ORIGINAL CONTRIBUTION

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The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study*

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SUMMARY

Background: *Free O_2^- radicals may cause precapillary sphincter abnormalities, resulting in epistaxis in hemizygous knockout mice for Endoglin. The* ***objective*** *of this study was to test if antioxidants, like N-acetylcysteine (NAC), are have a role in the treatment of epistaxis in hereditary hemorrhagic telangiectasia (HHT).*

Methods: *Forty-three patients participated in this study taking NAC 600 mg t.i.d for 12 weeks. Patients registered frequency, severity and duration of epistaxis and private and work-related quality of life (QOL), using a diary for two 6 weeks periods. The first period was prior to starting treatment and the second started after 6 weeks using NAC.*

Results: *There was a decrease in frequency ($p < 0.01$) and severity ($p < 0.01$) of epistaxis during the day. The improvement was most remarkable in male patients and patients with an ENDOGLIN mutation. In women and patients with an ALK-1 mutation, only a trend for improvement was found. Nocturnal epistaxis did not improve. The effect of epistaxis on the ability to work ($p = 0.02$) was reduced.*

Conclusion: *This pilot study was conducted to investigate whether animal experiments can be translated to humans with HHT regarding epistaxis. The positive results with NAC are promising and justify a randomised clinical trial.*

Key words: HHT, epistaxis, Rendu-Osler-Weber, quality of life, N-acetylcysteine

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber syndrome is an autosomal dominant inherited condition with an estimated prevalence of 1 in 10,000 people [(1)], but in some regions it is higher: the highest prevalence known worldwide is 1:1331 in the Afro-Caribbean population of the Netherlands Antilles [(2)].

The clinical diagnosis of HHT is based on the Curaçao criteria: recurrent epistaxis, telangiectases, visceral AVMs, or a first degree relative with HHT [(3)]. The diagnosis of HHT is definite, when 3 out of the 4 Curaçao criteria are present and the diagnosis is possible, when 2 criteria are present. In addition, the diagnosis can be established by genetic testing. Mutations in the endoglin *(ENG)* gene (OMIM 131195) on chromosome 9 [(4)] or the activin receptor like kinase 1 *(ACVRL1 / ALK-1)* gene (OMIM 601284) on chromosome 12 [(5)], respectively named *HHT-1* and *HHT-2*, comprise 80-95% of the HHT cases [(6)].

Patients with HHT present with a wide variety of symptoms which progress during life. The most disturbing symptom according to over 90% of the HHT patients is recurrent spontaneous epistaxis from nasal telangiectases. Patients experience these episodes of epistaxis as the most compromising event in their daily life [(7)]. The mean age of onset of epistaxis in patients with HHT is 12 years and symptoms progress with age. They experience a mean frequency of 18 epistaxis episodes per month [(8)].

At the moment, there is no satisfactory treatment available with lasting results for the management of recurrent epistaxis in patients with HHT. Current treatment modalities include laser therapy with Argon plasma or Nd:YAG laser, or septal dermoplasty according to Saunders [(9)], affording patients a surgical free period for an average of 12 months [(10)]. Another surgical option is closure of the nasal cavities, which prevents epistaxis, but is debilitating for patients [(11)].

In 2005, Toporsian et al. [(12)] described enhanced endothelium-dependant dilatation and an impaired myogenic response in the arteries of $Eng^{+/-}$ mice caused by the production of free O_2^- radicals. This pre-capillary sphincter dysfunction leads to an increased pressure on the vessels and the genesis of early

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HHT-like vascular lesions such as capillary loss and venular dilatation and ultimately to the development of telangiectases. Therefore, the objective of this pilot study was to investigate if HHT patients experience a reduction of epistaxis when treated with the O_2^--scavenger N-acetylcysteine (NAC).

METHODS

Patients

In 2005 the HHT-database of the St Antonius Hospital in Nieuwegein, The Netherlands, consisted of 456 patients with definite HHT. Patients were asked to participate in our study if they were over 18 years of age and had an average of at least 3 episodes of epistaxis or more a week. The requirement of blood transfusions was an exclusion criterion and during the study no change in iron medication or local treatment of nasal telangiectases was allowed. Sixty-two patients agreed to participate in the study.

Study protocol

Patients were asked to complete a diary 6 weeks (week 1-6) prior to starting the therapy and to recommence the diary 6 weeks after starting the therapy, again registering for a period of 6 weeks (week 13-18).

The therapy consisted of NAC 600 mg three times a day for a period of 12 weeks (week 7-18).

In the diary, the patients were asked to register the number of epistaxis, the severity of the epistaxis (1 = drops of blood, 2 = small gush, 3 = large gush) and the duration of the epistaxis in minutes daily. They registered these items for day- and nighttime bleedings separately.

