Rhinology, 38, 63–65, 2000

A prospective treatment trial of nasal polyps in adults with cystic fibrosis*

P.J. Hadfield, J.M. Rowe-Jones, I.S. Mackay

Departments of Otorhinolaryngology, Charing Cross and The Royal Brompton Hospitals, London, United Kingdom.

SUMMARY

This is the first prospective, randomised, double-blind trial of the treatment of nasal polyps in cystic fibrosis. We found that betamethasone nasal drops showed a statistically significant reduction in polyp size in comparison to placebo.

Key words: cystic fibrosis, nasal polyps, betamethasone

INTRODUCTION

Mutation of the cystic fibrosis gene within region q31 on chromosome 7 (Rommens et al., 1989; Kerem et al., 1989), results in cystic fibrosis. Five percent (McPherson, 1988), of caucasians are carriers of this gene which is inherited by the autosomal recessive mode. Cystic fibrosis is caused by a defective gene product, the cystic fibrosis transmembrane regulator (Riorden et al., 1989), which results in failure of ion transport across the respiratory and exocrine gland cell epithelium and impaired mucociliary clearance (Rutland et al., 1981). The mucus becomes more viscous than normal, and stasis of secretions with infective sinusitis ensues. Persistant infection may be the cause of the characteristic chronic hyperplastic mucosal changes (Oppenheimer et al., 1979) and polyp formation (Sørensen et al., 1977).

The median survival for patients with cystic fibrosis was 6 months in 1959 (Britton, 1989), the life expectancy has since increased and now is over 22 years (Lewis, 1995). The identification of optimal treatment methods becomes increasingly important as quality of life improves for these patients. Nasal polyps appear to be more common in cystic fibrosis patients than in the general population. Previous studies have reported prevalence rates of 6-48% (Parsons, 1992). Since nasal polyps in cystic fibrosis are a common chronic recurrent problem for which surgical treatment is not curative (Rowe-Jones et al., 1995), longterm medical treatment is indicated and conclusive evidence for current practice is needed. This prospective randomised controlled trial compared the efficacy of betamethasone nasal drops versus placebo in the treatment of nasal polyposis in cystic fibrosis.

MATERIAL AND METHODS

The study was a prospective randomised controlled trial, approval for which was obtained from the Ethics Committee of The Royal Brompton Hospital. Inclusion criteria were adult (over 16 years old) cystic fibrosis patients with nasal polyps. Exclusion criteria were pregnancy or breast feeding, patients taking oral steroids or more than 1500 micrograms of inhaled steroid per day, a severely deviated nasal septum and patients who had undergone a surgical polypectomy within the previous six months. Previous polyp history including medical or surgical treatment, and interval between previous treatment and current assessment was recorded. Diagnosis of nasal polyps was made by a single observer (PJH) using Hopkins rod rigid nasendoscopy (Storz, 4mm, 300 degrees). Polyp grading (0-3) was according to the Mackay and Lund system (Mackay et al., 1997). Subjective nasal symptoms were assessed prior to and six weeks after treatment. This was done using a visual analogue staging system (Lund and Mackay, 1993) including nasal blockage, headache, facial pain, problems of smell, nasal discharge and an overall symptom score.

The trial included 46 informed and consenting patients with nasal polyps who were stratified into two groups depending on polyp size. Group 1 included those with polyps extending up to and at the level of the middle turbinate, and Group 2 included those with polyps extending beyond the middle turbinate. The study was carried out double-blind and randomisation was conducted by the hospital pharmacy using random number tables.

Treatment was either active in the form of betamethasone sodium diphosphate nasal drops (Vista-Methasone, Martindale Pharmaceuticals Ltd, Bampton Road, Harold Hill, Essex, UK) or passive in the form of placebo drops which were produced by the hospital pharmacy and contained the identical vehicle but no active drug. The drops were prescribed as two drops (active = 50μg betamethasone) to be used twice a day for six weeks, in the head down and forwards position (Chalton et al., 1985). Outcome assessment was by endoscopic polyp grading as previously described (Mackay et al., 1997), performed by a single observer (PJH).

* Received for publication March 1, 1999; accepted October 11, 1999

Table 1. Endoscopic Polyp Grading before and after treatment. Wilcoxon signed rank test to compare before and after results both with active and passive treatment.

