COMPARISON OF INTEGRATIVE VS. CONVENTIONAL THERAPY OF CHRONIC OTITIS MEDIA WITH EFFUSION AND ADENOID HYPERTROPHY IN CHILDREN

Ph.D. doctoral thesis

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Introduction

I have chosen the research and presentation of chronic otitis media with effusion (COME) and adenoid hypertrophy (AH) as the theme of my dissertation, as it is a common entity in the pediatric population presenting a possibility of cooperation between pediatricians and otolaryngologists as integrative (IM) and conventional (COM) point of view at a certain bound of everyday praxis.

The wholeness of the theme is reflected by in the dissertation the almost 250 references cited. Although the elements of the investigated and presented IM concept are already known in the clinical praxis, it`s the first time they were used, investigated and presented at the complex and systematic setting I used.

Aims

The clinical aim was in both groups to insure the pneumatisation of the middle ear, in order to secure the appropriate hearing.

The aims of IM respecting and supplementing the guidelines of COM:

- To optimise or respectively reduce the need of invasive surgical interventions during the treatment of otitis media catarrhalis chronica serosa (COME) and adenoid hypertrophia (AH) in childhood.
- 2) To reduce the rate of associated episodes of recurrent acute otitis media (rAOM).
- Conform to the global trends to optimize or respectively reduce the need of antibiotics (AB) and analgesics (NSAR/NSAID) during the treatment of rAOM.
- 4) To reduce the rate of complications by improvement of adherence.

Hypothesis

We hypothesized, that:

- the pneumatisation of the middle ear improves by both, the IM and COM concepted treatments. By that audiometric and tympanometric findings will improve during the follow-ups in both groups;
- 2) the clinical aims (1-4) of IM mentioned above, will meet;
- the IM concept based on the salutogenetic principle will improve the independent selfmanagement and competency, accociated with better compliance and adherence;
- 4) reducing the number of invasive surgical interventions IM is a less traumatic concept than COM;
- 5) the indication frames of the investigated IM concept become definable and formulatable.

Materials and Methods

Study design: we conducted a GEP-conform, real situation, prospective observational study with non-randomized group assignment and descriptive comparison of outcomes of cohorts.

Setting: the study was conducted in our integrative pediatric practice (IM) and a conventional pediatric otolaryngological clinic (COM) in Hungary.

Patients recruitment: during the period between September 1st, 2013 and June 30th, 2014 we recruited 101 1-8 year old outpatients presenting with chronic otitis media with effusion and adenoid hypertrophy. In the IM group n = 46, in the COM group of the study n = 55 patients were included. We did not influence the patients self-selected participation in terms of therapy group assignment or locality. It was not an aim of the study to perform comparable initial groups; however the differences were evaluated and considered as bias.

Per definition, chronic otitis media was diagnosed when symptoms persisted for at least 3 months. Adenoid hypertrophy was diagnosed by a pediatric otolaryngologist.

Additional *inclusion criteria* were: baseline age 1-8 years; moderate or severe hearing loss (-30 dB or more on the less affected ear); having abnormal findings in tympanometry at least once during the first three visits. Children with anatomical abnormalities, congenital syndromes, concurrent illnesses requiring continuous medical treatment and previous otolaryngological surgical interventions were not included.

Patients lost to follow-up completing less than three visits after diagnosis were excluded from statistical evaluation as they did not fulfill required eligibility criteria.

Disease status at baseline: age, type of delivery (natural vaginal vs. cesarean section), prior number of antibiotic treatments per year, prior number of analgesic treatments per year, prior number of acute otitis media per year, prior indication of adenoidectomy by an otolaryngologist.

Desirable frequency of follow-ups: every 30 days.

Closing of data collection: at least one year, to a maximum of 400 days. Data collection was also stopped at the day of surgical intervention if performed.

Each initial visit lasted about 40 minutes while about 20 minutes was usual for follow-up visits.