To have an impression of the effect HHT has on private life, participants were asked to score this daily (1 = not at all, 2 = little, 3 = much, 4 = completely) and to score daily the influence HHT has on being able to work (0 = not applicable, 1 = not at all, 2 = little, 3 = much, 4 = completely).

Before starting NAC in week 7 and after taking NAC for 12 weeks (week 18) hemoglobin levels were measured. Weeks 7-12 were used as a run-in period.

Data analysis

All data were entered in Excel. The impact of epistaxis was calculated by multiplying the frequency, duration and severity scores. A paired Student t-test was performed on the average scores per person of frequency, duration, severity, impact of bleeding, impact on private life and on the ability to work and on the hemoglobin levels.

RESULTS

Sixty-two patients agreed to participate in the study performed between October 2005 and February 2006. In total, 50 patients returned the diaries and questionnaires. Seven patients were excluded from the study: 3 patients were not compliant in registering their epistaxis in the diary, 1 patient underwent Nd:YAG laser therapy during the run-in period of the study

Table 1. Patient characteristics.

Male/female	25 (58%)/18 (42%)
HHT-1/HHT-2	23 (58%)/18 (42%)
Average age in years (median)	53,3 (55)
Average age male/female (median)	53,6 (58)/ 53,0 (53)
Average age HHT-1/HHT-2 (median)	53,5 (58)/ 53,9 (54.5)

Table 2. Paired T-test on average scores of frequency of epistaxis per person.

	Day				Night			
	n	Average before	Average after	p	n	Average before	Average after	p
Total	43	1.35	1.11	<0.01	43	0.22	0.22	0.9
Male	25	1.21	0.95	0.02	25	0.22	0.18	0.3
Female	18	1.54	1.34	0.2	18	0.23	0.29	0.4
HHT-1	23	1.42	1.16	0.08	23	0.19	0.20	0.9
HHT-2	18	1.22	1.05	0.1	18	0.25	0.25	1.0

Total = total group, n = number of patients analyzed, average before = average number of epistaxis of the total group before treatment, average after = average number of epistaxis of the total group after treatment, p= 2-sided p value.

Table 3. Paired T-test on average scores of severity of epistaxis per person.

	Day				Night			
	n	Average before	Average after	p	n	Average before	Average after	p
Total	40	1.31	1.24	=0.01	31	1.37	1.32	0.5
Male	23	1.20	1.13	0.03	18	2.32	1.25	0.4
Female	16	1.46	1.39	0.2	12	1.62	1.41	0.3
HHT-1	20	1.30	1.23	0.1	13	1.50	1.31	0.1
HHT-2	17	1.30	1.24	0.09	15	1.29	1.30	0.9

Total = total group, n = number of patients analyzed, average before = average score of severity of epistaxis of the total group before treatment, average after = average score of severity of epistaxis of the total group after treatment, p= 2-sided p value.

Table 4. Paired T-test on average scores of duration of epistaxis per person.

	Day				Night			
	n	Average before	Average after	p	n	Average before	Average after	p
Total	40	3.64	3.01	0.07	42	1.14	0.94	0.6
Male	23	3.38	2.55	0.05	24	1.04	0.70	0.6
Female	17	4.00	3.62	0.5	18	1.28	1.26	0.9
HHT-1	21	3.12	2.25	0.02	23	1.29	0.75	0.4
HHT-2	17	4.04	3.77	0.7	17	1.03	1.24	0.7

Total = total group, n = number of patients analyzed, average before = average duration of epistaxis of the total group before treatment, average after = average duration of epistaxis of the total group after treatment, p= 2-sided p value.

Table 5. Paired T-test on impact of epistaxis per person.

	Day				Night			
	n	Average before	Average after	p	n	Average before	Average after	p
Total	39	6.29	5.35	0.02	31	3.11	2.73	0.5
Male	23	6.1	3.4	<0.01	18	0.90	0.34	0.5
Female	16	6.92	6.36	0.4	12	3.59	3.34	0.6
HHT-1	19	7.20	4.91	0.04	13	1.71	1.22	0.7
HHT-2	17	6.61	6.09	0.5	15	2.75	2.99	0.8

Total = total group, n = number of patients analyzed, average before = impact of epistaxis of the total group before treatment, average after = impact of epistaxis of the total group after treatment, p= 2-sided p value.

and another patient participated in another trial with thalidomide in the run-in period because of frequent epistaxis. Two other patients were excluded during the treatment phase: one underwent electrocoagulation of nasal telangiectases, which would have influenced the data in a positive direction and the other patient decided to quit the study because he experienced increasing epistaxis after starting the treatment with NAC, which could be regarded as treatment failure.

Patient characteristics are shown in Table 1. Two patients had a mutation of unknown origin.