Active (betamethasone)

Patient	Right		Left	
	pre	post	pre	post
1	1	1	1	0
3	1	0	0	0
4	1	0	1	0
8	1	0	2	1
12	1	1	1	0
14	1	0	1	0
16	0	0	1	0
18	1	0	1	0
20	2	1	2	1
21	1	0	2	1
Wilcoxon	p=0.016 (sig.)		p=0.004 (sig.)	

Passive (placebo)

Patient	Right		Left	
	pre	post	pre	post
2	1	0	1	1
5	2	2	2	2
6	1	1	0	0
7	0	0	1	1
9	1	0	0	0
10	1	1	1	1
11	1	1	0	0
13	0	0	3	1
15	2	1	0	0
17	1	0	0	0
19	1	0	0	0
22	0	0	3	1
Wilcoxon	p=0.06 (not sig.)		p=0.5 (not sig.)	

RESULTS

This trial of betamethasone nasal drops included 46 patients of whom 22 completed the course. There were no obvious differences between those who did and did not finish the trial, either in terms of the proportion prescribed the active drug (10/22=45% of completers, and 11/24=46% of non-completers) or polyp grade prior to starting treatment. Mean polyp grade for the right side was 0.95 for those who completed the course and 0.83 for those who did not (Mann-Whitney Rank Sum test showed no significant difference, p=0.42). Similarly, on the left side, the mean polyp grade was 1.05 for completers and 1.09 for non-completers, (Mann-Whitney Rank Sum test showed no significant difference, p=0.86). Subjective symptom scores showed an improvement in the overall score following treatment ($p<0.0001$), but this was not significant for either betamethasone or placebo alone, nor for individual symptoms. Previous nasal history identified an earlier diagnosis of polyps in 7/10 patients in the betamethasone group and 5/12 in the placebo group. Medical treatment (drops and/or sprays) had been previously tried in all these patients (but not for at least the past 6 months). One patient in each group had been treated surgically in the past, by simple polypectomy). The mean time interval between past polyp diagnosis and the current study was 11 years in the betamethasone group and 9 years in the placebo group.

Only three patients reported side-effects, these were slight bleeding, burning and tingling sensations. All three were in the active treatment group and all completed the course of treatment. Non-completers were contacted by phone or letter to ascertain the reason for discontinuing treatment. Most stated lack of symptoms at entry into trial, or difficulty in returning for the six week follow-up assessment due to distance of travel.

The change in polyp size as assessed by endoscopic grading was compared using the Wilcoxon signed rank test, since the data was not normally distributed. There was a statistically significant reduction in size for both right and left sided polyps after active (betamethasone) treatment (p=0.016 for right and p=0.004 for left), whereas passive (placebo) treatment had no effect (p=0.06 for right and p=0.5 for left) (Table 1).

DISCUSSION

Our randomised controlled trial of topical treatment for nasal polyps in cystic fibrosis showed a statistically significant reduction in polyp size with betamethasone nasal drops compared with placebo. We used betamethasone drops since these have previously been shown to be of benefit in nasal polyposis in patients without cystic fibrosis (Chalton et al., 1985) and unlike other authors we have anecdotally found them to be of benefit in cystic fibrosis nasal polyposis. Previous authors have described cystic fibrosis polyps as neutrophilic and therefore unresponsive to steroids, we have found this distinction unhelpful (Rowe-Jones et al., 1997).

Of the 46 patients who entered the trial, only 22 completed the course of treatment. This was due to a variety of reasons including lack of severity of symptoms, cystic fibrosis patients tend to underestimate their symptoms (Slavit et al., 1993, Kerrebijn et al., 1992) and one would expect such a group to be less compliant than patients with severe symptoms. The study was carried out in a tertiary referral cystic fibrosis clinic and some patients lived sufficiently far away to find the six week follow-up appointment inconvenient.

Although the overall symptom scores improved significantly following treatment, this was not demonstrated in either the betamethasone or placebo groups when analysed separately, nor for individual symptoms. It is likely that this is due to the small sample size. Although it would be useful to repeat this trial with a larger sample size, symptom alleviation is not the only reason to reduce polyp size in this group of patients. A very important benefit is avoidance of sinus ostia obstruction resulting in bacterial overgrowth, recurrent infections and preclusion from a heart-lung transplant.

