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Safety and efficacy of ant rush immunotherapy in children

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Abstract

Background: The Rush Immunotherapy (RIT) protocol is a valid alternative in order to reach the maintenance phase early. However, there are scarce studies in the literature that have evaluated the safety and the efficacy of an ant RIT process in children.

Objective: To evaluate the safety and the efficacy of an ant RIT protocol and to identify the risk factors for systemic reactions (SRs) during an RIT procedure in children.

Method: A retrospective review was conducted for those children who were receiving an ant RIT procedure. The 3-day RIT protocol consisted of hourly subcutaneous injections in order to achieve a 0.5 ml maintenance dose of a 1:100 weight/volume (wt/vol) of the *Solenopsis invicta* whole body extract. The safety for an RIT procedure was monitored by using the World Allergy Organization Subcutaneous Immunology Systemic Reaction Grading System. The efficacy was assessed by the reactions after a field ant re-sting.

Results: A total of 20 children who were receiving an ant RIT therapy were reviewed. The mean age was 9.5±3.07 years. There were 6 systemic reactions (SRs) from 324 injections during the RIT procedure (1.85%). All of the systemic reactions were Grade 1-2. There were no associations of SRs regarding age, gender, an atopic history, or the levels of immunoglobulin E (IgE) sensitization to the ants. Among the 14 patients who experienced a field ant re-sting, 4 (28.5%) patients developed Grade 3 SRs. These Grade 3 reactions were resolved after an increase of the maintenance dose to 0.5 ml of a 1:50 wt/vol. There was a significant difference in the mean age of those children who had ant re-sting systemic reactions and those who had no reactions (6.75±0.95 year vs. 10.8±3.29, p=0.036).

Conclusions: Rush immunotherapy with ant in children is safe and it has a low occurrence of severe systemic reactions. It is an alternative treatment for those patients requiring a rapid protection.

Keywords: Ant, Rush Immunotherapy, Insect, Children, Hymenoptera

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Introduction

Insects in the class order of hymenoptera, such as bees, hornets, wasps, yellow jackets and ants, can cause severe insect sting allergic reactions in approximately 1% - 7% of the general population.[1] Ants are found globally, especially in tropical regions such as Thailand.[2] A recent practice parameter for stinging insect hypersensitivity has recommended subcutaneous immunotherapy with ant for all patients who developed a systemic reaction to ant stings with positive skin test responses or positive allergen specific serologic test results with ant whole body extract.[3] Subcutaneous immunotherapy is regarded to be the only effective treatment for insect sting systemic hypersensitivity.[3] The treatment is usually administered in 2 phases: the buildup stage and the maintenance stage. A subcutaneous rush immunotherapy (RIT) protocol during the buildup phase may be a valid alternative in order to reach the maintenance phase early, if the treatment is well tolerated, especially in adults.[4] A subcutaneous immunotherapy with an ant's whole body extract has been demonstrated to prevent systemic reactions (SRs) after subsequent stings.[3,5] However, there are scarce

studies in the literature regarding data on the safety of a subcutaneous ant rush immunotherapy in children. The current study was conducted in order to evaluate the safety and the efficacy of an ant RIT procedure and to identify the risk factors for systemic reactions (SRs) during an RIT buildup in children.

Methods

The study design was a retrospective chart review that included all pediatric patients who were hospitalized for rush immunotherapy with ant whole body extract at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, between January 1, 2005 and December 30, 2015. The study was reviewed and approved by the Human Rights and Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. All of the enrolled patients had histories of an anaphylaxis that was caused by ants, together with the evidence of an immunoglobulin E (IgE) sensitization to ants, either by a specific IgE or a skin test. The 3-day RIT protocol consisted of hourly subcutaneous injections in order to achieve a 0.5 ml maintenance dose of a 1:100 weight/volume (wt/vol) of ant (*Solenopsis invicta*) whole body extract (ALK-Abello, Port Washington, NY, USA) (**Table 1**). The safety of the RIT procedure was monitored and was assessed based upon the World Allergy Organization Subcutaneous Immunology Systemic Reaction Grading System.[6] All of the patients received an H1 antihistamine premedication before starting the RIT process. The efficacy was assessed by the reactions after a field ant re-sting. The children who developed systemic reactions during the rush immunotherapy procedure, before reaching the maintenance dose, received appropriate treatment and their injections were stopped. The injections were then continued weekly during the buildup phase in order to reach the maintenance dose. During the maintenance phase, the injections were given at a regimen of 4-week intervals for 18 months, followed by a 6-week interval for 18 months, and then at 8-week intervals thereafter.[3]