Treatment guidelines of COM

In both groups, primary aim of therapy was to minimize hearing loss through improvement of nasal breathing, facilitation of the pneumatization of Eustachian tubes and size reduction of AH. In the COM group, treatment was performed according to Hungarian guidelines (released in 2008 and updated in 2010). Based on these guidelines, adenoidectomy was the standard surgical intervention. These guidelines differ from German guidelines as well as from American guidelines (American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP)).

According to the current guidelines, watchful waiting is recommended for at least 3 months with 1-3 monthly audiometry to assess hearing. Antibiotics, decongestants, antihistamines and steroids are not recommended as routine treatment for COME. The conservative treatment contains local warmth and decongestants, mucolytics. Otherwise healthy children with COME persisting over 4 months are considered for surgery if hearing loss exceeds 40 dB. PET insertion is recommended for children younger than 4 years of age. Over 4 years and/or resurgery adenoidectomy plus myringotomy with or without tube insertion is recommended. It is also the preferred initial surgical modality for children above 4.

The COM treatment of the study followed Hungarian guidelines in treating the patients.

Treatment of COME with methods of IM

Treatment for the IM group was based on a complex personalized, non-invasive therapeutic system approach. It included the use of local nasal preparations, non-allopathic medications, facilitation of pneumatization, external thermal interventions, parent and patient education and anti-allergic medications and/or diet if an allergic condition was present.

Local nasal preparations: Cydonia fruct. glycerinum extr. (APC 3.0): 9% volume with Citrus lemon fruct. 2 % volume in 1% NaCl solvent 4-5x per day both sides. The horizontal application of the nasal spray was a key feature in the application to more successfully reach of the adenoid and the meatus of the Eustachian tube.

Constitutional non-allopathic medications: Berberis/Quarz Glob. WALA (10 g containing Berberis vulgaris e fructibus ferm. 33c Dil. D2 0,1 g (HAB, Vs. 33c); Quarz Dil. D19 aquos. 0,1 g. Sucrose) 3x5 globuli per day as oral application for 3-6 months as typical medication.

Facilitation of pneumatisation:

- I. Passive techniques without pressure:
- Chewing and swallowing was encouraged to intensify the function of peritubular muscles with hard to chew food or chewing gum for several minutes 4-5x per day.
- Singing, gasping, piping, yawning was encouraged to cause the soft palate to move upward, the tongue to flatten, the pharynx to dilate, and the hyoid bone to move downward. The Eustachian tubes open at the acme of the yawn.
- Playful exercises to contract the velopharyngeal sphincter (extended with the method of Barrett and Straub for interdental pushing swallowing):
 - tongue movements such as sweeping the palate and moving the tongue backward;
 - soft palate movements such as contraction of the soft palate, first stage of swallowing, induced yawning;
 - protraction and side-to-side movements of the jaw;
 - combined movements of the tongue and soft palate, to which jaw movements are then added.
- Nasodiaphragmatic breathing exercises to transform asynchron thoracoabdminal breading (exercises against pressure from the parent's hand placed on the epigastric region).
- Nasal valve exercises: include acquiring awareness to nostril dilation and working against resistance (the parent's thumb and forefinger).

II. Low pressure exercises (0-ca. 50 mmHg):

blowing with one opened and one pinched nostril from greater distances (snuff out a candle, let off a paperball or feather, roll along a ping-pong ball on a long surface).

III. Middle pressure exercises (ca. 50-100 mmHg):

party noise makers blowed with well cleaned noses.

IV. High pressure exercises (ca. 100-150 mmHg):

autoinsufflation with strictly cleaned noses.

- Balloon techniques (OTOBAR, Otovent, Pisze orrballon Hungary);
- Valsalva maneuver;
- Misurya maneuver.

External warmth (thermal) interventions:

- local with infrared light or warming cap (OTO-THERM) 2-3x per week for few minutes on and around the ears;

- systemic measures such as avoiding cold areas on the patients body, warm (ca. $40-45^{0}$ C) foot-baths with 1-1,5% NaCl and Zingiber officinale pulvis in daily change.

