A randomized crossover study of bee sting therapy for multiple sclerosis

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Abstract—*Background:* Bee sting therapy is increasingly used to treat patients with multiple sclerosis (MS) in the belief that it can stabilize or ameliorate the disease. However, there are no clinical studies to justify its use. *Methods:* In a randomized, crossover study, we assigned 26 patients with relapsing-remitting or relapsing secondary progressive MS to 24 weeks of medically supervised bee sting therapy or 24 weeks of no treatment. Live bees (up to a maximum of 20) were used to administer bee venom three times per week. The primary outcome was the cumulative number of new gadolinium-enhancing lesions on T1-weighted MRI of the brain. Secondary outcomes were lesion load on T2*-weighted MRI, relapse rate, disability (Expanded Disability Status Scale, Multiple Sclerosis Functional Composite, Guy's Neurologic Disability Scale), fatigue (Abbreviated Fatigue Questionnaire, Fatigue Impact Scale), and health-related quality of life (Medical Outcomes Study 36-Item Short Form General Health Survey). *Results:* During bee sting therapy, there was no significant reduction in the cumulative number of new gadolinium-enhancing lesions. The T2*-weighted lesion load further progressed, and there was no significant reduction in relapse rate. There was no improvement of disability, fatigue, and quality of life. Bee sting therapy was well tolerated, and there were no serious adverse events. *Conclusions:* In this trial, treatment with bee venom in patients with relapsing multiple sclerosis did not reduce disease activity, disability, or fatigue and did not improve quality of life.

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Current treatments for multiple sclerosis (MS) can reduce the frequency of relapses and relieve symptoms, but despite all medical measures taken, the disease frequently and relentlessly worsens. Because of the limitations of conventional therapy, many patients with MS explore alternative treatment options.[1,2] Bee sting therapy has been practiced since ancient times and is becoming increasingly popular as an alternative treatment for MS. Venom of the honeybee contains substances with anti-inflammatory properties, including melittin and adolapin.[3,4] It also contains apamin, a polypeptide that crosses the blood-brain barrier and blocks the after-hyperpolarization potential, which plays a role in regulating neuronal activity by inhibiting calcium-activated potassium channels.[5]

Bee sting therapy consists of administering a series of honeybee stings at regular intervals, usually three times per week. This therapy is often administered by private beekeepers and other nonmedically qualified practitioners and entails a risk of fatal allergic reactions. Claims of disease stabilization and clinical improvement are based on anecdotal information. We conducted a medically supervised, randomized, open, crossover trial of 24 weeks of bee sting treatment vs no treatment in patients with relapsing-remitting or secondary progressive MS. Disease activity was assessed by serial MRI of the brain. In addition, we performed clinical assessments for disability, fatigue, and health-related quality of life.

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Methods. *Patients.* The protocol was approved by the local ethics committee. All patients provided written informed consent. Eligible patients were aged between 18 and 65 years and had clinically definite relapsing MS,[6,7] a baseline Expanded Disability Status Scale (EDSS) score up to 6.5 (scores can range from 0 to 10, with higher scores indicating more severe disease),[8] and at least one documented relapse during the past year or two documented relapses during the preceding 2 years or the presence of one gadolinium-enhanced lesion on T1-weighted MRI of the brain during the screening phase. Exclusion criteria were a history of allergy or drug hypersensitivity, hypersensitivity to bee venom, treatment with immunosuppressive or immunomodulating drugs in the preceding 3 months, treatment with corticosteroids in the preceding 2 months, use of beta-blockers, diabetes mellitus, mastocytosis, other neurologic disorders that could interfere with the

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assessments, pregnancy, or unwillingness to practice acceptable birth control. All eligible patients underwent a skin allergy test with standardized bee venom extracts, a bee venom IgE Rast test in serum, and screening for mastocytosis by serum tryptase determinations and methylhistamine and methylmidazole acid in urine.[9]

Study design. Patients were randomized to two groups. The first group received bee sting therapy for 24 weeks and was then switched to no treatment for the next 24 weeks. The second group received no treatment during the first 24 weeks and then started bee sting therapy for the next 24 weeks. Live bees (*Apis mellifera*) administered bee venom three times per week in the presence of a physician. Bees were removed from a jar with tweezers, held over the upper leg until they stung. Stings were administered three times per week with gradual increment of one additional sting at each session, to a maximum of 20 bee stings per session. Additional therapy consisted of ascorbic acid 1g/day orally. Alcohol intake was forbidden. The patient always carried an autoinjector with epinephrine for the treatment of anaphylactic shock (EpiPen Autoinjector).

