Efficacy and Safety of Speleotherapy in Children with Asthma Bronchiale

A Controlled Randomized Multicentre Study

Wirksamkeit und Verträglichkeit der Speläotherapie bei Kindern mit Asthma bronchiale

Eine kontrollierte, randomisierte, multizentrische Studie

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Schlüsselwörter
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Abstract

Spending time in a natural cave or a disused mine is a type of inhalation therapy called speleotherapy. The efficacy and safety of speleotherapy was investigated in a controlled, randomized multicentre study. Children aged 4–10 who were diagnosed with asthma bronchiale by a GP or pneumologist were eligible to take part in the study. In a 1-week pre-treatment phase, 3 spirometry tests were carried out and a diary was kept. During the 3-week treatment phase the children had a 2-h kindergarten programme every day except for Sundays. Children who were randomly placed in the speleotherapy group had their kindergarten programme in a natural cave or disused mine. Children who were randomly placed in the control group had the same programme at the same location – but aboveground. In a 1-week post-treatment phase, 3 spirometry tests were once again carried out and a diary was kept. The primary outcomes were the improvement in FEV_1 and the reduction in the use of sprays for acute treatment. 133 patients were enrolled in the study. Twelve children dropped out so a total of 121 patients were evaluated – 68 in the speleotherapy group and 53 in the control group. Most children had relatives with asthma and were on long-term medication. The median FEV_1 was 85% of normal values, and the median VC was 65% of normal values. The median improvement in FEV_1 during treatment was 10.5 percentage points in the speleotherapy group and 0.0 in the control group (adjusted $p=0.0002$). There was a reduction of acute spray applications in the speleotherapy group, but this was not significant ($p=0.56$). Twenty-four of 25 secondary outcome variables faired better in the speleotherapy group compared to the control group, and 12 of these were exploratively significant. The study demonstrated the efficacy and safety of speleotherapy in children with asthma. The outcome variables

Zusammenfassung

Der Aufenthalt von Patienten in einer natürlichen Höhle oder einem stillgelegten Bergwerk wird als Speläotherapie bezeichnet und ist eine besondere Form der Inhalationstherapie. Die Wirksamkeit und Verträglichkeit der Speläotherapie wurde in einer vom Deutschen Heilst llen-Verband und der Medizinischen Fakultät der Universität Ulm getragenen, kontrollierten und randomisierten Studie untersucht. In die Studie wurden Kinder im Alter von 4 bis 10 Jahren aufgenommen, bei denen ein Allgemeinarzt oder ein Pulmonologe die Diagnose Asthma bronchiale gestellt hatte. Die vom niedergelassenen Arzt verordnete Therapie wurde während der Studie unverändert fortgeführt. In einer 1-wöchigen Vorphase wurden 3 Spirometrien durchgeführt und ein Patiententagebuch geführt. Während der 3-wöchigen Behandlungsphase nahmen die Kinder täglich – ausgenommen sonntags – an einem zweistündigen Kindergartenprogramm teil. Kinder, die in die Speläotherapiegruppe randomisiert worden waren, erhielten dieses Kindergartenprogramm in einer natürlichen Höhle oder einem stillgelegten Bergwerk. Kinder, die in die Kontrollgruppe randomisiert worden waren, erhielten das gleiche Kindergartenprogramm am gleichen Ort, aber über Tage. In der 1-wöchigen Nachphase wurden wiederum 3 Spirometrien durchgeführt und das Patiententagebuch geführt. Hauptzielgrößen waren die Verbesserung des FEV_1 und die Verringerung des Bedarfs an Akutsprays. Die Studie wurde 2002 in dem stillgelegten Eisenbergwerk „Tiefer Stollen" in Aalen, im „Hella Glückstollen" in Neubulach (Schwarzwald) und in der „Teufelshöhle" in Pottenstein (Fränkische Schweiz) durchgeführt. Insgesamt wurden 133 Patienten aufgenommen. Als die Eltern am Ende der Vorphase das Ergebnis der Randomisation erfuhren, zogen 11 Eltern, deren Kinder in die Kontrollgruppe randomisiert wor-

had a high degree of concordance. Our study had only one week of follow-up, so we do not know how long the observed effect lasted without continued therapy.

