

LARYNGO-PHARYNGEAL REFLUX – A RANDOMIZED CONTROLLED TRIAL

A randomized, open label, three arm parallel design, single-site study, comparing the effects of esomeprazole and alginate on top of lifestyle guidance in patients complaining that the throat did not function, and having inter-arytenoids oedema in the larynx



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Abstract

- **Introduction:**

- There is a very relevant discussion whether or not laryngopharyngeal reflux does exist. When looking at high speed films, it is clearly seen that the mucus from the oesophagus comes up to the arytenoids, and disappears again within 0.2-0.3 seconds. The problem is which measures to use, in order to optimize diagnostics and treatment effect.

- **Material / methods:**

- 237 patients with baseline complaints that the larynx did not function, with inter-arytenoid oedema at high speed films and videostroboscopy (from the RFS) were calculated at entrance into the study, two weeks after treatment and at follow-up, after a two to three month period. 2 supplementary subjective complaint at least (from the RSI) were filed in the database.
- The patients were randomized into three groups of 1) lifestyle correction, 2) lifestyle correction and proton pump inhibitor, 3) lifestyle correction, proton pump inhibitor and alginate. The lifestyle treatment included correction of GERD related habits, especially intake of specific food, and also genetic intolerances, allergies, infections and environmental provocation.
- High speed films were used to validate inter-arytenoid oedema, supplemented with the MDVP programme by Laryngograph Ltd., measuring frequency and intensity variation on a sustained tone and on reading of a standard text, electroglottographic measures included. A power calculation showed that 49 patients in each group was necessary for a 5% difference with a 25% standard deviation.

- **Results / Conclusion:**

- There was a reduction of the oedema located at the inter-arytenoids region as well as of the laryngeal complaints. The acoustical measures could not be used for documenting effect of treatment. There was no difference between the three treatment approaches.

Trial start

Flowchart 1: Comparison of treatments for laryngo-pharyngeal reflux (LPR)

Eligible LPR patients

Requirement for inclusion was symptoms of LPR, with the subjective complaint that “my throat does not function” and inter-arytenoid oedema. The symptom duration was at least 2-4 weeks.

Supplementary inclusion criteria were the presence of two or more of the following subjective complaints:

- Hoarseness or a problem with your voice
- Clearing your throat / excess throat mucous or postnasal drip
- Difficulty swallowing food, liquids, or pills (dysphagia)
- Coughing after you ate or after lying down, troublesome or annoying cough
- Breathing difficulties or choking episodes (larynx spasms and hick ups)
- Sensations of something sticking in your throat or a lump in your throat (globules)
- Heartburn, chest pain, indigestion or stomach acid coming up, pain or burning feeling in the throat

Tests: High speed films, video-stroboscopy, voice analysis including jitter%, shimmer%, electroglottography (EGG) closed phase Qx% on a sustained tone (/ah/) frequency variation%, loudness variation%, electroglottography (EGG) closed phase Qx% on reading of a standard text.



N = number of included

Life style guidance

Life style guidance +
Proton pump inhibitors 1 X 40mg/day.

Life style guidance + Proton pump inhibitors 1 X 40mg/day + Gaviscon 1-2 chewing tablets after the main meal and at bedtime.

Clinical re-examination: high speed films, video-stroboscopy, voice analyses (reading of a standard text + sustained tone on /ah/). Assessment of inter-arytenoid oedema. Asking patients about subjective complaints.

Clinical re-examination and follow-up: high speed films, video-stroboscopy, voice analyses (reading of a standard text + sustained tone on /ah/). Assessment of inter-arytenoid oedema. Asking patients about subjective complaints.