A treating physician was responsible for the bee sting therapy and overall medical management of the patient. Three other physicians were responsible for clinical assessments and follow-up of relapses. Relapses could be treated with 500 mg IV methylprednisolone for five consecutive days.

MRI procedure. Dual fast spin echo sequences and T1-weighted spin echo sequences following IV administration of gadolinium (0.3 mmol/kg) of the brain (3-mm thick axial slices) were obtained during the screening phase (1 month before randomization), immediately before start of the treatment period or no treatment period, and every 6 weeks. (Gadolinium [Omniscan] was kindly donated by GE Healthcare, Chalfont St Giles, UK.) All MRI scans were performed at the Gemini Hospital in Den Helder and were analyzed, after the study was completed, by an independent center (Department of Radiology, Leiden University Medical Center, The Netherlands) whose members were unaware of the patients' treatment. Lesions were measured using a semiautomated method.[10]

Outcome measures. The primary outcome measure was the cumulative number of new gadolinium-enhancing lesions on T1-weighted MRI. Secondary MRI outcomes were the volume of enhancing lesions and lesion volume on T2*-weighted MRI.

Secondary clinical endpoints included the number of relapses, changes in the scores on the EDSS, Multiple Sclerosis Functional Composite (MSFC), Guy's Neurologic Disability Scale (GNDS), Abbreviated Fatigue Questionnaire (AFQ), Fatigue Impact Scale (FIS), and Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36). The MSFC is a multidimensional clinical outcome measure that includes quantitative tests of leg function/ambulation (timed 25-ft walk), arm function (nine-hole peg test), and cognitive function (paced auditory serial addition test).[11] The composite score is calculated as the mean of the Z scores of the three components compared to the task force pooled data set, which is used as a reference population.[12] A decrease in Z score represents deterioration in neurologic function. GNDS consists of a questionnaire covering 12 different domains at the level of disability during the past month (scores can range from 0 to 60, with higher scores indicating more severe disability).[13] The AFQ consists of four questions that have to be answered on a 7-point Likert scale.[14] A higher score indicates a higher degree of subjective fatigue (range 4 to 28). The FIS assesses the impact of fatigue on different areas of functioning (cognitive, physical, and psychosocial). The maximum score is 120, with lower scores indicating less impact of fatigue on activities.[15] The same assessing physician, who was trained to administer the EDSS and MSFC, evaluated the same subjects throughout the study.

Health-related quality of life was assessed with a validated Dutch translation of the SF-36. The SF-36 is a 36-item questionnaire that measures general health, physical function, pain, vitality, social function, physical role, emotional role, and mental health on eight subscales.[16] For each variable, scores are coded, summed, and transformed onto a scale from 0 (worst possible health) to 100 (best possible health).

Relapse was defined as the occurrence of a new neurologic symptom or worsening of an old one attributable to MS, accompanied by an appropriate neurologic abnormality lasting at least 24 hours without fever, and following a stable period of at least 30 days. All relapsing patients were assessed within 7 days of the relapse for objective confirmation by the assessing neurologist. All adverse events were recorded in a patient diary and confirmed by the treating physician.