den waren, ihr Einverständnis zur Studienteilnahme zurück. Bei einem Kind der Kontrollgruppe wurde die Studienbehandlung wegen Windpocken abgebrochen. Somit waren 121 Kinder nach Studienprotokoll behandelt und auswertbar, 68 Kinder in der Speläotherapiegruppe und 53 Kinder in der Kontrollgruppe. Trotz der Studienabbrecher waren die Gruppen gut vergleichbar. Die meisten Kinder hatten Verwandte mit Asthma und eine Dauermedikation. Der Median des FEV_1 war 85% der individuellen Normwerte, die mediane Vitalkapazität war 65% der individuellen Normwerte. Die mediane Verbesserung des FEV_1 während der Behandlung betrug 10,5 Prozentpunkte in der Speläotherapiegruppe und 0,0 in der Kontrollgruppe (für 2 Hauptzielgrößen adjustiertes $p = 0{,}0002$). Eine Wirksamkeit der Speläotherapie zeigte sich auch am rückläufigen Bedarf an Sprays zur Akutbehandlung, aber dieser Unterschied war nicht signifikant ($p = 0{,}56$). Von den insgesamt 25 sekundären Zielgrößen zeigten 24 eine tendenzielle Wirksamkeit der Speläotherapie, 12 davon waren orientierend signifikant. Bei drei Kindern traten unerwünschte Ereignisse auf: Ein Kind war während der Vor- und Nachphase nervös und unruhig, ein Kind entwickelte während der Behandlungsphase Windpocken und ein Kind eine Zahnfleischentzündung. Alle diese 3 Kinder waren in der Kontrollgruppe. Unsere Studie zeigt, dass Speläotherapie bei Kindern mit Asthma bronchiale wirksam und sicher ist. Die Zielgrößen zeigen eine sehr gute Übereinstimmung. Die Anforderungen an die Güte der Luft sind bei der Speläotherapie viel höher als bei Luftkurorten. Offensichtlich reicht den Atemwegen eine tägliche Expositionspause von 2 Stunden – das ist 8,3% der gesamten Zeit – aus, um sich zu regenerieren. Die Studie hatte nur eine einwöchige Nachbeobachtung, deshalb muss offen bleiben, wie lange der Therapieerfolg ohne weitere Speläotherapie anhält. Vermutlich ist Speläotherapie auch bei Erwachsenen wirksam, aber das wurde nicht untersucht.

1. Introduction and Purpose of the Study

Asthma bronchiale is a serious concern in modern civilizations. It is characterised by a variable and reversible obstruction of the airways due to inflammation and hyperreagibility.

Speleotherapy is a specific form of therapy that takes place in a specific climate. Spending time in a natural cave or disused mine with its cold, humid and nearly allergen free air is a type of inhalation therapy. It may therefore be helpful for patients with asthma bronchiale. However, there is little knowledge on the efficacy of speleotherapy. In a Cochrane review [1] only three trials including a total of 124 asthmatic patients met the relevant criteria. Only one [2] of these 3 trials had a reasonable methodological quality, but it investigated the effect of radon inhalation. As a contribution to evidence-based medicine in this field, we carried out a multicentre controlled randomized study to investigate the efficacy of staying in a cave or mine for 2 h per day over 3 weeks for children with asthma bronchiale.

In Germany, caves and mines used for therapy have to comply with the following maximum permissible values:

Temperature	>5 and <12 °C
Humidity	>85%
Nitrogen dioxide	<5.0 µg/m³
Small particle matter (<2.5 µg per particle)	<6.0 µg/m³
Large particle matter (>2.5 µg per particle)	<8.5 µg/m³

These conditions are much stricter than the regulations for recreation areas. The climate of the three caves or disused mines participating in this study is described in **Table 1**, more details are given in [3].

