ORIGINAL CONTRIBUTION

Rhinology, 48, 95-99, 2010

A follow-up study with acoustic rhinometry in children using nasal insulin*

Lotta E. Haavisto[1], Tero J. Vahlberg[2], Jukka I. Sipilä[1]

[1] Department of Otorhinolaryngology, Turku University Hospital, Turku, Finland
[2] Department of Biostatistics, University of Turku, Turku, Finland

SUMMARY

Acoustic rhinometry is a widely used method especially suitable with children, since it has no side-effects and is easy to perform. The role of normal development of height or body surface area, and their effect on acoustic rhinometric results, is still a matter of debate. The purpose of this study was to determine the presence of any differences in rhinometric findings or nasal symptoms between children receiving daily administered nasal insulin or placebo. The usefulness of acoustic rhinometry for follow-up in children was also considered. A subcohort of 77 children taking part in the Type I Diabetes Prediction and Prevention Study was invited for a follow-up study with acoustic rhinometry. Children aged 1-12 years received daily either nasal insulin or a placebo.

There was no difference between the two groups in nasal symptoms, minimal cross-sectional area or nasal volume measured with acoustic rhinometry. There was likewise no significant increase in rhinometric values during the two years of the follow-up. We conclude that acoustic rhinometry is a suitable method for objective follow-up in children. In a long-term follow-up the normal growth of the child should be taken into account.

Key words: acoustic rhinometry, minimal cross-sectional area, body surface area, child, follow-up

INTRODUCTION

Acoustic rhinometry (AR) is a widely used method for objective assessment of the nose. The Committee on Standardization has proposed guidelines for optimal application of the method [(1)]. The method is suitable for evaluating children: it is rapid and non-invasive, has no side-effects, and requires minimal cooperation [(1,2)].

Some reference values for children have been published [(3-6)], and there has been some discussion concerning the effects of the patient's age, height, weight and gender on the AR values [(6-10)]. Most of these studies are cross-sectional in character. Because of the large range of inter-individual variation, it has been suggested that normal values may not be useful [(11)].

In a two-year follow-up in children, Millqvist and Bende found an increase in minimal cross-sectional area (MCA) and nasal volume [(9)]. They concluded that normal height development should be taken into account in long-term studies.

The nasal route has been found to be an attractive way to administer medication, especially for children [(12-14)]. Hence, there is a need for an objective method for the follow-up of nasal changes in children. AR has previously been successfully used in children to compare surgical patients pre- and post-operatively [(15,16)], and is suggested to be a suitable method for other forms of follow-up use as well [(9,11)]. There have nevertheless been no follow-up studies with children under continuous medication.

The purpose of this study was to determine whether there is any difference in rhinometric findings or nasal symptoms between children daily administered with nasal insulin or a placebo. In addition, we investigated the usefulness of AR for follow-up in children.

MATERIALS AND METHODS

Patients

The study involved a total of 77 children. Written informed consent was elicited from the parents of the participants. The study was approved by the Joint Ethical Committee of University of Turku and the Turku University Hospital. The subjects were a subcohort of the Type I Diabetes Prediction and Prevention Study (DIPP), the study design of which has been described in more detail elsewhere [(13)]. The subjects, all of whom were at least one year old, were invited to participate in a randomised double-blind intervention trial comparing

*Received for publication: May 4, 2009; accepted: July 23, 2009

DOI:10.4193/Rhin09.080

intranasal insulin with a placebo. They received either recombinant human short-acting insulin (Actrapid®) in regular buffer or the buffer alone, in the form of a nasal spray, once a day. The randomisation was performed by the Turku University Hospital Pharmacy.

Data were available from the baseline visit, before starting any treatment, for 72 children, aged between 1.4 years and 12.7 years. There were 35 children in the insulin group (mean age 4.35 years, SD 2.52, range 1.39-12.7. years) and 37 children in the placebo group (mean age 3.87 years, SD 1.97, range 1.47-8.32 years).

The criterion for exclusion was any permanent nasal obstruction or septal deviation detected by anterior rhinoscopy at the first visit. A standard questionnaire concerning nasal symptoms was filled in with the children or their parents at every control visit.