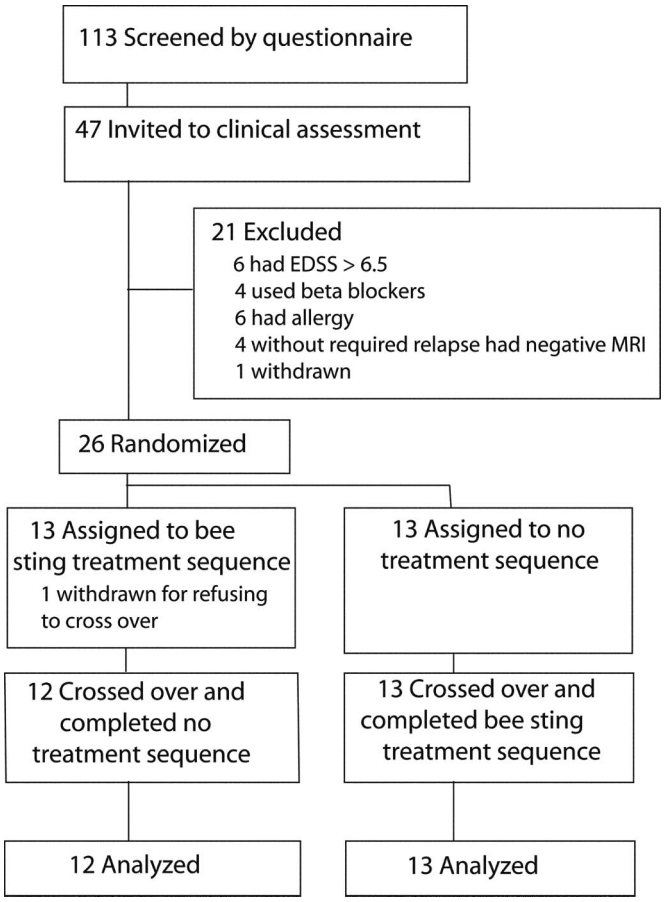

Figure. Flow of participants.

Statistical analysis. We considered a reduction of >50% in new MRI activity over 24 weeks on serial MRI as clinically relevant.[17] Based on sample size calculations as suggested by Silver et al.,[18] using the 0.3-mmol/kg dose of gadolinium, we needed 2×10 patients to detect a more than 50% reduction in the cumulative number of new active lesions with a power of 80%. The power was enhanced by performing serial MRI over 12 months instead of 6 months.[19] To allow for dropouts, the plan was to enroll up to 30 patients.

Between-treatment comparisons of MRI lesions and scores on the EDSS, MSFC, GNDS, AFQ, FIS, and SF-36 were tested with the general linear model repeated-measures procedure corrected for baseline values and treatment sequence. Fisher's exact test was used to compare proportions. Analyses were performed with the Statistical Package for the Social Sciences (SPSS 11.0 for Windows, Chicago, IL). All reported p values are two tailed.

Results. The study started in January 2004 and the follow-up was 1 year. One hundred thirteen patients volunteered for this study. To screen for eligibility, all were sent a questionnaire. Forty-seven patients were invited for further clinical screening, after which 26 were found eligible for inclusion (figure). Demographic and baseline data are shown in table 1. There were no differences between the two groups, although the second group was slightly more disabled. One patient in the group who started with bee sting treatment refused to stop bee sting therapy after the first 24 weeks and withdrew from the second part of the study. He arranged a beekeeper to continue therapy.

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Table 1 *Baseline demographic characteristics of participants*

	Bee sting therapy first, then off treatment, n = 13*	No treatment first, then bee sting therapy, n = 13
Age, y		
Mean ± SD	43.2 ± 7.9	45.0 ± 7.6
Sex		
Male/female	6/7	4/9
Type of multiple sclerosis		
Relapsing-remitting	6	7
Secondary progressive	7	6
Score on the Expanded Disability Status Scale		
Mean ± SD	4.9 ± 1.6	5.7 ± 1.6
Disease duration, y		
Mean ± SD	8.5 ± 5.6	9.2 ± 5.3
Screening T1-weighted MRI gadolinium-enhancing lesions (week 4)		
Scans with ≥1 enhancing lesions	9	12
No. of enhancing lesions		
Mean	2.0	1.7
Range	0–7	0–5

*One patient of this group withdrew from the study.

Safety and tolerability. Stings were administered three times per week with gradual increment of one additional sting at each session. The maximum of 20 bee stings per session was achieved by the end of week 6 in 23 patients, and because of extreme swelling of the upper legs by the end of week 9 in two patients. In one very slim female patient (40 kg body weight) the number of stings had to be limited to 15 per session. The most common side effect was local tenderness, swelling, and redness. Four patients had local itching, which was treated by menthol powder. Five patients had flulike symptoms the day after the bee stings, which lasted for less than 24 hours. These symptoms disappeared within 3 weeks. No anaphylactic reactions of other serious adverse events were recorded.

Primary outcome. There was no significant difference in the cumulative number of new gadolinium-enhancing lesions between the bee sting treatment period and the period with no treatment (table 2).