Anti-allergic therapy and/or diet in case of allergy:

Consumption of rough cow milk and dairy-products was generally restricted to 150 ml/day. In case of IgE or IgG positivity (to beta-lactoglobulin, albumin or casein) an elimination diet was undertaken.

Parental and patient education:

Given prior data that such education may enhance compliance and treatment efficacy we undertook. Its elements were: anatomical and physiological-functional illustrations, videos, brochures, feed-back sessions, detailed instructions on all interventional measures as well as on nasal hygiene, proper nose-blowing technique.

Applied statistical methods

To test variables for normal distribution: Shapiro-Wilk normality test.

To test hypothesis: Levene's test for equality of variances, Independent Samples Median test, Chi-Square test, two-tailed Mann-Whitney U test, two-tailed Fisher's exact test.

Analyzes were performed using IBM SPSS Statistics 22 software and Microsoft Excel. For all analyses, p < != 0.05 was considered as statistically significant.

Course of the study

| 1) Number of invasive surgical | Yes |
|---------------------------------------|--|
| interventions | No |
| 2) Tympanometric measurement | A-type curve: normal pressure |
| with evaluation of the worse ear | C- or D-type curve: under- or overpressure |
| | B-type curve: low admittance |
| 3) Audiometric measurement | normal hearing: -10 to -20 dB |
| with evaluation of the worse ear | light hearing loss: -30 to -40 dB |
| | middle hearing loss: -50 to -60 dB |
| | severe hearing loss: $>$ - 60 dB |
| 4) Frequency of acute otitis media | number |
| 5) Number of acute infection episodes | number |
| (AOM) needing antibiotic therapy | (local and systemic) |
| 6) Number of acute infection episodes | number |
| (AOM) needing analgesic therapy | (local and systemic) |

| 1) Parents' report on treatment outcome: | |
|--|----------------------------------|
| a) nasal congestion | a) subjective scales |
| | 1 = no, 2 = moderate, 3 = severe |
| b) hearing | b) subjective scales |
| | 1 = good, 2 = moderate, 3 = bad |
| 2) Adherence to therapy | subjective scale |
| | 1 = good, 2 = moderate, 3 = bad |
| 3) Median time of follow-ups | days |
| 4) Mean number of days counted from the | days |
| first visit during the follow-up period | |
| 5) Participation on the visits | number of patients, % |

Table 2. Secondary outcome variables

Results

Patients recruitment: a total of 101 patients aged 1-8 were recruited in the study, with 46 selecting integrative therapy and 55 conventional treatments. We had to exclude patients, who did not fulfill eligibility criteria (less than 3 visits): 18 (IM) + 20 (COM) = 38 (all).

In the IM group except one all other patients were excluded because of claiming an excessive distance from their home to the praxis. A single patient had to be excluded because of central hearing disorder. In the COM group 20 were excluded for not following up at least thrice.

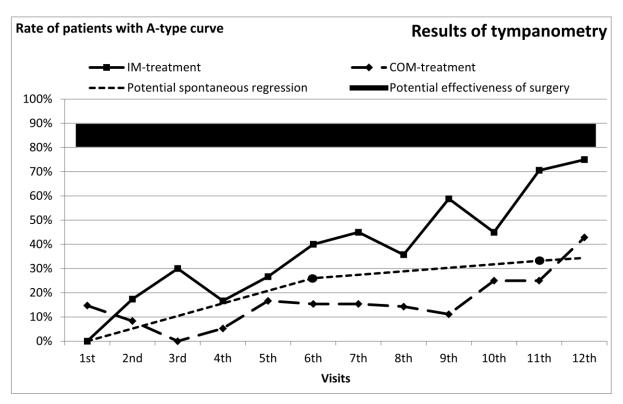
Results concerning primary outcomes:

1) The *number of invasive surgical interventions* were significantly different in the two groups (IM: n = 1 (out of 28) = 3.6%, COM: n = 15 (out of 35 $\ddot{O} = 42.9\%$, OR 20.250: 95% CI: 2.467-166.229, Mann-Whitney test p < 0.001).

