ORIGINAL RESEARCH

Treatment of Imported Fire Ant Stings With Mitigator Sting and Bite Treatment—A Randomized Control Study

David C. Hile, MD; Troy P. Coon, MD; Carl G. Skinner, MD; Lisa M. Hile, MD; Phillip Levy, MD; Manish M. Patel, MD; Michael A. Miller, MD

From Darnall Army Community Hospital, Fort Hood, TX (Drs Hile, Coon, Skinner, Levy, Hile, and Miller); Wayne State University–Detroit Receiving Hospital, Detroit, MI (Dr Levy); and Emory University, Atlanta, GA (Dr Patel).

Objective.—To evaluate the efficacy of the commercially available product Mitigator Sting and Bite Treatment in reducing the pain after imported fire ant stings.

Methods.—Twenty-four volunteer subjects were exposed to imported fire ant stings on both forearms. The subjects received Mitigator paste on 1 arm and calamine lotion on the opposite arm, in a blinded manner, from 90 seconds to 10 minutes after exposure. Subjects recorded pain on a 100-mm visual analog scale 60 seconds, 20 minutes, and 3 days after exposure. A 2-tailed paired *t* test was used to compare the difference in reduction of pain over time between the Mitigator-treated arms and the calamine-treated arms.

Results.—At 60 seconds, the mean visual analog scale pain score was 23.9 mm for the Mitigator group and 24.5 mm for the calamine group. At 20 minutes, the mean score was 7.6 mm ($\Delta = 16.3$) for the Mitigator group and 12.7 mm ($\Delta = 11.8$) for the calamine group. At 3 days, the mean score was 2.4 mm ($\Delta = 21.5$) for the Mitigator group and 2.9 mm ($\Delta = 21.6$) for the calamine group. There was no significant difference between groups for change in visual analog scale pain score at 60 seconds, 20 minutes ($P = .256$), or 3 days ($P = .64$).

Conclusions.—There was no significant difference in pain relief between calamine and Mitigator for imported fire ant stings.

Key words: imported fire ant, Hymenoptera, calamine lotion, insect bites and stings, therapeutic techniques and equipment, pain management, analgesia, Mitigator

Introduction

Imported fire ants (IFAs) are widely distributed across the south-central and southeastern United States, having been introduced from their native habitat in sub-Ama-zonian South America many decades ago. By far, the most common and widely distributed species is *Solenopsis invicta*, the red IFA. In recent years, red IFAs have also been discovered in New Mexico, in California, and on many Caribbean islands, as well as in Australia and New Zealand.¹

It is estimated that IFAs sting more than 1 million people in the United States annually, and tens of thousands of people will seek medical treatment for allergic and infectious complications related to these stings.² The severity of the stings can range from mild, local pustule formation to rare cases of anaphylaxis in predisposed individuals.^{3,4} Development of a local inflammatory response is typical and may result in temporary debilitation. In the wilderness, allergic or infectious complications may create a potentially life-threatening situation.

Efforts to diminish the duration and severity of symptoms once a person has been stung have not yielded positive results.^{5–7} Mitigator Sting and Bite Treatment (American Natural Technology Sciences, Rogers, AR) is a recently developed paste that targets the local inflammatory reaction associated with IFA stings. Mitigator is hypothesized to work by rendering the IFA venom ineffective, possibly by protein denaturation. Although anecdotal evidence of successful IFA treatment with Mit-

This abstract was presented at the annual conference of the Society for Academic Emergency Medicine, May 22 to 25, 2005, in New York, NY.

There was no funding in the production of the above manuscript. Mitigator product was provided courtesy of Mr Pat Kennedy of www.mitigator.net. We are not aware of any conflicts of interest.

Corresponding author: David Hile, MD, 2014 Lakefront Dr, Harker Heights, TX 76548 (e-mail: hile.16@yahoo.com).

igator exists, no randomized trials have been conducted. This study was therefore designed to investigate the clinical benefit of Mitigator through comparison with a common standard therapy.