2. Methods

2.1 Patients

Those eligible for the study were children with asthma bronchiale as diagnosed by a GP or pneumologist in accordance to the rules set out by European paediatric pulmonologists [4]. The children had to be between 4 and 10 years-old and able to do a spirometry test. Children with $FEV_{1second}$ of less than 1.5 l/s, serious heart disease, mucopurulent infections, other consumptive diseases like cancer, and children in hospital or scheduled for a hospital stay were not included to the study. Treatments prescribed by the GP or pneumologist were continued without change.

2.2 Treatment Groups

Children randomized to the speleotherapy group stayed in a natural cave or a disused mine for 2 h per day over 3 weeks. During their stay they took part in a children's programme – similar to that of a kindergarten or nursery – which was headed by a children's nurse. Children who were randomly placed in the control group received the same programme at the same loca-

	Tiefer Stollen, Aalen	Glückstollen, Neubulach	Teufelshöhle, Pottenstein
temperature °C			
min – max	11–12	5–10	8.9–9.5
humidity	≥95%	≥85%	>95%
nitrogen dioxide [µg/m³]			
summer			
mean ± sd	0.50 ± 0.56	1.05 ± 0.46	0.67 ± 0.34
winter			
mean ± sd	1.04 ± 0.60	4.64 ± 1.50	0.63 ± 0.73
small particle matter [µg/m³]			
summer			
mean ± sd	4.78 ± 1.54	1.87 ± 0.78	3.65 ± 1.33
proportion of reference	80%	31%	61%
winter			
mean ± sd	9.82 ± 1.79	4.07 ± 1.12	7.66 ± 2.08
proportion of reference	164%	68%	128%
large particle matter [µg/m³]			
summer			
mean ± sd	1.18 ± 0.49	4.49 ± 1.35	1.94 ± 1.70
proportion of reference	14%	53%	23%
winter			
mean ± sd	3.34 ± 3.16	1.25 ± 0.56	0.68 ± 0.21
proportion of reference	39%	15%	8%

Table 1 Climate in the Participating Caves and Mines.

All measurements were taken at the location of the therapy and during the therapy. Therefore, contaminations due to patients and staff are included. Small particle matter is defined as <2.5 µg per particle, large particle matter as >2.5 µg per particle. Reference is the maximum permissible value mentioned in the introduction. Data from [3]

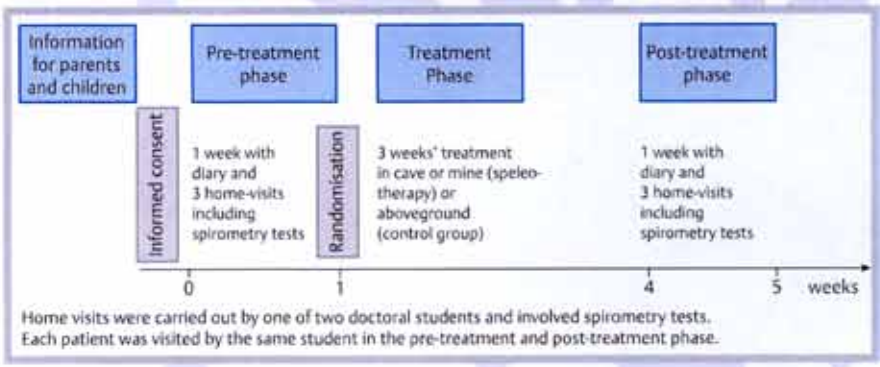

Fig. 1 Course of Study.

tion but in a room aboveground. The two children's nurses at each participating centre alternated with each other, spending one day in the cave and one day aboveground. This ensured that differences between the speleotherapy group and the control group were not influenced by the personality of the study staff.

2.3 Agenda of the Study

The study consisted of 3 consecutive phases, see **Fig. 1**.

Pre-Treatment Phase of 1 Week

Each child was visited 3 times at home by one of the study's two doctoral students [5]. A spirometry test was taken with a portable device during each of the visits. Furthermore, the parents or – if possible on account of their age – the child filled in a daily case report form (CRF) or "diary".

Randomization

The randomization schedule was established by the Department of Biometry at the University of Ulm. It was stratified for 3 centres, 2 cohorts, 2 genders and whether the child was already at school or not. (The study was performed during school holidays). In total there were 24 strata.