Secondary MRI outcomes. There was no difference in the total volume of enhancing lesions between the bee sting treatment period (2092 ± 2484/mm^3) and the no treatment period (2768 ± 5177/mm^3; $p = 0.22$). In the group of patients who started with bee sting therapy, the total lesion volume on T2*-weighted MRI increased from 26.70 ± 23.08 cm^3 at baseline to 27.26 ± 24.26 cm^3 at the end of the treatment period and to 28.61 ± 24.65 cm^3 at the end of the study; in the group of patients who started with no treatment, it increased from 20.76 ± 15,80 cm^3 at baseline to 21.27 ± 17.70 cm^3 at the end of the first crossover period and to 21.95 ± 17.29 cm^3 the end of the bee sting treatment period.

Clinical outcomes. Table 3 summarizes the data on relapses. No significant differences between the treatment and no treatment periods were found for the EDSS, MSFC, GNDS, AFQ and FIS (see table E-1 on the *Neurology* Web site at www.neurology.org), and the SF-36 (see table E-2).

Discussion. In patients with relapsing-remitting and relapsing secondary progressive MS, we found that bee sting therapy had no significant effect on

Table 2 *Findings on gadolinium-enhanced T1-weighted MRI scans of the brain*

Finding	Bee sting therapy first, then off treatment, n = 12	No treatment first, then bee sting therapy, n = 13	Overall, n = 25 (p value)
Mean no. ± SD of new enhancing lesions/patient			
Bee sting period	11.3 ± 15.7	8.8 ± 11.2	8.8 ± 11.2
No treatment period	18.5 ± 28.9	7.1 ± 6.7	12.6 ± 21.6 (0.17)
New enhancing lesions, no. of patients			
Bee sting period			
No lesions	1	0	1
1–10 lesions	8	9	17
>10 lesions	3	4	7
No treatment period			
No lesions	2	0	2
1–10 lesions	5	8	13
>10 lesions	5	5	10
Scans showing activity, %			
Bee sting period	56	69	63
No treatment period	67	67	67 (0.22)
Mean no. ± SD of new enhancing lesions/patient on the past two scans			
Bee sting period	7.5 ± 12.4	5.9 ± 8.4	6.8 ± 10.1
No treatment period	13.5 ± 20.6	4.4 ± 3.7	8.3 ± 15.0 (0.43)
No. of patients with enhancing lesions on the past two scans			
Bee sting period	8	9	
No treatment period	8	10	

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Table 3 *Relapses*

Finding	Bee sting therapy first, then off treatment, n = 12	No treatment first, then bee sting therapy, n = 13	Overall, n = 25 (p value)
No. of relapses			
Bee sting period	3	7	10*
No treatment period	8	6	14† (0.39)
No. of relapses during the past 3 mo of the			
Bee sting period	1	5	6
No treatment period	3	1	4 (0.72)
No. of patients who remained relapse free			
Bee sting period	9	8	17
No treatment period	5	8	13 (0.38)

* Two relapses.
† Five relapses were treated with corticosteroids.

disease activity as measured using gadolinium-enhanced MRI of the brain. Our study is limited by its small sample. However, given the high sensitivity for detecting pathologic activity in relapsing MS, serial T1-weighted gadolinium-enhanced MRI has been shown to be a reliable tool for short-term exploratory trials of new interventions.[17] The study was powered to detect a more than 50% reduction in the cumulative number of new active lesions on MRI, which is considered clinically relevant.[17] A reduction of 50 to 80% in new MRI activity has been reported with the beta-interferons,[20,21] and a reduction of approximately 90% was seen with natalizumab.[22] Bee sting therapy did not stop the progression of the total lesion load on T2*-weighted MRI scans. We found no effect of bee sting therapy on relapses, disability, fatigue, or health-related quality of life.

Our aim was to evaluate bee sting therapy as it is commonly being practiced by apitherapists. An alternative method of administering bee venom is to collect the venom in sterilized vials and inject it under the skin, without or with a local anesthetic. This approach would allow a double-blind study design. However, we opted for bee sting therapy because bee venom that has been exposed to air is thought to have lost some of its potency. Special precautions were taken to avoid anaphylactic reactions, which did not occur. In general, bee sting therapy was well tolerated.