Methods

This study was designed as a randomized, single-blind comparison trial of IFA sting treatment with Mitigator vs calamine lotion purchased from a Walgreens store. Mitigator is considered safe and nontoxic when applied topically. The main ingredients are water, walnut shells, emulsifying wax NF, pentaerythrityl tetracaprylate, isopropyl palmitate, cetearyl alcohol, polysorbate 60, sodium bicarbonate, papain, alcohol denatured, sodium hydroxide, methylparaben, propylparaben, and phenoxyethanol. At the time of this writing, Mitigator costs approximately \$6 for 1 ounce of scrub in comparison with \$2.79 for 6 ounces of calamine lotion. Institutional review board approval was obtained before study initiation, and written informed consent was obtained from all subjects.

Volunteer subjects were recruited by using publicly displayed bulletins. Individuals who expressed interest in the study were gathered at a single-day event. After hearing an explanation of the intent and design of the trial, those who were willing to participate were given a health-screening questionnaire. All female subjects were required to take a urine pregnancy test before participation. Subjects who met the following inclusion criteria were consented and enrolled: age 18 to 50 years with prior exposure to IFA stings, absence of a serious medical condition, absence of previous IFA stings or allergic reactions to insect bites or stings, absence of asthma or other reactive airway diseases, and absence of a known allergy to walnuts. In addition, those willing to participate had to ensure ability to attend a follow-up session 3 days later. Subjects who were pregnant or were regularly using oral corticosteroids, anti-inflammatory agents, or antihistamines were excluded.

Twenty-four enrolled subjects (7 [28%] women and 17 [68%] men) were exposed to IFA stings on a small shaved area of both forearms with a small cup containing 10 live IFAs (Figure). Sting exposure was for 10 seconds, based on a rough estimation of time for a typical IFA encounter. After exposure, the subjects were allowed to remove the ants, as would be standard procedure for a reasonable person. At 1 minute, all subjects were given cards labeled 'L' (left) and 'R' (right) to indicate body site. The cards contained a visual analog scale (VAS), 100 mm in length, with ends labeled "most pain" and "least pain." The subjects were asked to draw a line through the VAS indicating pain level before treat-

Sting technique.

ment on each card, with response for each arm considered independently. At 90 seconds after the stings, treatment with 0.5 ounces of Mitigator paste was applied to a randomly selected envenomation site (left or right forearm), and standard 0.5 ounces of calamine lotion was applied to the alternative arm. Subjects were blinded to treatment allocation. Treatment randomization (right or left) was predetermined by a coin flip. The paste or lotion was vigorously rubbed into the affected area for 2 to 3 minutes, left in place for 10 minutes, and then rinsed off as per the package instructions for Mitigator. At 20 minutes poststing, subjects were asked to repeat the pain rating on another pair of 100-mm VAS cards labeled "L" and "R" without seeing their initial responses. Subjects were then dismissed and allowed to treat the stings as desired for the next 72 hours. At 72 hours, the subjects returned for direct follow-up with study investigators and completed a third set of VAS cards.

Baseline VAS responses were recorded and statistical analysis was performed for the self-pairing study sample. A 2-tailed paired *t* test (parametric) and the Wilcoxon signed rank test (nonparametric) were used to compare differences in pain-score change from 60 seconds to 20 minutes and from 60 seconds to 3 days for grouped data of the Mitigator- and calamine-treated arms. By using 13 mm as the statistically significant difference in change of pain over time between groups, with a power of 80% and a 2-tailed alpha of 0.05, we determined that a minimum of 21 subjects would be needed. We also used a random-effects repeated-measures analysis of variance and found similar results as with the paired *t* test (results not reported).