Acoustic rhinometry

Acoustic rhinometry (Acoustic Rhinometer A1, GM Instruments Ltd., UK) was performed according to the recommendations of the Committee on Standardisation of Acoustic Rhinometry [1] using special soft nosepieces for children or medium-size anatomical nose adaptors for adults. If necessary, ultrasound gel was used to prevent acoustic leakage. No nasal decongestant was used.

Three measurements were performed on each side. The mean values of the three most acceptable curves were used in the calculations. Curves with a significant deviation were excluded and the measurement was repeated if needed. One author (LH) reviewed the whole data to ensure that curves were acceptable and MCA was correctly collected from the curves. The measurements were carried out by the same trained nurse.

The points of special interest in the follow-up were at 3 months, 6 months, 12 months and 24 months. After that point the data were too few to allow any further conclusions (see Table 1).

At each point we calculated the body surface area (BSA) using data on height and weight, and noted any nasal symptoms reported by the child or parents. AR was performed on every visit. The values of special interest were the minimal cross-sectional area (MCA, calculated as the sum of the left and right side) and the total nasal cavity volume at a distance of 0-3 cm from the nostril, calculated as the sum of the right and left sides (VOL).

Statistics

For the statistical analysis of the baseline, we compared values in the insulin and placebo groups for age, BSA, nasal symptoms, MCA and VOL. Since the continuous variables were not normally distributed, we used the non-parametric Mann-Whitney U-test.

For the follow-up of symptoms, logistical regression analysis with random intercept (PROC GLIMMIX) was used to compare changes within each group and between the groups during the follow-up of 3, 6, 12 and 24 months.

For the follow-up of BSA and the acoustic rhinometric values MCA and VOL, the Wilcoxon signed rank test was used to compare changes within both groups during the follow-up of 3, 6, 12 and 24 months. To compare changes between the two groups at the control points we used the Mann-Whitney U-test. The software used was SAS9.2 for Windows. P-values less than 0.05 were considered statistically significant.

Table 1. Number of children at control points during the 24 months follow-up and mean visits per child at any control point in insulin and placebo groups.

Control Point	Insulin	Placebo	Total	Mean visits	SD
Baseline	35	37	72		
3 Months	24	25	49	2	0
6 Months	20	20	40	2.825	0.385
12 Months	19	15	34	3.5	0.749
24 Months	12	12	24	4.67	0.637

RESULTS

The follow-up time was up to 72 months. In the course of the study each child had 1-9 visits to the rhinologist; some of the children were measured only once (baseline visit). A total of 247 measurements were performed (Table 1).

Baseline

At the baseline, 23 out of the total of 72 children (32 %) mentioned some form of occasional nasal symptoms (occasional congestion, discharge or nosebleeds). There was no statistical difference at the baseline between the insulin group and the placebo group with regard to age ($p = 0.510$), BSA ($p = 0.210$), nasal symptoms ($p = 0.270$), or acoustic rhinometry values MCA ($p = 0.451$) or VOL ($p = 0.668$). Table 2 shows the variables for both groups.

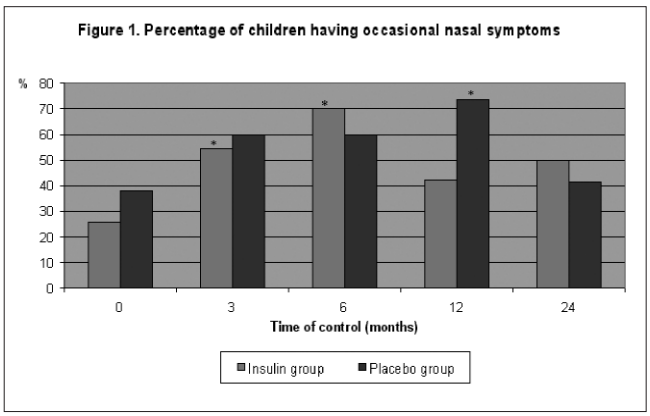

Figure 1. Percentages of nasal symptoms in the insulin and placebo groups during the follow-up of 24 months. No statistical differences were found between the two groups in changes in nasal symptoms at any control point. Number of children (insulin/ plasebo) at control point of 0, 3, 6, 12 and 24 months were 35/37, 24/25, 20/20, 19/15 and 12/12. * = significant increase in the extent of symptoms when compared to the baseline.