ASSESSMENT OF OUTCOME

Statistical comparison of the outcome of the three groups → formation of a conclusion

14 days

2-3 months

Appearance of mucus

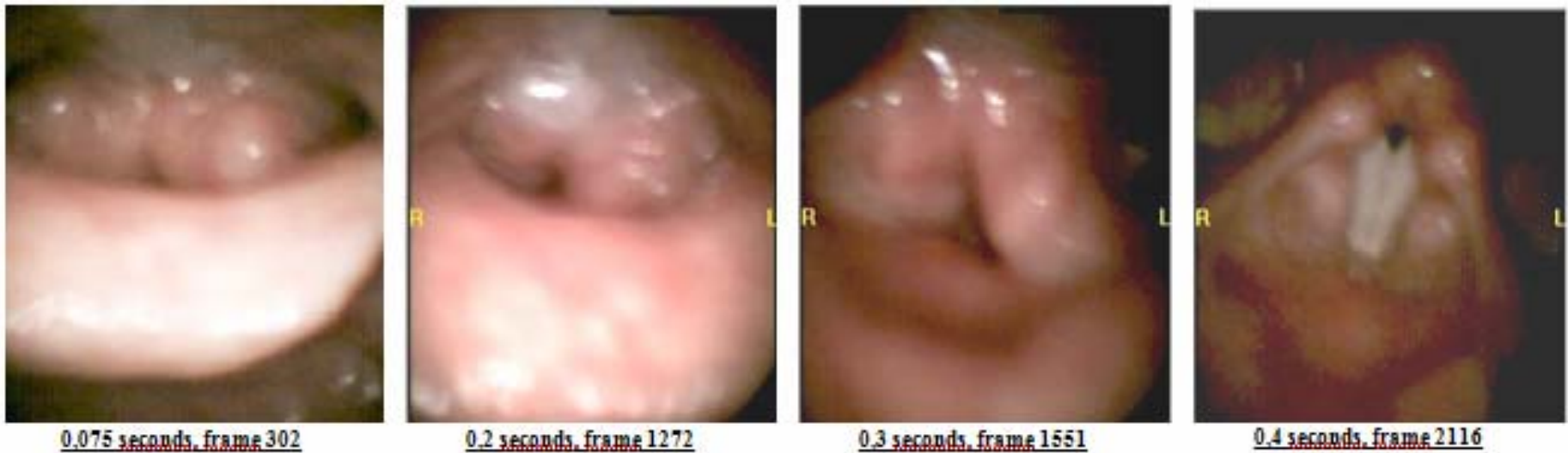


Figure 1: Frames taken from a high-speed video set on recording 4000 pictures per second. The picture, at frame 1272 shows the appearance of mucus in the larynx, and shortly after (frame 1551) it is reduced. On frame 2116, the mucus has disappeared. The process took a total of 0.2 seconds.

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	Lifestyle	Lifestyle + PPI	Lifestyle, PPI + Alginate
	N=78	N=70	N=89
Age (yrs)			
<i>Mean</i>	42.1	42.2	41.4
<i>SD</i>	15.6	15.1	15.6
Gender			
<i>Males</i>	22 (28%)	17 (24%)	26 (29%)
<i>Females</i>	56 (72%)	53 (76%)	63 (71%)

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	<u>First consultation</u>			<u>Second consultation</u>			<u>Third consultation</u>		
	<u>Number of patients with complaints</u>			<u>Number of patients with complaints</u>			<u>Number of patients with complaints</u>		
	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate
	N=78	N=70	N=89	N=65	N=59	N=71	N=46	N=43	N=55
<i>Subjective complaints</i>									
<i>"My throat/voice does not function"</i>	78	70	89	52	60	55	22	40	33
<i>Sensation of something sticking in your throat or a lump in your throat (globules)</i>	48	64	54	36	36	31	17	27	24
<i>Hoarseness or a problem with your voice</i>	54	70	61	36	48	47	16	30	25
<i>Excess throat mucous or postnasal drip/clearing your throat</i>	65	75	66	44	55	47	26	37	31
<i>Breathing difficulties or choking episodes (larynx spasms and hick ups)</i>	31	34	29	23	23	18	9	11	7
<i>Heartburn, chest pain, indigestion/stomach acid coming up, pain or burning feeling in the throat</i>	40	52	42	24	23	27	9	14	12
<i>Difficulty swallowing food, liquids, or pills (dysphagia)</i>	31	46	32	17	20	18	12	17	15
<i>Coughing after you ate or after lying down, troublesome or annoying cough</i>	39	53	48	28	36	31	11	19	15
Total number of symptoms									
Mean	5.22	5.40	5.35	3.54	3.76	3.34	2.06	1.90	2.17
SD	1.49	1.36	1.49	2.39	2.27	2.27	2.46	2.26	2.30
Difference to Lifestyle (=LS) means [95% CI]					0.12 [-0.59; 0.82]	-0.28 [-0.94; 0.39]			
p-value (#)					0.75	0.41			

