Interactions between basic and clinical research

Evaluation of vocal cord nodules

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Abstract

1. Introduction

After forty years of research in the area of voice function one of the author's batons for the next generation seems to be: evidence.
The set-up of evidence is accepted although not optimal in e.g. the pharmaceutical industry - and cancer research in which field the (chosen) instructor for a protocol on vocal cord nodules was found in the year 2002. An ear-nose-throat specialist for singers in Paris, and a trained resarcher in Oxford edited the protocol, and a randomisation was planned. The protocol seemed to be the first for interventions for vocal cord nodules. A Vonod-team for the randomisation was build after the given suggestions, but the team did not succeed to get money, even if the Danish State Health Care Research Foundation in November 2003 approved the present author´s application for the study, they have very small funds. Other/several teams and models should be considered. Experiences from our two pilot studies with their own protocols will be given.

2. Methods

Every time an idea in natural science is cooked down to a hypothesis a protocol (and following trial) is needed to document the evidence. In the protocol the background of the hypothesis is probably the main issue, because all ideas have a historical reference. This is why the statisticians should be feared and handled with care: Evidence is related to the basic background of the relevant field. At best the area of voice research should educate their own statistcians as in other fields.
Inclusion criteria should be handled and thereafter the 0 hypothesis clearly discribed. Types of randomisation and interventions together with types of outcomes and follow-up time must be well documented in relation to the background studies. Thereafter the protocol can be discussed with a relevant statistician who carries out the standardised practical, blinded randomisation and statistical calculations based on the hypothesis and outcome as made by the researchers. A relevant statistical knowledge on the researchers side is necessary now-a-days to argue with statisticians without knowledge of our field. Mostly a two-tailed significancy of $p<0.01$ is relevant. The Type 1 error (e.g.1%) and Type II error (e.g.10 %) gives the power of the analysis (e.g. 90%). The difference % between the intervention arms must be calculated. A good data monitoring and safety group has a high order.

3. Materials and Models

A description of the statistically necessary populations/models (e.g. patients, apparature/s, genes or other scenario) is made. The objectives and outcomes are described based on an intention to treat /to use. The trial design thereafter demands a statistical calculation based on a comparison and randomisation between at least two groups of populations/models. The amount of experiments/ subjects is depending on the outcome and significancy, chosen by the researchers.
The protocol also includes description of ethics, assessment of efficacy and safety, access to documents, data handling and record keeping, finance and reassurance, publication policy, spin-off projects and references. Appendices must include detailed description of procedures including consents ect. The person/s behind the idea must be aware of the responsibility which cannot be left to the statisticians or the funding.

4. Results and Discussion

Only two -recent- evidence based studies (RCTs) have been found in an electronic search that include vocal cord nodules. For laryngo-pharyngeal reflux three evidence based studies (RCTs) have been found. A meta-analysis seems not to be possible for the three studies. Examples and references will be given.

Key words: Voice - research - evidence

1. Introduction

After a generation of research in the area of voice analysis and function where the role of the Vocal Fold Physiology research since 1981 has played a major role, one of the batons for the next generation seems to be: evidence.

Till now no internationally famous girls choirs (as evaluated e.g.by the professional music companies) have shown up, even if 850 years of famous boys choirs (also as evaluated e.g. by the companies) have presented the one more beautiful CD/DVD than the other. In a thesis it was shown that well trained girls voices before and in puberty had the same qualities as boys [2-5]. An attempt to evaluate male puberty has earlier been made [6]. The acceptance of evidence as the basic tool was never discussed in the comparison of male and female voices [7].

The other aspect which lead to the question of evidence was the Cochrane approach of evidence for treatment of vocal cord nodules. Counting the patients and surgeons: 97% of the patients were females and 100% of the surgeons were males, and there was no evidence neither of diagnosis nor treatment (Cochrane 2000-2001) [8].

1.1 Background

The set-up of evidence is accepted although not optimal e.g.in the pharmaceutical industry - and cancer research, in which field the instructor was chosen for a protocol on vocal cord nodules in the year 2002. A specialist for singers in Paris, and a trained researcher in Oxford edited the protocol, and a randomisation was planned. Discussions were also made with a research fellow from Prag.The protocol seemed to be the first for evidence based interventions for vocal cord nodules. A Vonod-team for the randomisation was build after the given suggestion, but the team did not succeed to get money, even if the Danish State Health Care Research Foundation in November 2003 approved the present author´s application for the study, they have very small funds. Other/several teams and models should be considered.