Skin Tests

Skin tests were performed with ant (*Solenopsis invicta*) whole body extract (ALK-Abello, Port Washington, NY, USA). A skin prick test was used as the first step (a dilution of 1:1,000 wt/vol). If the result of this test was negative, the testing proceeded with an intradermal method. This was administered by an injection of 0.02 ml of ant antigen into the dermis, starting with 1:1,000,000 wt/vol for the ant extract and then increased sequentially by 10 times the previous amount up to 1:1,000 wt/vol for the ant extract. The testing was stopped when the skin test was positive (the reaction wheal was at least 3 mm greater than the wheal that was produced by the control solution). If the maximal intradermal dose was reached without a positive response, the test result was considered to be negative.[7] Histamine dihydrochloride (1mg/ml) and a normal saline dilution were used as positive and negative controls, respectively.

Specific Immunoglobulin E (IgE) to the Solenopsis invicta Ants

The specific concentrations of Immunoglobulin E (IgE) to the *Solenopsis invicta* ants were measured by using the CAP -System (Thermo Fisher Scientific, Waltham, Massachusetts, United States). The lower detection limit is 0.35 kUA/L.

Statistical Analysis

All of the analyzes were performed when using SPSS Statistical Software Version 18.0 (SPSS Inc., Chicago, IL, USA). A descriptive analysis was used for the characterization of the study's population. The results were expressed as the mean ± SD (age), median (IgE sensitization to ants) or percentages (gender, atopic status, symptoms of previous systemic reactions and systemic reactions per injection). In order to compare between the different groups, the t-test, the Mann–Whitney U test, the chi-squared test or the Fisher's exact test were used, as appropriate. A p-value of < 0.05 was considered to be statistically significant.

Results

Between January 2005 and December 2015, 20 children aged 5 to 15 years underwent an induction of specific ant subcutaneous immunotherapy by using the rush regime in the inpatient unit of Ramathibodi Hospital, Bangkok, Thailand. Twenty ant allergic children received a 20 rush immunotherapy (RIT) course, resulting in 324 injections. The mean age was 9.5±3.07 years and 12 (60%) of the children were male. All of the children had experienced a systemic allergic reaction due to field ant stings before the initiation of the RIT course. The clinical symptoms of the systemic reactions to field ant stings are shown in **Table 2**. All of the patients reached the maintenance dose of 0.5 ml of a 1:100 wt/vol after the initiation of the RIT course.

We recorded 6 systemic reactions from 324 injections during the RIT course. One systemic reaction occurred from 94 injections during the build up period and 1 systemic

Table 1. Ant rush immunotherapy schedule

Concentration	Day 1	Concentration	Day 2	Concentration	Day 3
1:100,000 wt/vol	0.1 ml	1:1,000 wt/vol	0.1 ml	1:100 wt/vol	0.1 ml
	0.2 ml		0.2 ml		0.15 ml
	0.4 ml		0.3 ml		0.2 ml
1:10,000 wt/vol	0.1 ml		0.35 ml		0.3 ml
	0.3 ml		0.4 ml		0.4 ml
	0.5 ml		0.5 ml		0.5 ml

Table 2. Baseline characteristics

	N=20
Age : year, mean+sd	9.5±3.07
Gender: M/F	12/8
Atopic disease: N(%)	11(55)
Clinical manifestations of previous systemic reaction to ant sting: N(%)	
• Skin	20(100)
• respiratory	14(95)
• Cardiovascular	2(10)
• Gastrointestinal	3(15)
• Other	1(5)
Level of specific IgE to ant : kUA/L, median (IQR)	7.77 (3.20-10.98)
Level of positivity of skin test to ant: N(%)	
• Prick 1:100 wt/vol	3(15)
• ID 1:1,000,000 wt/vol	5(25)
• ID 1:100,000 wt/vol	6(30)
• ID 1:10,000 wt/vol	2(10)
• ID 1:1,000 wt/vol	4(20)

Table 3. Systemic adverse reaction per injection of ant immunotherapy

	Rush N=324	Build up N=94	Maintenance N=807
Systemic reaction: N(%)	6 (1.85)	1(1.06)	1(0.12)
• Grade 1	4 (1.23)	1(1.06)	1(0.12)
• Grade 2	2 (0.62)	0	0

Table 4. Comparison between children with systemic reaction and without systemic reaction during RIT