Very few patients experienced side-effects, the three who did were all in the active treatment group and all completed the treatment course. There was no statistical difference between those who did and did not complete the course either in terms of treatment prescribed or polyp grade prior to entering the trial.

CONCLUSION

As life expectancy for cystic fibrosis increases, it becomes even more important to find the most effective treatment for nasal polyps in these patients. This is for two reasons, the first is to provide a patent nasal airway thereby reducing symptoms and allowing improved quality of life, the second is to prevent sinus ostia obstruction. Without treatment this leads to stasis of secretions with bacterial overgrowth. This can be the source of recurrent respiratory infections, especially with *Pseudomonas aeruginosa* and *Staphylococcus aureus,* which if resistant to antibiotics can preclude a heart-lung transplant.

This is the first randomised controlled trial to demonstrate the benefit of betamethasone nose drops for nasal polyps in adult patients with cystic fibrosis, we would therefore recommend its use in this group of patients.

REFERENCES

1. Britton JR. (1989) Effects of social class, sex and region of residence on age at death from cystic fibrosis. Brit. Med. J. 298, 483-487.
2. Chalton R, Mackay IS, Wilson R, Cole P. (1985) Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. Brit. Med. J. 291, 788.
3. Kerem BS, Rommers JM, Buchanan JA, et al. (1989) Identification of the cystic fibrosis gene: Genetic analysis. Science 245, 1073.
4. Kerrebijn JDF, Poublon RML, Overbeek SE. (1992) Nasal and paranasal disease in adult cystic fibrosis patients. Eur Respir J. 5, 1239-1242.
5. Lewis PA. (1995) The epidemiology of cystic fibrosis. In Cystic Fibrosis (eds Hodson ME, Geddes DM.) pp1-13. Chapman and Hall Medical, London.
6. Lund VJ and Mackay IS. (1993) Staging in rhinosinusitis. Rhinology, 31, 183-184.
7. Mackay IS, Lund VJ. (1997) Imaging and staging. In Nasal Polyps: an inflammatory disease and the treatment. (ed Mygind N, Lildholdt T) Copenhagen, Munskgaard, p137-144.
8. McPherson MA. (1988) Recent advances in cystic fibrosis. J. Inher. Metab. Dis. 11(Suppl. 1): 94-109.
9. Oppenheimer EH, Rosenstein BJ. (1979) Differential pathology of nasal polyps in cystic fibrosis and atopy. Laboratory Investigation 40(4), 445-449.
10. Parsons DS. (1992) Sinusitis and cystic fibrosis. In Pediatric Sinusitis (ed Lusk RP) New York, Raven Press, p65.
11. Riorden JR, Rommens JM, Kerem BS, et al. (1989) Identification of the cystic fibrosis gene: Cloning and characterisation of complimentary DNA. Science 245, 1066.
12. Rommens JM, Ianuzzi MC, Kerem BS,. (1989) Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 245, 1059.
13. Rowe-Jones JM, Mackay IS. (1995) Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. Presented at The Royal Society of Medicine, Section of Laryngology and Rhinology Meeting. May 5th, 1995.
14. Rowe-Jones JM, ShembekAR M, Trendell-Smith N, Mackay IS. (1997) Polypoidal rhinosinusitis in cystic fibrosis: a clinical and histopathological study. Clin. Oto. 22, 167-171.
15. Rutland J, Cole PJ. (1981) Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with with sinusitis and bronchiectasis. Thorax 36, 654-658.
16. Slavit DH, Kasperbauer JL. (1993) Ciliary dysfunction syndrome and cystic fibrosis. In Systemic disease and the nasal airway. (ed. Thomas McCaffrey) Thieme Medical Publishers Inc., New York, p139-149.
17. Sørensen H, Mygind N, Tygstrup I, Winge Flensborg E. (1977) Histology of nasal polyps of different etiology. Rhinology 15 (3), 121-128.

P.J. Hadfield,
Clinical Fellow, ENT Department,
Great Ormond Street Hospital for Children,
London, WC1N 3JH
United Kingdom