(#) Comparison of means between treatment groups to Lifestyle treatment group. The test is a two-sided test in the linear statistical model that includes baseline number of symptoms as a covariate and treatment as a fixed effect. (CI =confidence interval)

	<u>First consultation</u>			<u>Second consultation</u>			<u>Third consultation</u>		
	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate	Lifestyle	Lifestyle + PPI	Lifestyle + PPI + Alginate
Oedema of the inter-arytenoid region	<i>Number of patients</i>			<i>Number of patients</i>			<i>Number of patients</i>		
<i>Grade 1</i>	0	0	0	9	8	11	13	13	13
<i>Grade 2</i>	35	29	35	35	29	40	23	21	28
<i>Grade 3</i>	34	33	41	18	17	19	9	9	13
<i>Grade 4</i>	8	8	13	3	2	0	1	0	0
<i>Grade 5</i>	1	0	0	0	0	0	0	0	0
N	78	70	89	65	56	70	46	43	54
Mean grade	2.68	2.70	2.75	2.23	2.23	2.11	1.96	1.91	2.00
SD	0.712	0.667	0.695	0.745	0.738	0.649	0.759	0.718	0.700
Range	2-5	2-4	2-4	1-4	1-4	1-3	1-4	1-3	1-3
Difference to Lifestyle treatment (LS) means [95% CI]					-0.03 [-0.25; 0.20]	-0.14 [-0.35; 0.07]			
p value (#)					0.81	0.20			

(#) Two sided test comparison to Lifestyle treatment group in a statistical model including baseline as covariate and treatment group as fixed effect. (CI = confidence interval)