Therefore results from two pilot studies with their own protocols are presented, the first pilot protocol took into account that for dysphonia, medical treatment is necessary of infections, allergies and disorders provoced by the surroundings: a mean score of Voice Related Quality of Life [9] showed, that medical treatment improved the quality of life with a factor of 13.2-20.8, and interestingly a medical voice hygiene group was also better with a factor of 7.1-8.2. [10]. Results are also given from the our second pilot protocol, of treatment of vocal cord nodules, with a comparison between Zagreb and Copenhagen, at both places also to normal persons. [11] The modified Cape-V test, jitter and shimmer and quality of life were better at both places after medical therapy for among others the infections of the larynges, that seemed to be the overall most common reason for the voice disorder in Copenhagen and in Zagreb as well (table 1-4 Pedersen et al. 2003).

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2. Methods

Every time an idea in natural science is cooked down to a hypothesis a protocol (and following trial) is needed to document the evidence (clinical trials) [7,12]. In the protocol for an evidence based study the background of the hypothesis is probably the main issue, because all ideas have a accepted historical reference even if meta-analysis only can be based on evidence based studies (the Cochrane Handbook, updated version 2003) [13,14]. This is why the statisticians should be feared and handled with care: Evidence is related to the basic background of the relevant field. At best the area of voice research should educate their own statistcians as in other fields.

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The protocol also includes description of ethics, assessment of efficacy and safety, access to documents, datahandling and record keeping, finance and reassurance, publication policy, spin-off projects and references. Appendices must include detailed description of procedures including consents ect. The person/s behind the idea must be aware of the reponsibility which cannot be left to the statisticians or the funding.

The levels of evidence are (the Cochrane Handbook) : 1a systematic reviews of RCTs, 1b individual RCTs, 1c life or death evidence based controlled prospective trials. 2a systematic reviews of prospective cohort studies with controls, 2b individual prospective cohort studies with controls, 3a prospective systematic cohort studies, 3b individual prospective cohort studies, 4 communication studies. The weakest: 5, is expert opinion.

4. Experiments and Results

Only two recent evidence based studies (RCTs) have been found apart from the two pilot studies referred to [10,11], that include vocal cord nodules: [15,16], referred to in: Pedersen M and McGlashan J, A Cochrane review update of vocal cord nodules, to be printed. Before that a survey showed that during the later years stroboscopy and objective measurements were given, but prospective analyses and works with control groups were not found. [14].

The study by Benninger [15] compared microspot Co2 laser and microdissection for limited vocal fold benign lesions in a blinded prospective study of 37 patients. Time costs was evaluated, statistical analysis involved an evaluation of a design of 80% power to detect a difference of 1.2 SD between the two groups (alpha = 0.05, twosided test) with 12 subjects in each group. A two-sample Student t test was used for continuous

variables and Fischer´s Exact test for categorical variables. A secondary analysis was also repeated on patients with complete data. An ANOVA procedure was carried out.
In the study by MacKenzie et al.[16] comparing speech therapist treatment with no treatment of non-organic dysphonia including vocal nodules, computer generated random numbers produced in a restricted randomisation form were supplied by an independent worker in a separate department. The intended number of patients to be recruited in the treatment and non-treatment groups was determined by assuming a medium effect size of treatment (0.5 SD units). Greater than 90% power was sought with alpha set at 0.05 (two tailed). The target chosen was 100 patients in each group, which offered 94% power. At the end of the study the power was 82% (70 and 63 patients in the groups). Statistical analysis compared the mean difference in the outcome variables between the groups with and without treatment by speech therapist. Separate analysis was conducted at the end of treatment and at follow-up. An analysis of covariance was used for both the end of treatment and follow-up analysis. Assessment of pathophysiological outcomes needed a categorical approach: a subtraction for each patient was made from baseline (visit one) of visit two and visit three for each feature score. Patients were then assigned to a category (0, 1 or 2) according to whether they had improved, deteriorated or stayed the same. A series of Chi-square tests were made for inter-group comparisons, treatment effect as mean differences at the relevant outcome at visit two and three using an analysis of covariance in SPSS 9/10.
In the prospective randomised pilot study of dysphonia: medical treatment and medical voice hygiene advice approach [10], the parametrical statistical analysis was made with the SAS program. The McNemar non-parametrical test was used for the videostroboscopy and t-tests for the quality of life tests. In the results of the phonetograms, the lowest and highest tones in semitones (Hz) and the area in decibels times semitones were compared, one-way analysis of variance was made, geometric means were computed and the difference from before and after were presented as a ratio, after/before. In the prospective randomised pilot study comparing treatment of vocal nodules in Zagreb and Copenhagen [11] the patients were compared with normals of the same age and sex at the same time at both places. The McNemar test was used again for stroboscopies and for the modified Cape-V, t-tests were used for quality of life comparisons. The difference in jitter and shimmer % from 1. to 2. examination was compared by a 2-way analysis og variance grouped by centre and treatment analysed with the parametric SAS statistical program.