Treatment Phase of 3 Weeks

Children participated in the kindergarten-like programme over 3 weeks, except on Sundays. Hence, treatment spanned a total of 18 sessions of 2 h each. Depending on randomization the children participated in the programme underground or aboveground at the same location. The parents' task was to bring their child to each treatment session and to pick him or her up afterwards. They were not present during the programme.

Post-Treatment Phase of 1 Week

Each child was visited 3 times at home by the same doctoral student as in the pre-treatment phase. A spirometry test was taken during each of the 3 visits and the same diary/CRF was filled in as in the pre-treatment phase.

2.4 Criteria for Treatment Success

All values from the spirometry tests were entered as a percentage of the reference value of the child in question. The primary outcome variable was improvement of FEV_1. The difference between the pre-treatment phase and the post-treatment phase was calculated separately for each child. The median of the 3 measurements taken during the pre-treatment phase for each

child was subtracted from the median of the 3 measurements taken during the post-treatment phase. A positive sign (+) therefore indicates an increasing FEV_1 during treatment.

The other primary outcome variable was the use of short-term β_2-mimetica (sprays). The total number of spray applications taken during the post-treatment phase for each child was subtracted from the total number of spray applications taken during the pre-treatment phase for the child in question. Hence, if the outcome variable has a positive sign (+) this indicates a decrease in the use of the spray and therefore an improvement of the disease.

A global level of significance of two-sided 5% was specified in the study protocol. For the two primary outcome variables a Bonferroni-Holm adjustment of type I error probability [6] was also established in the protocol.

The secondary outcome variables were vital capacity (VC), forced vital capacity (FVC), maximum expiratory flow at 25% of FVC (MEF 25), and MEF 50. They were computed the same way as for FEV_1. Further secondary outcome variables regarding symptoms and quality of life were taken from the diaries that were filled in during the pre-treatment and post-treatment phases. For all secondary outcome variables a positive sign (+) indicates an improvement during treatment.

2.5 Enrolment and Ethics

The study protocol and CRFs were submitted to the Ethical Committee of the University of Ulm and approved. Local newspapers and radio programmes in the areas of the participating centres reported on the study, called on people to participate, and provided the relevant contact details. People who were interested received written information on the study and an application form. Applications were accepted on the basis of the inclusion and exclusion criteria mentioned above. All parents gave written informed consent. If the child was randomized to be in the control group, he or she received free tickets for 18 visits to the cave or mine after termination of the study.

2.6 Responsibilities and Performance

The study was performed according to Good Clinical Practice (GCP) [7]. It was headed by the University of Ulm's Medical Faculty, Children's Hospital and Department of Biometry. The study was carried out between 8 April and 20 July 2002 at the following three locations in Germany:

- Tiefer Stollen, a disused iron-mine at Aalen – Helene Weber, MD.
- Hella Glückstollen, a natural cave at Neubulach (Black Forest) – Gabriele Hartmann, GP
- Teufelshöhle, a natural cave at Pottenstein ("Franconian Switzerland") – Franz Macht, MD.

Each study centre treated consecutively 2 cohorts of about 20 children each – 10 children in the speleotherapy group and 10 children in the control group. The study began one week later in the second centre and two weeks later in the third centre. This staggered start enabled the two doctoral students of the study to carry out the pre- and post-treatment phase at all 3 study centres.

Sponsors of the study were the Medical Faculty of the University of Ulm and the German Association for Speleotherapy (Deutscher Heilstollen-Verband). A detailed biometrical report [8] was issued on 2 July 2003.

3. Results

3.1 Number of Cases and Drop-outs

A total of 133 children were enrolled, participated in the pre-treatment phase, and were randomized into the two groups – 68 children for the speleotherapy group and 65 children for the control group. The small difference in group size was due to the 24 strata of randomization. However, the parents of 11 children who were randomized to the control group withdrew their consent for participation. These 11 withdrawals were similar to the patients in the study for all observed aspects including anamnesis, diagnoses, application of sprays and results of spirometry. During treatment one child of the control group developed a varicella zoster infection and was excluded from further study treatment. Therefore, 121 patients were evaluated, 68 with speleotherapy and 53 with the control treatment.