2) Similarly, *frequency of antibiotic use* was less in the IM group (5 out of 28 = 17.9%) compared to the COM group (29 out of 35 = 82.9%, OR: 22.233, CI: 6.018 – 82.147), Mann-Whitney test, p<0,001.

3) Frequency of analgesic or antipyretic medication (NSAR/NSAID) during AOM was also less in the IM group (6 out of 28 = 21.4%) compared to the COM group (18 out of 35 = 51.4%, OR:3.882: 95% CI: 1.267 – 11.898). The difference was statistically significant Fisher's exact test (p = 0.020).

4) *Improvement in tympanometric measurement:* A-type curve with normal pressure was higher in IM patients compared to expected spontaneous remission.



1. figure A-type tympanometric findings in the two groups

These findings were *affirmed* by improvement in *audiometric measurement* in IM patients compared to expected spontaneous remission.

Results concerning secondary outcomes:

1) *Frequency of acute otitis media* was not significantly different between the IM vs. the COM group (Mann-Whitney test p = 0.488).

2) Objective outcomes as measured by audiometry correlated well with *subjective outcomes as reported by parents* on most of the visits: Spearman's Rho of 0.54-0,99 (from p < 0.001 to p = 0.014). On the 4th and 5th follow-up visits this correlation was less marked with a Spearman's Rho of 0.33-0.36 and were not significant.

3) Complience with prescribed therapies respectively rounded values of personal means using the non-parametric Mann-Whitney test, was not significantly different: p = 0.424. This was confirmed by Fisher's exact test: p = 0.39.

4) *Median duration of follow-up (adherence)* was not significantly different: IM: 40 days, COM: 32 days, Independent Samples Median Test p = 0.843.

5) Number of follow-ups was significantly different in the two groups (IM: 8; COM: 5 visits

out of maximum 12; Mann-Whitney test; p < 0.001). In the IM group the frequency of visits was higher.

6) Regarding *adverse reactions*, a total of 2% was reported in the IM group. All adverse reactions were described as mild and temporary. Mild nasal mucosa-irritation and cutaneous blush. Adverse effect report was not collected in the COM group. The expected rate of adverse reactions using historical data would have been 6-10%.

Discussion: evaluation of the study and its findings, statements, conclusions Statements concerning points of hypothesis

1) We hypothesized, that pneumatisation of the middle ear improves by both treatments which will be reflected by audiometric and tympanometric findings. Both (IM and COM) therapeutic concepts proved to be effective. Based on clinical experience and EBM literature surgical interventions are effective solutions. We could not follow this data, as most of the patients returned to the assigning specialist.

The conservative therapy of COM consisted of mostly short term nasal decongestants and local steroids if allergic diathesis was confirmed.

Compared audiometric and tympanometric findings: improvement in the IM group was better than in the COM group or the measures of expected spontaneous remission.

2) The hypothesis, that clinical aims (1-4) of IM will meet, was confirmed.

3) The IM concept based on the salutogenetic principle will improve the independent self-management and competency. The performance of recommended therapies (compliance) was similarly good in both groups.

Regarding the comparison of the adherence following have to be taken in account:

- participation on the visits was significantly higher in the IM group,

- median duration of days between follow-up was not significantly different in the two groups. Based on this the adherence in total was appropriate, slightly higher in the IM group, ensuring a safe treatment.

4) Reducing the number of invasive surgical interventions IM is a less traumatic concept than COM. Although we did not perform statistically evaluated measurements, children usually liked the external interventions, care, exercises performed independently or with the parents. This was mirrored indirectly by the high compliance.

10

The complex strategy of IM requires more activity (dosage of medication, care, exercise) than conventional therapy. While this may not be suitable to all parents and patients. What nevertheless (in the light of our results in compliance) was not the case in our study.

5) The indication frames of the investigated IM concept become defined, formulated.

Statements concerning objectives of the study:

1) The optimal indication and performance of surgery under appropriate conditions and in the appropriate time is important and necessary out of professional point of view.