Results

Mitigator was placed on the left arm in 8 subjects and on the right arm in 16 subjects, with calamine lotion

Table 1. Perceived pain (in millimeters) by individual subjects on the visual analog scale

Subject	Mitigator			Calamine		
	60 s	20 min	3 d	60 s	20 min	3 d
1	22	4	0	10	4	0
2	57	11	2	32	11	0
3	67	42	9	58	17	9
4	17	3	0	15	13	4
5	2	0	8	5	4	28
6	3	0	0	3	0	0
7	19	7	0	23	6	0
8	32	1	0	9	6	0
9	33	15	10	24	21	4
10	7	2	2	4	21	2
11	11	0	0	5	12	0
12	51	32	14	64	14	3
13	17	1	0	74	25	1
14	26	0	0	27	0	0
15	7	0	6	19	7	0
16	2	2	0	1	3	0
17	27	24	0	32	10	0
18	16	9	1	17	6	0
19	22	0	2	23	9	0
20	27	19	4	8	0	1
21	49	5	0	49	57	3
22	48	6	0	52	35	4
23	8	0	14	30	25	11
24	4	0	0	4	0	0

applied to the opposite respective arm in each individual. There were no systemic reactions to IFA stings or adverse reactions to treatment. Within-group baseline VAS scores (Table 1) were generally similar, with the exception of subject No. 13. There were no significant between-group differences in mean VAS scores at baseline, 60 seconds, or 3 days (Table 2). Mean change in VAS scores over time was statistically equivalent between groups (Table 3). Only 3 of the subjects described the use of any at-home therapy between day 1 and their follow-up visit: 2 subjects used oral diphenhydramine and 1 subject used oral aspirin and topical 1% hydro-

cortisone cream on both arms. Subject No. 9 sought medical care for her IFA stings, which had resulted in bilateral arm hives when she went to work at a local hospital 1 hour after her participation. She was treated with diphenhydramine orally and a 5-day prescription for prednisone. She had no complications at her 3-day follow-up visit.

Discussion

Although fewer than 20% of those who seek medical attention for IFA envenomation (1% of all who receive IFA stings) will require an intervention such as treatment of local infection or systemic reaction,^{8,9} identification of effective treatment for IFA stings is important. Venom from IFAs is composed of a mixture of allergens and alkaloids, which shares some similarities to other Hymenoptera species.^{3,10,11} The humoral responses invoked by the envenomation include neurogenic inflammation and cytokine cascade initiation as well as the generation of humoral antibodies.^{11,12} Adverse local reactions may occur as a result, and there have been several case reports of IgE-mediated anaphylaxis.^{4,10} Immunotherapy

Table 2. Mean perceived pain (in millimeters) by each subject as recorded on the visual analog scale

Time	Mean pain		Difference (95% CI)	P value
	Calamine	Mitigator		
60 s	24.5	23.9	0.583 (−6.22, 7.39)	.861
20 min	12.8	7.63	5.13 (−1.94, 12.2)	.147
3 d	2.92	2.42	0.500 (−1.88, 2.88)	.668

Table 3. Mitigator vs calamine lotion mean decrease in pain (in millimeters) from the visual analog scale

Time	Mitigator	Calamine	Difference (95% CI)	P value
60 s to 20 min	16.3	11.8	4.54 (−3.53, 12.6)	.256
20 min to 3 d	5.21	9.83	−4.625 (−11.4, 2.12)	.150
60 s to 3 d	21.5	21.6	−0.083 (−7.00, 6.83)	.640

has emerged as a potential therapy for people with severe allergic reactions, but no advances have been made regarding treatment of local pain and inflammation. Multiple cellular processes are involved in the pain response, and once initiated, pharmacotherapeutic intervention is difficult. Although prophylactic treatment may effectively block similar processes, as demonstrated in a recent trial involving *Chrysaora fuscescens* and *Chiropsalmus quadrumanus* (jellyfish) envenomations,¹³ this is not a practical approach for IFA stings, as exposure is rarely anticipated. Consequently, interventions directed at minimizing pain are needed.

Available data on the treatment of IFA envenomations are limited, and the manner of appropriate management is uncertain. We believe this study is the first to address the treatment of IFA stings through a randomized clinical trial. We chose to investigate a commercially available product (Mitigator) in an attempt to substantiate subjective reports of its efficacy. However, we were unable to demonstrate any statistical difference in relief of pain when Mitigator was compared with a standardized regimen with calamine treatment, and the situation remains unresolved.