The results of the four prospective randomised blinded studies with relevant follow-up show that for the first one by Benninger there was no difference between the two procedures of surgery. For the second one by MacKenzie et al. there was no effect of speech therapy on the dysphonia in the blinded evaluation. In the third one by Pedersen et al. the quality of life was improved in a group of patients medically treated with relevant immunological, antibiotic and environmental therapy. But the medical voice hygiene advice had an effect too. In the fourth study comparing medical treatment of vocal nodules in Zagreb and in Copenhagen the medical cause of the nodules was mainly infection in both countries, and in both places a significant improvement of quality of life (t-test, $p<0.01$), shimmer /i/% in the MDVP (SAS parametrical program, $p<0.02$), and of a modified Cape-V (McNemar, $p<0.01$)was found after medical treatment.

For laryngo-pharyngeal reflux as a possible provocator of nodules three evidence based studies (RCTs) have been found that included hoarseness out of an electronic search that included 290 papers. A protocol for the Cochrane Library (2004) has been made.
The prior conclusion was that no meta-analysis seems to be possible for the three studies that were evidence based [18,19,20].

5. Discussion

For singers clinical trials of evidence is the only scientific approach for their pathologies. Christa Ludwig [21] presents the dialogue between the singer, director of orchestra, instructor and teacher. Art developes with new vocal demands [22,23], science develops with new epidemiological understanding [24], scientific theory of music develops [25,26] – and so does the treatment aspect, one of the basics for medical doctors of laryngology being the analyses of stroboscopy [27]. The next one, possibly is the highspeed video camera of the vocal cords in the clinic, foreseen by the kymographic approach. .
There is among highly qualified laryngologists a hidden approach of alternative medicine, on the other side many surgeons operate, where they never should, having never understood the demands of evidence (personal communication Jan Olafsson). If the scientists do not accept to make the research of voice evidence based, so that every clinician can make statements to the patients of evidence, the field of voice research will be handicapped. It is crucial to acknowledge the treatment differences between the sexes, the ages, the environmental provocations [28], infections, allergies ect. before operations are made, because we know that there is no evidence based documentation of the effect of surgery on benign neoplasms of the vocal cords. The quality of life aspects must be taken into account (Voice Handicap Index, SF 36) [29,30], and careful allround advice must be given referring to the scientific status.

6. Conclusion

An introduction to four evidence based studies in adults that included vocal nodules has been made, one study showed that the laser could be used for surgical treatment, another that speech therapy in a blinded setting had no evidence, the third one showed effect of medical treatment for hoarseness with reflux, allergy and infection therapy, but also of a medical voice hygiene therapy (with an effect factor of 3:1). The fourth study showed that both in Zagreb and in Copenhagen infections were seen more often in patients with vocal nodules than in others, and medical treatment had an effect in both places measured with the acoustical analysis of shimmer, the perceptive test of modified Cape-V and qualty of life questionaire. In the three –only- evidence based studies of reflux as the cause of dysphonia, out of 290 electronically searched studies for a Cochrane review, no evidence based connection usable for a meta-analysis was found.

Acknowledgment

This presentation was carried out with the advice from Michala Pedersen, Dr.phil. Oxford, Erkki Bianco, Doctor of the opera

lyrique in Paris, and Alice Beranova, ENT specialist, Charles Univerity, Prag..
Statistical advice was made by the East Danish Health Science Forum´s Consultant Service

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Table 1. Medical groups of included test patients with vocal cord nodules and normal controls. Patients with vocal cord nodules and controls for the pilot study were collected in a period of two months.