3.2 Missing Observations

All children had at least one spirometry test in the pre-treatment phase as well as in the post-treatment phase. Hence, FEV_1 as primary outcome was present for every case. Values were, however, missing in the diaries. If CRF-entries for at least 4 days were available in both phases then the median was calculated from the available observations. The number of β_2-mimetica sprays and other frequencies were then extrapolated to 7 days. If less than 4 days of the diary were filled in then the variables were considered to be missing. Missing observations were not replaced – all results are based on observed cases.

3.3 Description of Study Patients and Comparability of Groups

72 boys and 49 girls participated in the study (○ **Table 2**). The median age was 6 years. Most children had relatives with asthma (78%), were on long-term medication (73%) and had in mean 5.4 spray applications during the one week pre-treatment phase. The median FEV_1 was 85% of the normal value, and the median vital capacity was 65% of the normal value.

Despite the 12 drop-outs in the control group, the speleotherapy group and control group were similar with regard to gender (the percentage of boys was 60% vs. 58%), age (median of 6 years in both groups), relatives with asthma (82% vs. 72%), long-term medication (70% vs. 75%), number of spray applications (mean 5.7 vs. 5.0 during one week), FEV_1 (median 83% vs. 87% of normal value) and vital capacity (61% vs. 68% of normal value) – see ○ **Table 2**. None of these differences between the speleotherapy group and the control group is significant.

3.4 Primary Outcomes

FEV_1 is expressed as a percentage of the normal value of a child of the same gender and age. The median FEV_1 of the pre-treatment and post-treatment phase is shown in ○ **Table 3** and depicted in ○ **Fig. 2**. In the speleotherapy group the individual changes of FEV_1 ranged from −28.0 (deterioration) to +46.0 (improvement). The median of individual changes was +10.5 and the mean change was +9.8. In the control group the individual changes of FEV_1 ranged from −24.5 (deterioration) to +22.0 (improvement). The median of individual changes was 0.0, and the mean change was −0.3. After adjustment by the Bonferroni-Holm procedure [6] for 2 tests the two-sided p-value was 0.0002.

The other primary outcome was the number of spray applications with short-term β_2 mimetica. Positive differences indicate

Table 2 Description of Patients at Start of Study.

		Speleotherapy group n=68	Control group n=53	Total n=121
cave or mine	Aalen	26	22	48=40%
	Neubulach	25	20	45=37%
	Pottenstein	17	11	28=23%
gender	boys	41=60%	31=58%	72=59%
	girls	27	22	49
age	median	6 years	6 years	6 years
sisters, brothers or other relatives with asthma	yes	56=82%	38=72%	94=78%
	no	12	12	24
	missing	0	3	3
long-term medication (Some patients used more than one medication)	glucocorticoids	22	17	39
	degranulat. inhibitors	20	16	36
	beta 2 mimetics	12	15	27
	H1 antagonists	9	3	12
	any long-term medic.	48=70%	40=75%	88=73%
	no long term medic.	20	13	33
no. of spray applications per week	mean	5.7	5.0	5.4
FEV_1 (% of normal value)	median	83%	87%	85%
vital capacity (% of normal value)	median	61%	68%	65%

Table 3 Therapeutic Success in Primary Outcomes (FEV1 and Number of Sprays).

FEV_1 (Percentage of the reference value)	Speleotherapy group	Control group	Total
pre-treatment phase			
min – max	31–117	35–132	31–132
median	83.0	87.0	85.0
mean ± sd	79.97 ± 18.53	86.46 ± 18.03	82.81 ± 18.52
post-treatment phase			
min – max	33–128	48.5–145.5	33–145.5
median	88.5	83.0	87.0
mean ± sd	89.77 ± 18.41	86.12 ± 18.99	88.17 ± 18.68
intraindividual differences (1st primary outcome)			
min – max	−28–+46	−24.5–+22	−28–+46
median	+10.5	0.0	+4.0
mean ± sd	9.80 ± 14.80	−0.34 ± 11.26	5.36 ± 14.24
Number of sprays applied			
pre-treatment phase			
min – max	0–54	0–56	0–56
median	0.0	0.0	0.0
mean ± sd	5.74 ± 10.34	4.96 ± 10.94	5.41 ± 10.56
post-treatment phase			
min – max	0–34	0–56	0–56
median	0.0	0.0	0.0
mean ± sd	5.40 ± 9.18	5.14 ± 10.59	5.29 ± 9.75
intraindividual differences (2nd primary outcome)			
min – max	−25–+26	−13–+19	−25–+26
median	0.0	0.0	0.0
mean ± sd	+0.11 ± 5.74	+0.07 ± 4.19	+0.09 ± 5.11