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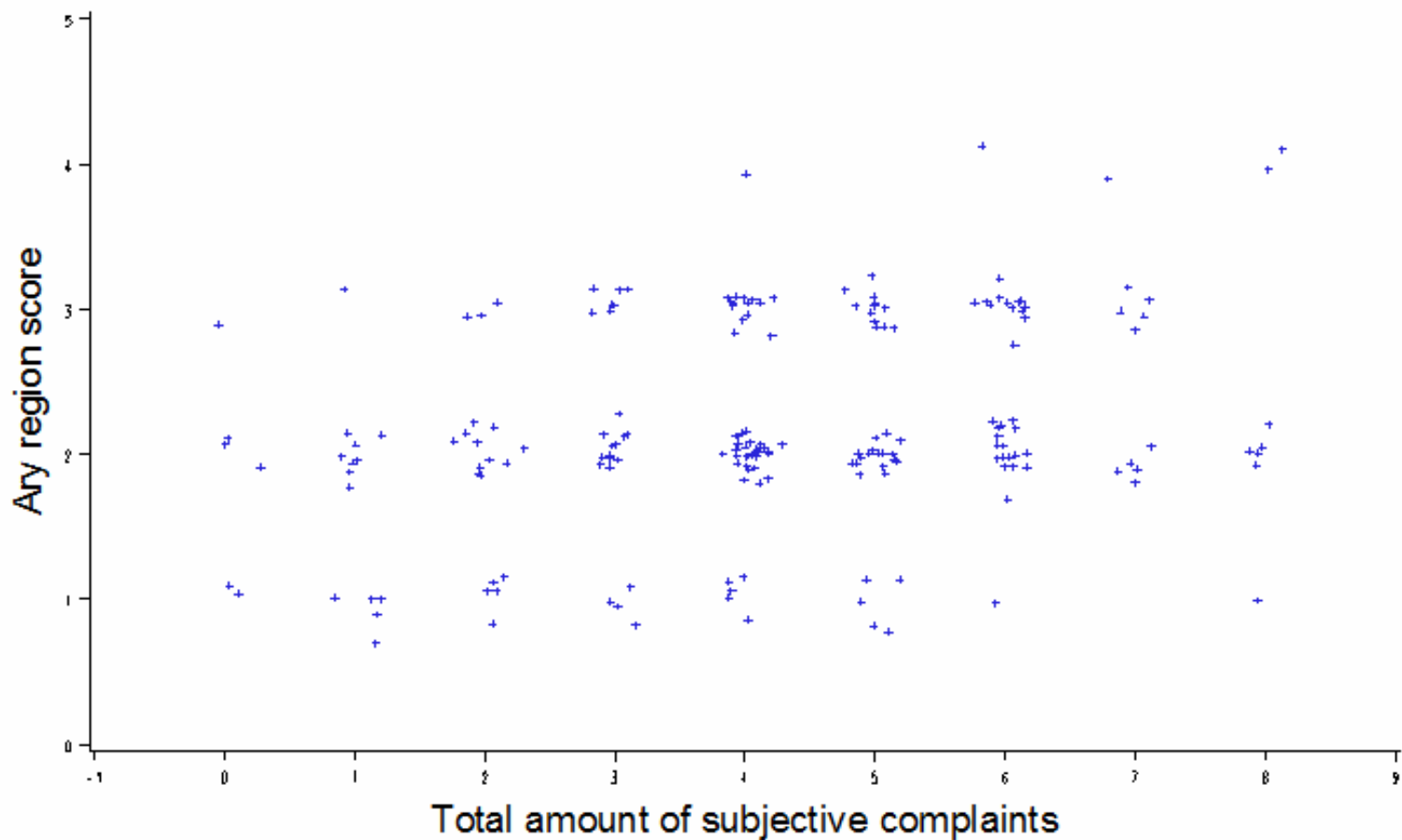
	<u>First consultation</u>				<u>Second consultation (week 2)</u>						<u>Third consultation</u>				
	<i>Raw data</i>				<i>Raw data</i>				<i>Difference to Lifestyle (##)</i>		<i>Raw data</i>				
	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>	<i>Adjusted Mean</i>	<i>95% CI</i>	<i>p-value</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>
Lifestyle Reading															
<i>Frequency% (#)</i>	77	10.2	10.3	2.6-56	64	9.5	8.07	2.6-54				45	8.60	6.74	2.3-39
<i>Intensity% (#)</i>	76	15.7	5.57	9.3-46	63	15.2	4.28	7.5-31				45	15.0	2.72	10-20
<i>QX%</i>	77	47.7	6.10	25-60	64	47.6	5.56	31-61				45	47.9	5.22	36-59
<i>Sustained Tone /ah/</i>															
<i>Jitter% (#)</i>	76	3.5	11.14	0.21-78	63	3.2	9.18	0.23-62				44	2.51	7.31	0.16-46
<i>Shimmer% (#)</i>	75	9.9	11.05	1.9-38	62	8.2	4.84	2.1-26				44	7.21	3.94	0.72-20
<i>QX%</i>	76	45.5	7.759	28-64	63	46.7	7.36	30-66				44	47.5	8.95	10-69
Lifestyle + PPI Reading															
<i>Frequency% (#)</i>	69	11.0	9.44	0.30-59	59	9.0	6.36	1.3-38	-6%	[-23%;15%]	0.56	42	10.7	10.26	0.53-61
<i>Intensity% (#)</i>	68	16.2	5.15	7.5-41	59	14.8	3.94	4.7-28	-6%	[-14%;2%]	0.16	42	16.2	6.05	4.7-47
<i>QX%</i>	69	47.7	5.76	35-58	59	48.9	5.61	34-60	0.86	[-0.77;2.48]	0.33	42	48.0	6.41	32-57
<i>Sustained Tone /ah/</i>															
<i>Jitter% (#)</i>	69	2.4	6.19	0.24-49	59	1.83	3.65	0.19-24	-11%	[-37%;26%]	0.52	42	3.00	6.33	0.17-35
<i>Shimmer% (#)</i>	68	8.8	6.23	1.9-38	59	7.24	4.07	0.77-19	-15%	[-29%;2%]	0.089	42	8.17	4.78	0.32-19
<i>QX%</i>	69	47.8	9.61	24-67	58	46.2	7.00	26-64	-1.92	[-4.06;0.22]	0.078	41	45.9	6.71	28-59
Lifestyle + PPI + Alginate Reading															
<i>Frequency% (#)</i>	89	11.0	8.04	2.4-57	71	9.67	8.27	2.2-54	-5%	[-22%;15%]	0.60	57	9.36	7.82	0.61-48
<i>Intensity% (#)</i>	89	16.8	4.04	6.8-35	71	15.7	4.15	4.6-33	-1%	[-9%;7%]	0.82	58	16.1	3.65	7.7-26
<i>QX%</i>	89	47.6	6.24	34-63	70	47.1	6.00	27-58	-0.78	[-2.34;0.77]	0.32	58	46.9	5.96	29-58
<i>Sustained Tone /ah/</i>															
<i>Jitter% (#)</i>	89	2.6	6.83	0.19-57	70	1.13	1.43	0.22-7.6	-20%	[-42%;12%]	0.20	57	2.24	7.15	0.18-53
<i>Shimmer% (#)</i>	89	9.3	6.09	1.3-35	70	7.86	4.22	2.2-25	1%	[-15%;20%]	0.94	58	8.39	4.84	2.4-29
<i>QX%</i>	89	46.0	8.41	29-66	70	46.5	7.30	29-63	-0.64	[-2.67;1.38]	0.53	58	47.6	7.09	26-61