	Developed RIT systemic reaction N=6	No RIT systemic reaction N=14	P value
Age: year, mean+sd	10.67±1.97	9.0±3.37	0.27
Sex: M/F	3/3	9/5	0.64
Atopy: N(%)	4(66.7)	7(50)	0.64
Level of skin test positivity: N(%)			
• Prick test	0(0)	3(21.4)	0.52
• Intradermal	6(100)	11(78.6)	
IgE to ant: kUA/L, median(IQR)	10.8(3.61-13.65)	6.51(3.05-12.17)	0.5
Clinical manifestations during previous ant sting: N(%)			
• Skin	6(100)	14(100)	NA
• Respiratory	6(100)	13(96.5)	1
• Cardiovascular	1(16.7)	1(7.1)	0.52
• GI	2(33.3)	1(7.1)	0.2
Injection during RIT : shot, mean+sd	14+4.6	17.14+4.03	0.14
Systemic reaction during maintenance: N(%)	0(0)	1(7.1)	1

Table 5. Comparison between children with field sting systemic reaction and without systemic reaction

	Developed systemic reaction N=4	No systemic reaction N=10	P value
Age: year, mean+sd	6.75±0.95	10.8±3.29	0.036
Sex: M/F	1/3	3/7	1
Atopy: N(%)	3(75)	5(50)	0.58
Level of skin test positivity: N(%)			
• Prick test	0(0)	2(20)	1
• Intradermal	4(100)	8(80)	
IgE to ant before RIT: kUA/L, median(IQR)	6.51(3.31-7.96)	10.6(4.1-12.25)	0.3
IgE to ant post RIT: kUA/L, median(IQR)	1.83(0.9-8.36)	8.36(2.89-20)	0.22
Clinical manifestations during previous ant sting: N(%)			
• Skin	4(100)	10(100)	NA
• Respiratory	3(75)	10(100)	0.28
• Cardiovascular	0	0	NA
• GI	1(25)	1(10)	0.5
Systemic reaction during RIT: N(%)	0(0)	4(40)	0.251
Systemic reaction during maintenance :N(%)	0(0)	(0)	NA

reaction resulted from 807 injections during the maintenance period. The rate of systemic reactions per total injections was 1.85%. All of these systemic reactions were Grade1-2 (**Table 3**). The clinical manifestations during the systemic reactions were skin problems (66.7%), respiratory system issues (33.3%), gastrointestinal tract difficulties (33.3%) and cardiovascular complications (16.7%). Eighty three percent of the systemic reactions materialized during the injections at a concentration of the maintenance dilution.

When comparing between the children who experienced systemic reactions during the RIT procedures and those children without any systemic reactions, there were no significant differences in age, gender, their atopic history, their levels of IgE sensitization to the ant or their clinical symptoms during previous ant sting (**Table 4**).

Fourteen field ant re-stings occurred in 14 children and 4 children developed Grade 3 systemic reactions. These Grade 3 reactions were resolved after the maintenance dose was increased to 0.5 ml of a 1:50 wt/vol of ant whole body extract. There was a significant difference in the mean ages of the children who had ant re-sting systemic reactions and those who had no reactions (6.75±0.95 year vs. 10.8±3.29, p=0.036). However, there were no significant differences in gender, their atopic history, their levels of IgE sensitization, clinical symptoms of previous systemic reactions after an ant sting, or a history of previous systemic reactions during an RIT administration (**Table 5**).

Discussion

Severe systemic reactions to a hymenoptera (honey-bee, wasp and fire ant) sting are a life threatening event. The usual treatment for a sting's systemic reaction is an intramuscular administration of epinephrine.[3,8] A prevention for further systemic reactions include insect avoidance and subcutaneous immunotherapy.[3] Conventional subcutaneous immunotherapy requires 1-3 injections per week for 3-6 months during a build up phase in order to reach the maintenance phase.[4] Rush immunotherapy (RIT) is an accelerated immunotherapy buildup schedule involving an administration of incremental doses of allergen every 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved.[4] An RIT procedure has been shown to provide a symptomatic improvement shortly after reaching the therapeutic dose.[9] In the current study, a 3-day ant RIT treatment has been shown to be safe. The systemic reactions as a result of the RIT injection were only 1.85% and all of these systemic reactions were deemed to be Grade 1-2. These rates of a systemic reaction are similar to a previous report of a 3-day RIT protocol of flying hymenoptera (honey-bees and wasps) stings in adults which demonstrated 1.5% of systemic reactions due to an RIT injection.[10] Hirata et al. have reported that 2 systemic reactions (2.1%) occurred in 95 adults that were treated with a 7-day RIT procedure for flying hymenoptera (bees and wasps).[11]