Positive differences indicate improvement over time, negative differences indicate deterioration

a reduction of the need for sprays and therefore an improvement. However, during the pre-treatment phase only 37% of the children applied a spray at least once. Therefore, most changes were zero. The mean of the individual differences in the number of spray applications was +0.11 in the speleotherapy group and +0.07 in the control group (p=0.56). For details see ○ **Table 3**.

3.5 Secondary Outcomes

A total of 25 secondary outcome variables were specified in the study protocol: 4 variables from spirometry tests, 11 symptoms from the diaries and 10 variables on quality of life, which were also from the diaries. Details are presented in ○ **Table 4**. Twelve secondary outcome variables (2 variables from spirometry tests, 5 symptoms, and 5 variables for quality of life) faired better in the speleotherapy group and were exploratively significant, whereas another 12 secondary outcome variables also faired better in the speleotherapy group, but were not significant. Only one secondary outcome variable, namely the number of cough attacks at night, tended to fair better in the control group.

3.6 Safety

Three children developed adverse events. One child was nervous and restless during the pre-treatment and post-treatment phases. Another child developed a varicella zoster infection during the treatment phase and was therefore excluded from further participation in the study. A third child had gingival inflammation during the post-treatment phase. All three children were in the control group.

4. Discussion

Medications, surgery and physical treatments are the most important types of medical therapies. While the efficacy and safety of drugs are well investigated with controlled randomized trials, this is rarely done for surgical procedures and for physical therapies. Valid information is rare regarding the efficacy of speleotherapy [1]. When we wrote our protocol the published studies either had no control group or other major deficiencies [9–11]. Therefore we designed and performed a controlled randomized multicentre trial to investigate the efficacy and safety of speleotherapy, a physical treatment for asthma bronchiale. Studies

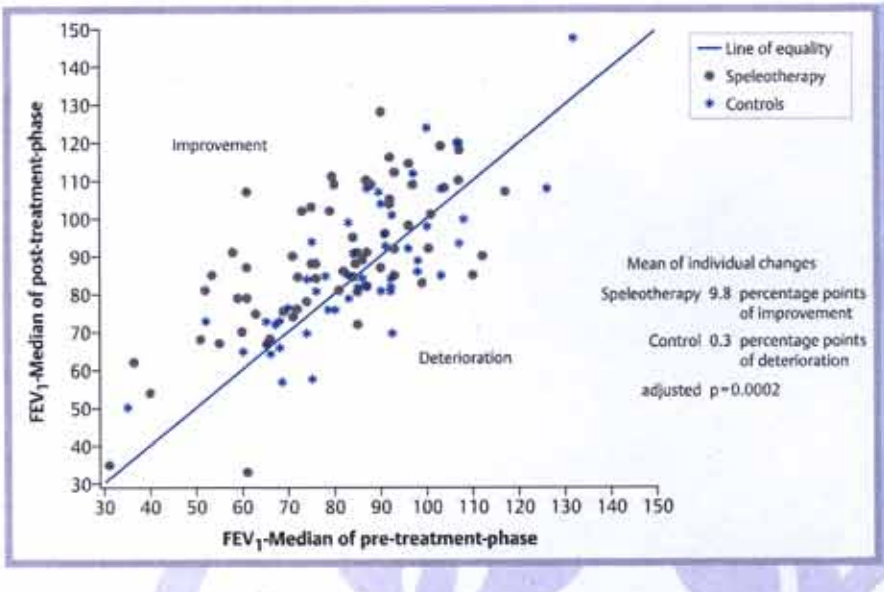

Fig. 2 FEV1 as Primary Outcome as a Percentage of the Reference Value.

published in the meantime [12–16] also failed to deliver really convincing results on the efficacy of speleotherapy in asthma bronchiale.