2) The frequency of invasive interventions was different in the two groups as well as compared to international data. In case of similar baseline parameters it suggests the presence of subjective factors, which are not explained by the protocols and methodological guidelines. Possible reasons were discussed in the description of the methods.

3) Number of invasive interventions (AT versus AT) and their distribution (AT versus PET) in the COM group was higher than international standards. The reason for higher rates of AT is assumed to be a higher rate of lower socioeconomic status (income, education, smoking). On the other hand, the clinical decision is influenced by subjective factors (institutional traditions, standards, financial and organizational criterion, conditions etc.).

Along the Hungarian methodological recommendations and professional tradition AT and AT + MT were primarily used as invasive interventions. The absence of grommet implantation is considered as a local characteristic, which is different from present recommendations, especially under the age of 4.

4) It is assumed that general practitioners, specialists submit the children to the hospital clinic rather for surgery. In addition, parents of families with lower socioeconomic status are less able to afford home care. They tend to choose fast and efficient solutions.

5) In contrast, the indication of operations and/or postponement, delay of indicated surgery may have different reasons: not yet reached the age of 4; seasonally fluctuating symptoms (improvement from spring to autumn, first stage of COME); durable spontaneous remission; acute respiratory infections; parents inherently prefer conservative treatment or change their mind in the meantime; differences or clarifying laboratory values; waiting list period.

6) Parental attitude concerning surgery with waiting, delaying attitude raised up about by half of the COM group, in the IM group this preference was even more prevalent. The complete rejection of surgical interventions is rare, and can be avoided by sufficiently informative communication. 7) As the demand for non-invasive solutions is a growing social phenomenon, it is worth to deal with it from a professional point of view. A more detailed examination has exceeded the scope of our study, however, it would be desirable.

Strengths and limitations of the study

Strengths of the study:

We were able to evaluate several objective and subjective variables in a *real-world clinical setting*. Due to a *long follow-up period* short term- and spontaneous fluctuation was excluded. Spontaneous regression was considered. The adherence and the compliance was good and similar in the two groups. Confounding factors have been clarified and minimized.

Limitations, bias:

Selection bias:

Similarities and differences of the baseline parameters:

a) Similar baseline parameters in the two groups:

- 1. Indication of adenoidectomy prior to first visit.
- 2. Prior number of antibiotic treatments per year.
- 3. Prior number of antibiotic or analgesic treatments per year.

4. Parents' report on the grading of nasal congestion. In the COM subgroup the ranking of severity of the symptoms was higher.

b) Different baseline parameters in the two groups:

1. *Age at presentation* was nevertheless significantly different between the groups; though mostly remaining in the typical range (2-6 years) of COME and AH. An important factor in this age difference might have been that parents who opted for integrative treatment might have had the tendency to avoid interventions even before the study due to perhaps a more conservative attitude.

2. *Pathological tympanometry findings* (B+C+D type curves) was higher in the IM group at baseline. Probably because of the higher age and symptoms persisted longer.

3. *Prior number of rAOM episodes* was also higher in the IM group, presumably for similar reasons.

4. *Parents' report on hearing loss* was also more striking in the IM group. Presumably because of the higher age and symptoms persisted longer. This correlated with the objective measurements.

5. Occurrence of cesarean section at birth. IM group mean 13%, COM group 25% (though both groups had a lower rate than previously reported in the Hungarian population of 35%).

Regarding the selection bias in total, it can be stated, that prior symptoms had a longer duration and higher severity in the IM group. Because this natural and general disadvantage in baseline characteristics made any beneficial baseline confounding so unlike, no further measures were needed to exclude them.

Adherence to therapy was similar in the two groups; number of follow-ups and mean time between the visits was higher in the IM group, though relatively good in both groups further reducing confounding effects of miscellaneous factors.

Attrition bias:

A number of patients had to be *excluded* from both groups due to non-adherence to follow-up visits (at least 3 visits). In the IM group, 18 patients were excluded, in the COM group for this indication was similar (n = 20).