#) log transformed prior to analysis. Differences are presented as ratios.
##) Two sided test comparison to Lifestyle treatment group in a statistical model including baseline as covariate, treatment group as fixed effect, CI= confidence interval

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Figure 2: Scatter plot of the total amounts of subjective complaints (abscissa) versus oedema of the inter-arytenoid region, week 2 (ordinate)



Data are jittered (added noise) to show all data points

Spearman correlation: 0.280 [95%CI: (0.149;0.410)]

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Conclusion

- Lifestyle correction, added with esomeprazole, and added with esomeprazole and alginate, were randomly studied on laryngo-pharyngeal reflux (LPR) in 237 patients based on a power calculations for a sufficient number of patients in the three groups. All three treatment options were effective for treatment. The study was based on a Cochrane review on laryngeal reflux and hoarseness showing that earlier materials were too small with various baselines for hoarseness.
- Adding esomeprazole or adding the combination of esomeprazole and alginate on top of lifestyle advice does not give a clinically relevant benefit to the patient in LPR. This study supports that laryngo-pharyngeal reflux is treated unnecessary with proton pump inhibitor drugs, and that further evidence is needed from the pharmaceutical companies before laryngo-pharyngeal reflux patients can be recommended to use proton pump inhibitors to treat their symptoms. A p value of <0.0001 was found for the correlation between the subjective complaints and inter-arytenoid oedema on high speed films. The visual score of oedema of the inter-arytenoid region on high speed films together with subjective complaints are usable for documentation of the effect of eventual new drugs.

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