In our trial the children of the control group took part in exactly the same kindergarten programme as the speleotherapy group, had identical staff, and were treated at the same location – but aboveground. It was of course impossible to mask the treatment groups. However, the primary outcome was assessed by spirometry tests, delivering rather objective, "hard" data. Furthermore, values from the pre-treatment phase and the post-treatment phase are based on three spirometry tests for each child.

The children enjoyed undergoing the spirometry tests with the same female doctoral student in both the pre-treatment and post-treatment phase. They also enjoyed the kindergarten programme during the treatment phase. We therefore do not assume that the children treated aboveground tried to reduce their performance in spirometry tests in the post-treatment phase. We performed this study with children because we felt they are more influenced by the kindergarten programme and the staff of the study (which was exactly the same in both groups), while adults would have been more influenced by the purpose of the study.

Our study has 12 drop-outs, all of them in the control group. At the end of the pre-treatment phase the parents were told which group their child had been randomly placed in. Of the 65 children who were randomized to the control group, 11 (17%) had parents who were so disappointed that they withdrew their informed consent to participate in the study. From the legal point of view this is in order. But a higher proportion of drop-outs in one group can disturb the comparability of groups achieved by randomization and can bias the results. We checked all variables observed in the pre-treatment phase and had the impression that no bias was introduced by these drop-outs.

The primary outcome was the individual improvement of FEV_1. Children of the speleotherapy group improved in median by 10.5 percentage points, in mean 9.8 percentage points, while the control group was practically unchanged. The effect size in the speleotherapy group is 69% of the standard deviation of the total. This is clinically relevant. For the primary outcome FEV_1, we found the local p-value to be 0.0001. Adjustment for two primary outcome variables by the Bonferroni-Holm procedure for multiple tests [6] resulted in the two-sided multiple p-value of 0.0002. This is a convincing p-value.

The primary outcome of acute medication with short-term β_2 mimetica (spray) also faired better in the speleotherapy group, but this was not significant. This may be due to the fact that only 45 of 121 children (37%) used acute medication at least once during the one-week pre-treatment phase. Only these 45 children – 26 in the speleotherapy group and 19 in the control group – could demonstrate an improvement. The study was underpowered for such a "seldom event".

The study has 25 secondary outcome variables. This is a remarkably high number. More importantly, all these variables – except one – had better results in the speleotherapy group. Under the overall null-hypothesis we would expect that half of the variables would fair better in one group, and the other half would fair better in the other group. In a soccer game a result of 24 to 1 would convince everybody that the winning team is much better than the losing team.

Twelve of the 25 secondary outcome variables were significant, and all 12 faired better in the speleotherapy group. The significance of these 12 variables is of course only explorative, not confirmative. Under the overall null-hypothesis with a local level of significance of 5% we would expect that 5% of the 25 tests, i.e. 1.25 tests, would be "falsely significant". Hence, we can assume that – out of these 12 significant tests – 1 test or maybe 2 or even 3 tests, but not more, may be falsely significant.

Summarizing primary and secondary outcome variables, we find a high degree of concordance amongst all outcome variables. This is really convincing, especially with the methodological approach of a controlled randomized trial.

Unfortunately we cannot compare our own results with the results of other studies of comparable design. We would be happy if our results would be re-examined by other studies.

Speleotherapy is a specific form of inhalation therapy that involves spending time in specific climactic conditions. Conditions for speleotherapy are much stricter than for recreation areas [3]. Breathing practically perfect air for 2 h each day – or more straightforwardly, undergoing an inhalation treatment of 2 h each day – is equivalent to 8.3% of the total time. It is reasonable to assume that this a sufficient "dose" to improve asthma.

We assume that breathing humid, clean and practically allergen free air has an effect similar to a reduction of disease load. It may

Table 4 Therapeutic Success in Secondary Outcomes.