Since not all patients completed the diary entirely, some patients were excluded from the analysis of the severity and duration of day and night-time epistaxis as well as for the assessment of influence on private life and work.

The mean frequency of epistaxis during daytime was reduced from 1.35 to 1.11 in the total group of participants ($p < 0.01$) and even more in the male population (Table 2). There was no effect of NAC on the average frequency of the nocturnal epistaxis.

The severity of epistaxis by day decreased from significantly when patients started to take NAC. The decrease was significant for the entire group and the male subgroup (Table 3).

The effect of NAC on the duration of daytime epistaxis showed a decrease from 3.64 minutes to 3.01 minutes ($p = 0.07$) in the total group (Table 4). In the male population and the patients with *HHT-1* the reduction was significant.

The severity of daytime epistaxis was reduced in the entire group, the male group and the patients with *HHT-1* (Table 5). Sixty-seven percent (26/39) of the total group noticed an reduction of the severity of daytime epistaxis after treatment (Figure 1). The impact of nocturnal epistaxis was less than the impact at daytime ($p < 0.01$).

The impact of epistaxis on private life decreased insignificantly from an average score per person of 1.65 before treatment to 1.58 after treatment ($p = 0.14$). However, there was a positive effect of NAC on the impact of epistaxis to the ability to work, with a reduction in the average score per person of 1.59 before to 1.37 after treatment ($p = 0.02$).

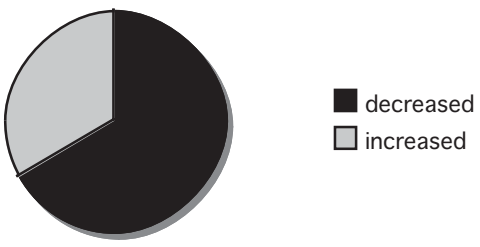

Figure 1. Impact of epistaxis in total population after treatment

The average hemoglobin level showed an insignificant increase from 7.9 mmol/l prior to treatment to 8.1 mmol/l after treatment ($p = 0.5$).

DISCUSSION

In this study we demonstrated that the use of the O_2^- scavenger NAC in patients with HHT decreases the frequency, severity and impact of epistaxis during daytime. The effect on frequency, severity, duration and impact is more obvious in the male population and in the patients with a mutation in the *END* gene (*HHT-1*). The release of O_2^- radicals is only described in mice with the *End* mutation [12], so one can wonder if an effect of O_2^- radical scavengers can be expected in patients with a mutation in the ALK-1 gene or other gene mutations causing HHT. The number of patients with *HHT-2* was only slightly smaller than that of patients with *HHT-1*. Also, there was no consistent difference in the aspects of epistaxis before treatment between *HHT-1* and *HHT-2*.

There was only a minor effect of NAC on nocturnal epistaxis. This can be explained by the lower frequency, duration, severity and impact of epistaxis during the night. Another possible explanation is that patients do not always wake up during a nocturnal epistaxis. In the morning they find bloodstains on their pillow or they have swallowed the blood without leaving marks. The registration of nocturnal epistaxis might not be reliable.

In this study there was no effect of NAC treatment on the hemoglobin levels of the HHT patients demonstrated. However, this is not surprising, since the hemoglobin levels were already within the normal range before starting the therapy.

Because epistaxis is the most common symptom of HHT and has a negative impact on QOL and lifestyle, it is important to evaluate the effect on quality of life [7], especially as the therapy consists of taking a medication three times daily. Patients in this study did experience an improvement of work-related quality of life, which may result in a good compliance. The study-population did not experience any adverse reactions to NAC.

NAC is a widely known radical scavenger, with the advantage of rarely causing adverse reactions. In the past there have been some doubts concerning the reactivity of NAC with O_2^- [13]. Benrahmoune et al. [14] found that O_2^- does interact with NAC, but at a rate constant lower than those reported for glutathione or cysteine. These were all studies performed *in vitro*. An indirect anti-oxidant effect of NAC can arise by deacetylation of NAC into L-cysteine, an important precursor of cellular glutathione synthesis [6,15].

Remarkable is the higher frequency, longer duration and worse severity of epistaxis in the female population, besides its reduced response to NAC compared to men. Four of the 5 women noting an increased frequency of epistaxis after treat-

ment with acetylcysteine were older than 55 years. Partially, this effect can be explained by the post-menopausal reduced levels of oestrogen and progesterone, which may have a positive influence on epistaxis. This does not however explain the impaired response to N-acetylcyseine in the post-menopausal female population.

This pilot study is conducted to investigate whether animal experiments can be translated to humans with HHT regarding epistaxis. The results with NAC are promising, as well for *HHT-1* as *HHT-2*, and justify a randomised trial in the future.

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