Table 2. Baseline values for insulin and placebo groups.

Variable		n	Mean	SD
Insulin Group				
	Age (yr)	35	4.35	2.52
	BSA (m^2)	34	0.77	0.21
	MCA (cm^2)	25	0.40	0.12
	VOL (cm^3)	23	1.94	0.85
Placebo Group				
	Age (yr)	37	3.87	1.97
	BSA (m^2)	33	0.73	0.22
	MCA (cm^2)	20	0.42	0.11
	VOL (cm^3)	16	2.06	0.62

BSA = Body surface area; MCA = minimal cross-sectional area as the sum of right and left side; VOL = total volume between 0-3 cm from the nostril as the sum of right and left side. There was no statistical difference at the baseline between the insulin group and the placebo group with regard to age (p = 0.510), BSA (p = 0.210), nasal symptoms (p = 0.270), or acoustic rhinometry values MCA (p = 0.451) or VOL (p = 0.668).

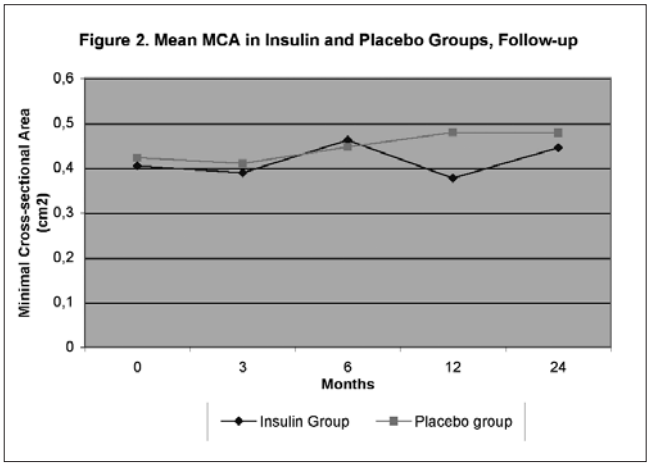

Figure 2. Changes in mean MCA during the follow-up of 24 months in the insulin and placebo groups. No significant differences were found between the two groups at any control point.

Symptoms

The main nasal symptom was an unpleasant sensation in the nose after administration of the nasal spray. Other irritating symptoms caused by the spray were itching, hurting and sneezing. At the first control point at 3 months 28 out 49 (57 %) children controlled, mentioned some nasal symptoms. Figure 1 illustrates the percentages of nasal symptoms in the insulin and placebo groups during the follow-up up to 24 months. At each point only those cases are reported for whom data are available at both the baseline visit and that control point. The insulin group showed a significant increase in the extent of symptoms at 3 months (OR = 4.87, 98% CI 1.23-19.32, p = 0.0262) and 6 months (OR = 9.034, 95% CI 1.83-44.72, p = 0.0096), but not at 12 or 24 months when compared to the baseline. The placebo group showed a significant increase in the extent of symptoms during the 12 months follow-up (OR = 5.67, 95% CI 1.00-32.10, p = 0.0496), but not at any of the other control points. In any case, there was no statistically significant difference between the insulin and placebo groups in the change in nasal symptoms at any of the control points (3 months p = 0.550, 6 months p = 0.234, 12 months p = 0.533, 24 months p = 0.177).

Acoustic values and BSA

The mean values of MCA, VOL and BSA during the follow-up in the insulin and placebo groups are shown in Table 3. There was no significant increase in acoustic values MCA and VOL during the follow-up period of two years. Instead, BSA increased significantly in the insulin ($p < 0.001$) and placebo ($p < 0.002$) groups during the follow-up. There was no significant difference between the two groups in the change in MCA, VOL or BSA. Figure 2 illustrates the changes in the mean MCA during the follow-up.

Table 3. Body surface, minimal cross-sectional area, and volume in the insulin and placebo groups, follow-up results.