There may be multiple etiologies for the lack of statistically significant differences in this study. Although our study population was small, the number needed to show a clinical difference on our VAS was sufficient. In a study of this type, one would expect a curvilinear decrease in pain, with the greatest difference in treatment effect initially. Although there was a “trend” toward a decrease in the Mitigator-treated arm at 20 minutes, the difference was not significant. We acknowledge that subject No. 13 in our study had a wide variability in pain at onset between the calamine- and Mitigator-treated arms. However, excluding this subject from the database and recalculating the data still failed to demonstrate a significant difference between the 2 treatments. Among the multiple possible reasons for this is the inability of the clinical setting to adequately reproduce the natural environment. As those who have been stung will recall, IFAs frequently “attack” in unison, and a person may easily receive 10 to 20 stings before the ants can be removed. Although approximately 10 ants were present in each container in this study, many subjects experi-

enced just 2 or 3 stings. Furthermore, it is likely that the ants expended their venom during the collection process and therefore may have had less venom available during the study than in the natural environment. This may have led to decreased initial pain in the study population, thus decreasing the apparent treatment effect. Because the initial pain described by the subjects was low, demonstration of therapeutic benefit from Mitigator, if it exists, may require more volunteers than this study enrolled. Future studies may benefit from attempts to increase initial pain levels either by increasing the total number of stings or by “resting” the IFAs for a number of days to ensure that high levels of venom are present in the study ants.

Conclusion

There was no demonstrable difference in immediate or delayed pain relief between Mitigator and calamine lotion therapy for IFA stings. These envenomations remain a source of potential morbidity, and further investigation into appropriate treatment is needed.

Acknowledgments

We thank the Brooke Army Medical Center Institutional Review Board for reviewing and approving this study. Mitigator Sting and Bite Treatment was provided upon request for this study by Mr Pat Kennedy and American Natural Technology Sciences, Rogers, AR; however, no financial relationship exists between the investigators and the manufacturer or distributors of Mitigator Sting and Bite Treatment.

References

1. Morrison LW, Porter SD, Daniels E, Korzukhin MD. Potential global range expansion of the invasive fire ant, *Solenopsis invicta*. *Biol Invasions*. 2004;6:183–191.
2. Caldwell ST, Schuman SH, Simpson WM Jr. Fire ants: a continuing community health threat in South Carolina. *J S C Med Assoc*. 1999;95:231–235.
3. Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol*. 1992;90:210–215.

4. Caplan EL, Ford JL, Young PF, Owenby DR. Fire ants represent an important risk for anaphylaxis among residents of an endemic region. *J Allergy Clin Immunol*. 2003;111:1274–1277.
5. Ross EV, Badame AJ, Dale SE. Meat tenderizer in the acute treatment of imported fire ant stings. *J Am Acad Dermatol*. 1987;16:1189–1192.
6. Bruce S, Tschien EH, Smith EB. Topical aluminum sulfate for fire ant stings. *Int J Dermatol*. 1984;23:211.
7. Parrino J, Kandawalla NM, Lockey RF. Treatment of local skin response to imported fire ant sting. *South Med J*. 1981;74:1361–1364.
8. Yeager W. Frequency of fire ant stinging in Lowndes County, Georgia. *J Med Assoc Ga*. 1978;67:101–102.
9. Adams CT, Lofgren CS. Incidence of stings or bites of the red imported fire ant (Hymenoptera: Formicidae) and other arthropods among patients at Ft. Stewart, Georgia, USA. *J Med Entomol*. 1982;19:366–370.
10. Stafford CT. Hypersensitivity to fire and venom. *Ann Allergy Asthma Immunol*. 1996;77:87–97.
11. Minton SA, Bechtel HB, Erickson TB. North American arthropod envenomation and parasitism. In: Auerbach PS, ed. *Wilderness Medicine*. 4th ed. St Louis, Mo: Mosby; 2001:863–887.
12. Freeman TM. Hymenoptera hypersensitivity in an imported fire ant endemic area. *Ann Allergy Asthma Immunol*. 1997;78:369–372.
13. Kimball AB, Arambula KZ, Stauffer AR, et al. Efficacy of a jellyfish sting inhibitor in preventing jellyfish stings in normal volunteers. *Wilderness Environ Med*. 2004;15:102–108.