred. These included headache, temporarily reduced visual acuity, fatigue and barotrauma in the HBO group and headache in the control group.

Table 13 AEs by SOC, PT and degree, Safety n=14 N: Number of patients, N AE: Number of AEs

Adverse Events by SOC, PT and Grade			HBO n=7		Control n=7		Total n=14	
			N	N AE	N	N AE	N	N AE
Any AE		Grade 1	1	1	1	1	2	2
		Grade 2	2	3	0	0	2	3
		AE total	2	4	1	1	3	5
Nervous system disorders		Grade 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
	Headache	Grade 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
Eye disorders		Grade 1	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
	Visual acuity reduced transiently	Grade 1	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
Ear and labyrinth disorders		Grade 1	0	0	1	1	1	1
		AE total	0	0	1	1	1	1
	Ear pain	Grade 1	0	0	1	1	1	1
		AE total	0	0	1	1	1	1
General disorders and administration site conditions		Grad 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
	Fatigue	Grade 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
Injury, poisoning and procedural complications		Grade 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1
	Barotrauma	Grade 2	1	1	0	0	1	1
		AE total	1	1	0	0	1	1

For all AEs in the HBO group, the causality for HBO treatment was assessed as certain (Table 14). The AEs are listed by patient in Table.

Table 14 Adverse events (MedDRA version 16.1 EN), Safety n=14

Arm	PATID	reported AE	Preferred Term (PT)	CTC-Grade	Start Day	End Day	Causal. HBO	Outcome
HBO	01-001	Barotrauma II d. Mittelohrs re. (Paukenerguss)	Barotrauma	2	15	16	yes	recovered/resolved with sequelae
	01-003	Kopfschmerzen	Headache	2	15	68	yes	recovered/resolved
		Muedigkeit	Fatigue	2	15	68	yes	recovered/resolved
		reversible Visusminderung	Visual acuity reduced transiently	1	64	68	yes	recovered/resolved
Contr.	01-005	Ohrenschmerzen	Ear pain	1	62	62	no	recovered/resolved

20.2.1 Serious Adverse Events

No SAEs were reported.

20.2.2 Deaths

No deaths were reported.

20.3 Conclusions

Due to poor recruitment, the study had to be terminated prematurely. Therefore, no significant conclusions can be drawn from the study. However, the evaluation of the relatively few patients in the HBO group compared to the non-HBO group did not show any indication of an improvement in the saliva flow rate. In the subjective evaluation of dry mouth, the HBO therapy seems to relieve the symptoms a little. Nothing more can be derived from these few data. However, the results, although they must be interpreted with all due caution, seem to indicate that a renewed attempt to use HBO therapy to alleviate radiogenic xerostomia is not indicated once again.

The included patient population had the expected characteristics, which did not differ significantly in both groups. Due to this small number of cases (14 instead of 100 patients) for the primary endpoint analysis and the high number of missing values, no statistical tests were used for the analysis of the secondary endpoints. The improvement in quality of life using the QLQ-H&N35 could not be determined because only isolated questionnaire data were available. The number of AEs was the same in both groups. The severity of all AEs was between 1-2, so that HBO treatment for this patient group can be considered safe.

21 Appendix

21.1 CONSORT Flow Diagramm

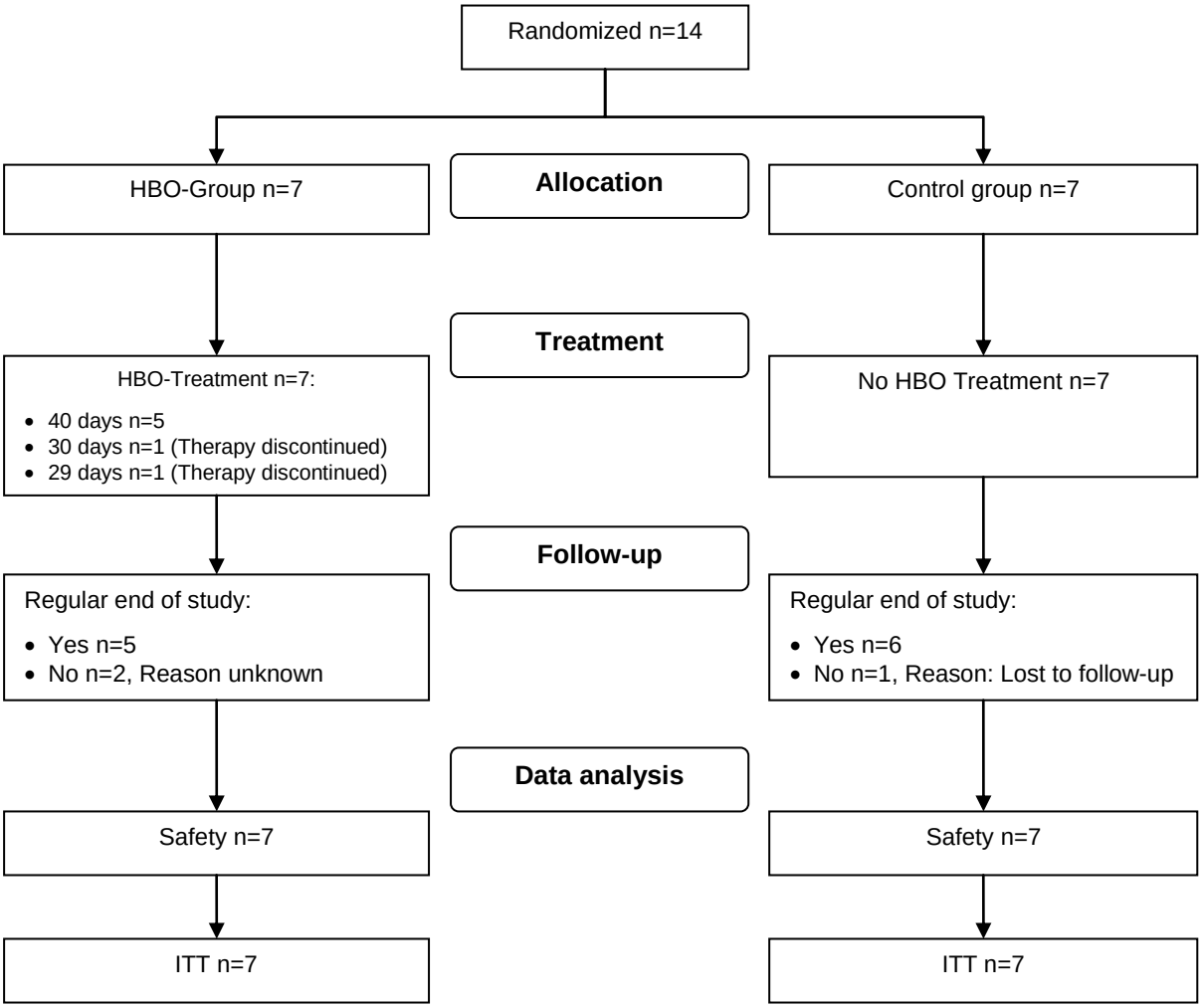

Figure 5 Consort flow diagram