Groups:	**with vocal nodules from Denmark**	**10**	**mean age 30.3y**
	with vocal nodules from Croatia	**6**	**“ 38.5y**
	without vocal nodules from Denmark	**13**	**“ 40.0y**
	without vocal nodules from Croatia	**11**	**“ 39.7y**

Sex – M:0 F:40

Inherited illnesses in the family: None
Currently general health state of the subject: all well

	Denmark		**Croatia**	
	Tests	**Controls**	**Tests**	**Controls**
Number of persons				
Illnesses in the past of the voice	**3**	**1**	**4**	**0**
Infection upper airways	**5**	**0**	**4**	**0**
Allergy upper airways	**4**	**9**	**0**	**0**
Reflux/helicobakter infect. (GERD and LPRD)	**3**	**3**	**2**	**0**
Environmental disorders	**1**	**0**	**0**	**0**
Others	**1**	**0**	**0**	**0**

Table 2.Voice-related quality of life questionnaire (V-RQOL), results of the prospective pilot study of the new patients before medical treatment and after treatment, one month later, compared with controls. All controls function was optimal (factor 100).

	Denmark			**Croatia**		
Mean score all in percent	before treatment	after	diff%	before treatment	after	diff%
Social emotional domain	64	76.5	12.5	66.5	79.5	13
Physical functioning domain	56.3	64.7	8.4	67	74.3	7.3
Overall voice related quality of life	59.8	74.9	15.1	69.6	76.4	6.8

Statistical calculation with t-test shows a better V-RQOL test in both Denmark and Croatia ($p < 0.01$) after treatment, the score of the physically functioning domain is significantly ower in Copenhagen ($p < 0.05$).

Table 3. The multidimensiomal voice program (MDVP) acoustical analysis: mean jitter% and shimmer% of /a/ and /i/ at the first and second examination with one month´interval.

The first measurement (MDVP) and second measurement of all patients compared with controls.
A significant reduction of shimmer% /i/ was found between the first and second examination (p<0.02). For shimmer% /a/ the same tendency was seen but not significantly (p=0.053)
For description of sentence jitter%, see text.

	Denmark		**Croatia**	
1. EXAMINATION	patients	controls	patients	controls
jitter% /a/	**2.9**	**1.1**	**2.9**	**1.4**
jitter % /i/	**2.4**	**1.8**	**2.5**	**1.3**
shimmer% /a/	**12.3**	**3.5**	**11.0**	**4.9**
shimmer % /i/	**11.3**	**4.6**	**7.7**	**3.4**
sentence jitter%	**6.1**	**4.5**	**6.0**	**4.2**
2 **shimmer% /a/**	**7.2**	**4.3**	**5.0**	**2.0**
shimmer % /i/	**7.2**	**5.6**	**5.0**	**2.3**

. EXAMINATION	patients	controls	patients	controls
jitter% /a/	**2.9**	**1.1**	**2.0**	**1.1**
jitter % /i/	**2.8**	**1.8**	**2.0**	**0.9**

CapeV	Denmark		diff.D/C		Croatia			diff. all
	TESTS		CONTR.		TESTS		CONTR.	
	1.ex	2.ex	1.ex	2 ex.	1.ex	2.ex	1.ex. 2.ex	
Overall Severity MI MO SE1	52.5	25.7	1	1	42.6	32.6	2.7 2.7	C I /100
Roughness MI MO SE 1	63.5	42.4	1	1	49.0	45.5	1 1	C I /100
Breathiness MI MO SE	20.7	4.7	1	1	61.5	47.6	1 1	C I /100
Strain MI MO SE	61.0	31.2	1	1	44.6	39.6	1 1	C I /100

Pitch (Indicate the nature of the abnormality)=0

246 242 234 229 186 190 211 220 C I /100

MI MO SEement of fundamental frequency in continuous speech: MI

:

COMMENTS ABOUT RESONANCE: NORMAL OTHER (Provide description):
ADDITIONAL FEATURES (for example, diplophonia, fry, falsetto, asthenia, aphonia, pitch instability, tremor, wet/gurgly, or other relevant terms):

Clinician:
Legend:C = Consistent I = Intermittent
MI = Mildly Deviant
MO =Moderately Deviant
SE = Severely Deviant