Variable		BSA (m^2)			MCA (cm^2)			VOL (cm^3)		
		n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline	Insulin	34	0.77	0.21	25	0.40	0.12	23	1.94	0.85
	Placebo	33	0.73	0.22	20	0.42	0.11	16	2.06	0.61
3 Months	Insulin	24	0.87	0.31	19	0.39	0.08	17	1.75	0.41
	Placebo	23	0.79	0.28	15	0.41	0.09	14	1.940	0.59
6 Months	Insulin	20	0.90	0.28	16	0.46	0.15	16	2.14	0.77
	Placebo	19	0.83	0.36	15	0.45	0.11	15	2.067	0.680
12 Months	Insulin	19	0.89	0.29	10	0.38	0.10	9	1.71	0.74
	Placebo	14	0.95	0.31	11	0.48	0.12	11	2.33	0.56
24 Months	Insulin	12	1.01	0.38	8	0.45	0.08	7	2.36	0.77
	Placebo	12	1.04	0.42	7	0.48	0.13	5	2.65	0.99

BSA = Body surface area; MCA = minimal cross-sectional area as the sum of right and left side; VOL = total volume between 0-3 cm from the nostril as the sum of right and left side.

DISCUSSION

Our results showed that AR is a good method for the objective follow-up of children. It is rapid, reliable and non-invasive, has no side effects, and requires minimal cooperation.

During the two-year follow-up period, up to 73% of the children receiving either nasal insulin or placebo mentioned some form of nasal symptoms. The most common complaint in both groups was an unpleasant sensation in the nose after administration of the spray. This might be due to the mildly irritant buffer of the spray. There was no difference between the insulin and placebo groups in the change in nasal symptoms at any control point. The occurrence of nosebleeds did not increase during the study. The same result was also obtained in our pilot study with adults [12].

At the last control point of 24 months, the rate of symptom occurrence was very low. This may partly mean that children get used to the spray, and the sensation in the nose may be less unpleasant. On the other hand, it should be kept in mind that some children may have dropped out of the study because of the occurrence of side effects. One of the principles in the DIPP study design was that a subject could leave the study without giving a reason. In any case, the over-all drop-out rate from the study was not significant [13].

At the baseline there was no difference between the groups. The two-year follow-up showed no increase or decrease in MCA or VOL in either the insulin or the placebo group at any control point. The stability of AR values indicates that nasal insulin has no persistent effect on the nasal mucosa. The same result was obtained in our pilot study with adults [12]. The stability observed also indicates that the growth of nasal dimensions over two years is not significant.

Millqvist and Bende, in their two-year follow-up, found a similar, statistically nonsignificant increase in the nasal geometry with age [9]. They nevertheless recommended that the normal development of height should be taken into account in long-term studies with AR in children over seven years of age. We conclude that the increase in AR values during a two-year follow-up is not significant in children under 13.

We preferred to use the sum of the right and left sides of the nose to avoid the effect of the nasal cycle. Gallego et al. have recently found that children aged 2-11 years present nasal cycles; half of them seemed to be of irregular pattern rather than the classic pattern [17].

The follow-up time in our study was up to 72 months, but in the statistical analysis we used control points of 3, 6, 12 and 24 months. The number of patients after 24 months was too small to allow any statistical conclusions. This is partly a consequence of the study design of DIPP. There was a continuous intake of children into the study until it was terminated in 2007, and some of the children were able to visit only once or twice before then.

We were surprised that only a small fraction of the AR measurements had to be rejected because of poor cooperation by a child. Overall, the main reason for rejection involved technical problems (including sound leakage). This was discussed in more detail in our previous publication [10].

The present study is the first follow-up with AR in children under nasal medication. There have been to our knowledge no other publications with such frequent AR measurements. The study shows that even long term follow-up with AR is possible and informative with children.

We conclude that AR is a suitable method for objective follow-up in children, especially in this type of profile study. In long-term follow-up, however, the BSA or height of the child should be taken into account.

ACKNOWLEDGEMENTS

We thank the whole staff of the DIPP study for their assistance in collecting the data. In particular, we wish to thank Kirsti Näntö-Salonen M.D. for her help and Leena Leskinen for assistance with the nasal measurements.

The study was supported financially by the Turku University Hospital Research Fund.

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Lotta E Haavisto, M.D.
Department of Otorhinolaryngology
Turku Univeristy Hospital
PL 52
20521 Turku
Finland

Tel: + 358 2 3130 054
E-mail: lotta.haavisto@tyks.fi