Preclinical studies with bee venom are scarce. A small number of studies conducted on animal models of arthritis suggest that bee venom may have some ability to lessen the pain and inflammation.[23-25] However, we are unaware of any studies that have investigated the effects of bee venom in experimental allergic encephalomyelitis, which serves as an animal model of the inflammatory component of MS. It is unknown whether the anti-inflammatory substances of bee venom are able to modulate the immunopathogenic pathways involved in lesion formation in MS.

Patients with MS should be advised to refrain from bee venom therapy unless better evidence to justify its use becomes available.

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References

1. Pucci E, Cartechini E, Taus C, Giuliani G. Why physicians need to look more closely at the use of complementary and alternative medicine by multiple sclerosis patients. Eur J Neurol 2004;11:263–267.
2. Marrie RA, Hadjimichael O, Vollmer T. Predictors of alternative medicine use by multiple sclerosis patients. Mult Scler 2003;9:461–466.
3. Somerfield SD, Stach JL, Mraz C, Gervais F, Skamene E. Bee venom melittin blocks neutrophil O2- production. Inflammation 1986;10:175–182.
4. Banks BE, Dempsey CE, Vernon CA, Warner JA, Yamey J. Anti-inflammatory activity of bee venom peptide 401 (mast cell degranulating peptide) and compound 48/80 results from mast cell degranulation in vivo. Br J Pharmacol 1990;99:350–354.
5. Maylie J, Bond CT, Herson PS, Lee WS, Adelman JP. Small conductance Ca2+-activated K+ channels and calmodulin. J Physiol 2004;554:255–261.
6. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231.
7. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127.
8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
9. Dubois AE. Mastocytosis and hymenoptera allergy. Curr Opin Allergy Clin Immunol 2004;4:291–295.
10. Grimaud J, Lai M, Thorpe J, et al. Quantification of MRI lesion load in multiple sclerosis: a comparison of three computer-assisted techniques. Magn Reson Imaging 1996;14:495–505.
11. Cohen JA, Cutter GR, Fischer JS, et al. Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. Arch Neurol 2001;58:961–967.
12. Fischer JS, Jack AJ, Knicker JE, Rudick RA, Cutter G. Administration and scoring manual for the Multiple Sclerosis Functional Composite Measure (MSFC). Canada: Demos, 1999.
13. Rossier P, Wade DT. The Guy's Neurological Disability Scale in patients with multiple sclerosis: a clinical evaluation of its reliability and validity. Clin Rehabil 2002;16:75–95.

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14. Alberts M, Smets EM, Vercoulen JH, Garssen B, Bleijenberg G. ['Abbreviated fatigue questionnaire': a practical tool in the classification of fatigue]. Ned Tijdschr Geneeskd 1997;141:1526–1530.
15. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res 2004;56: 157–170.
16. Ware JE Jr. SF-36 health survey update. Spine 2000;25:3130–3139.
17. Miller DH, Albert PS, Barkhof F, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. US National MS Society Task Force. Ann Neurol 1996;39:6–16.
18. Silver NC, Good CD, Sormani MP, et al. A modified protocol to improve the detection of enhancing brain and spinal cord lesions in multiple sclerosis. J Neurol 2001;248:215–224.
19. Sormani MP, Miller DH, Comi G, et al. Clinical trials of multiple sclerosis monitored with enhanced MRI: new sample size calculations based on large data sets. J Neurol Neurosurg Psychiatry 2001;70:494–499.
20. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1995;45:1277–1285.
21. Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. Ann Neurol 1999;46:197–206.
22. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003;348:15–23.
23. Park HJ, Lee SH, Son DJ, et al. Antiarthritic effect of bee venom: inhibition of inflammation mediator generation by suppression of NF-kappaB through interaction with the p50 subunit. Arthritis Rheum 2004;50:3504–3515.
24. Lee JH, Kwon YB, Han HJ, et al. Bee venom pretreatment has both an antinociceptive and anti-inflammatory effect on carrageenan-induced inflammation. J Vet Med Sci 2001;63:251–259.
25. Lee JD, Kim SY, Kim TW, et al. Anti-inflammatory effect of bee venom on type II collagen-induced arthritis. Am J Chin Med 2004;32:361–367.

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