The *exclusion of patients* (due to non-adherence) was unlikely to result attrition bias as there were no statistically significant differences between the clinical characteristics of evaluated and not evaluated (excluded) patients of the two groups: baseline age (IM group Mann-Whitney test p = 0.620; COM group p = 0.759). The gender (girl:boy) of evaluated and not evaluated (excluded) patients of the two groups was also similar and nearly 1:1. Number of prior surgical interventions were all similar. IM group Fisher's exact test p = 1.000; COM group p = 1.000. Grading of baseline symptoms were similar in evaluated and not evaluated (excluded) patients. Tympanometric finding IM-group: Fisher's exact test p = 0.642, COM-group: p = 0.068. Audiometric findings: IM-group: Fisher's exact test p = 0.163. In addition, all exclusions occurred within the first three months of the observation period. It can be stated, that prognostic factors for spontaneous remission and treatment outcomes were similar in the two groups for both the excluded and the included patients. So the assessment of the effectiveness of the treatment was not distorted by that.

Dropouts during the observational period occurred in both groups only due to surgical interventions. Dropout rates were widely different amounting to only 1 out of 28 (4%) in the IM group, while reaching 15 out of 35 (43%) in the COM group after a mean of 5.64 visits. After surgery data collection was stopped.

Overall, the attrition bias could be estimated as moderate.

A *detection bias* was also present, as the COM group had an inadequate audiometry and tympanometry data. Due to that we needed historical data to create a base for comparison for IM group measurements (expected/potential spontaneous remission, ESR).

Observational and reporting bias: the data were congruent. A negligible small bias was possible as audiometry was measured on the worse ear as reported by the parent for the better side, a subjective judgment.

Conclusions

Conditions of indication of the outlined integrative concept based on the study:

Suggestible:

- in case of fluctuating symptoms in 1st stage of COME;
- during the 3 month of watchful waiting in 2nd stage of COME;
- in case of non- compromised children, if parents delay surgical interventions looking for conservative solutions.

The mere use is not recommended:

- 3rd stage of COME;
- in case of significantly hypertrophic adenoid vegetation;
- if of any risk (severe hearing loss, lack of communication skills etc),
 sever (sleep apnea, a general developmental delay, etc.),
 complicated (adhesions, cholesteatoma etc.) runoff.

All indications should be followed by an otolaryngologist.

Serving as a preliminary study, based on the results additional studies may be performed with more objective, instrumental investigations, larger number of patient groups, different patient populations and the separate elements of the complex IM system.

Added value

This study is the first non-randomized, non-double-blind controlled, comparative clinical study in our country, which used a complex method IM containing a number of elements in the analysis of the therapeutic circumstances of COME, subsequent hearing loss, and intercurrent AOM.

Even though that effectiveness of IM is slightly lower than surgical interventions of COM, remission of COME shows significantly higher rates by using IM, than the rate of spontaneous regression or as the exclusive use of conservative treatment methods of COM.

The integrative approach is characterized by using less invasive surgical interventions, antibiotics and NSAR/NSAID, accompanied by a much better compliance.

With this, the IM concept fits into the current trend of international professional recommendations.

Under properly controlled circumstances IM integrates the various therapeutic options with a secure algorythm. Considering this, the approach of the integrated use of IM and COM might lead to a combination of an adequate ratio and individual consideration regarding conservative and surgical solutions.

Clinicians may consider the use of the IM concept described above, so they can enrich, broaden, improve the efficiency of conservative therapeutic tools in the period of watchful waiting before surgery.

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Publications

Publications closely related to the topic of the thesis:

Henrik Szőke MD, Márta Maródi MD, Zsuzsa Sallay MD, Balázs Székely MSc, Martin-Günther Sterner MD, Gabriella Hegyi Prof. MD PhD: Integrative versus Conventional Therapy of Chronic Otitis Media with Effusion and Adenoid Hypertrophy in Children: A Prospective Observational Study, Forschende Komplementärmedizin, 2016;23:231–239, (ISSN: 1661-4119; DOI: 10.1159/000448440)

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16