	Speleotherapy			Control			expl. p-value
	pre-t	post-t	Diff	pre-t	post-t	Diff	
spirometry							
vital capacity as % of reference value	61.29	70.63	9.43	67.27	67.54	0.26	0.0001*
forced vital capacity (FVC) as % of r.v.	73.51	82.49	8.98	78.92	77.04	−1.89	0.001*
MEF 25	76.46	88.75	11.40	80.57	83.78	3.22	0.10
MEF 50	71.32	78.34	6.50	75.54	76.32	0.78	0.30
symptoms from diary							
no. of cough attacks during the day	12.29	6.63	5.63	12.25	14.70	−2.77	0.008*
severity of cough attacks during the day (4 level rating scale)	0.65	0.40	0.24	0.59	0.59	−0.01	0.054
no. of cough attacks at night	5.50	4.02	1.35	10.02	6.03	3.84	0.29
severity of cough attacks at night (4 level rating scale)	0.45	0.33	0.10	0.47	0.46	0.03	0.55
no. of days with respiratory depression	0.38	0.18	0.20	0.24	0.76	−0.51	0.038*
no. of days without loss of appetite	6.03	6.32	0.28	6.38	6.29	−0.08	0.40
no. of nights without interrupted sleep	5.19	6.22	1.03	5.38	5.71	0.36	0.048*
no. of days with inhalations	2.34	1.65	0.72	2.61	2.90	−0.32	0.019*
no. of inhalations	5.10	3.51	1.59	5.17	5.49	−0.60	0.014*
no. of days with acute medications (sprays)	2.09	2.06	−0.03	1.83	2.00	−0.11	0.86
no. of days with contact to physician	0.10	0.10	0.00	0.06	0.22	−0.16	0.092
quality of life							
physical condition (parents' view)	74.03	83.33	9.26	77.39	80.69	3.08	0.058
physical condition (child's view)	54.70	56.84	2.14	56.61	54.76	−1.94	0.099
symptomatology (parents' view)	75.33	84.18	7.41	75.34	75.51	1.24	0.097
symptomatology (child's view)	24.47	27.56	3.22	25.38	25.26	0.26	0.013*
burden of disease and therapy (parents' view)	83.93	88.22	4.10	85.58	81.94	−3.58	0.021*
psychical condition (parents' view)	72.53	77.82	5.16	76.28	75.74	−0.75	0.027*
feeling of health (parents' view)	76.54	82.84	6.18	79.65	79.79	0.02	0.004*
feeling of health (child's view)	67.16	70.60	3.44	66.94	68.50	1.63	0.44
overall assessment of quality of life (parents' view)	1.25	0.79	0.47	1.10	1.02	0.09	0.069
overall assessment of quality of life (child's view)	1.94	1.62	0.33	1.61	1.88	−0.24	0.044*

Three figures are presented for each variable and for each of the two groups. The first number is the mean during the pre-treatment phase, the second number is the mean in the post-treatment phase and the third number is the mean of the individual differences. All p-values are computed from the individual differences. * indicates explorativ significant

All differences are calculated in such a way that a positive difference indicates an improvement. All variables faired better in the speleotherapy group except the number of cough attacks at night

work like an interruption of the enemy's fire in a battle. Such a break of exposure to allergens may enable the body to reduce the severity of the disease and to regenerate. This is supported by the fact that symptoms of asthma are reversible.

We conclude that speleotherapy is efficient and safe for children aged 4–10 years-old with asthma bronchiale. At present we do not know how long the improvement achieved during the 3 weeks of speleotherapy will last, because our study only had a follow-up period of one week. We surmise that the therapeutic effect will decrease slowly, and may be reduced after half a year.

The patients in the study were children aged 4–10 years-old. We assume that speleotherapy is effective in adults as well. However, this is an extrapolation.

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Conflict of Interests: W. G. was head of the Institute of Biometrics of the Medical Faculty of the University of Ulm, Germany. He retired in 2004. The study had no fiscal sponsor. There is no conflict of interests.

H. W. is a GP in her own practice in Aalen. She participated in the study as one of the investigators. For her participation she received no financial support. There is no conflict of interests.

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