In the current study, we found no associations with age, gender, and their levels of ant sensitization to the development of systemic reactions during the RIT process. This was in contrast to a report from Gorsa et al. who reported that women had more of a frequency to a systemic reaction during a 5-day RIT administration due to bee or wasp stings in adults.[12] Systemic reactions to conventional ant immunotherapy have been reported as 0.4% per injection and 9.1% per patients.[13] These systemic reactions have been shown to be associated with having a systemic reaction to skin testing.[13] However, there were no systemic reactions to skin testing in the current study. A greater number of enrolled children may be needed in order to explain the different findings of the risks for the development of a systemic reaction from an ant immunotherapy between adults and children.

A recent study of a 1-day fire ant RIT treatment in adults has demonstrated a rate of systemic reactions at 24.3% (9 of 37 patients) in non-premedicated patients and 9.5% (4 of 42 patients) in premedicated patients.[14] The systemic reactions in our 3-day ant RIT administration occurred in 6 of 20 children (30%) which was higher than previously reported cases in adults.[14] A case report of 3 children who underwent a 1-day fire ant RIT procedure with a *Solenopsis invicta* and *Solenopsis richteri* mix from Hollister-Stier laboratories showed that no systemic reactions occurred.[15] However, a different species of ants were used for the RIT procedure in the current study where *Solenopsis invicta* ants from ALK were used. In addition, we used a dosage of 0.5 ml of a 1:100 wt/vol ant extract as a target dose for the RIT procedure which was higher than what was used in other RIT protocols.[10,14,15] As a result, the difference in the rates of the systemic reactions may be explained by the different sources of allergen extracts and the differences in the rush protocols.

The recommendations for a maintenance dose of ant ranges from 0.5 mL of a 1:10 wt/vol vaccine/extract to 0.5 ml of a 1:200 wt/vol vaccine/extract with either *Solenopsis invicta* or a mixture of *Solenopsis invicta* and *Solenopsis richteri* extract.[3] We selected to use 0.5 ml of a 1:100 wt/vol of *Solenopsis invicta* since this dosage is recommended in current practice parameters[3] and *Solenopsis invicta* is the only commercially available ant extract in Thailand. All children who had histories of anaphylaxis from ant with evidence of ant sensitization in the current study were received RIT according to the recommendation of current practice parameter for stinging insect hypersensitivity.[3] We have demonstrated that the efficacy of the ant immunotherapy at a dosage of 0.5 ml of a 1:100 wt/vol was effective in preventing systemic reactions in only 60% of children after a field ant re-sting. However, all of the 4 children who had a systemic reaction upon an ant re-sting had no further systemic reactions after the maintenance dose was increased to 0.5 ml of a 1:50 wt/vol. We have found that those children who developed field ant re-sting systemic reactions had a significantly lower age. This may suggest that children at a younger age, at the onset of an ant systemic reaction, may require a higher maintenance dose. Interestingly, all of the children who experienced a field ant re-sting in the current study had no systemic reactions during the RIT protocol. This may imply that systemic reactions during an RIT procedure did not predict a further re-sting reaction.

We are of the opinion that our study is the first study reporting on the safety and the efficacy of ant rush immunotherapy in children. The limitation of our study is that the commercially available ant antigen in Thailand is *Solenopsis invicta* which is not the common ant species in Thailand. The common invasive ant species that have an important role on clinical ant hypersensitivity in Thailand are *Solenopsis geminata, Tetraponera rufonigra,* and *Odontoponera denticulata*.[2] There is evidence of similar main toxic chemicals from *Solenopsis geminata* and *Solenopsis invicta*[16] and there is a highly cross-reactivity among the *Solenopsis* species.[2] The current study has supported the evidence of a cross reactivity between *Solenopsis geminate* and *Solenopsis invicta* and their impact on clinical use. However, there is limited data on the protein allergens of *Tetraponera rufonigra* and *Odontoponera denticulata*.[2] Further studies on these ants and the respective major allergens, together with their cross reactivity with other ants, are needed for the proper ant allergen extract immunotherapy in Thailand.

In conclusion, we have demonstrated that a 3-day ant RIT procedure was safe, tolerable and effective in children. It is an alternative treatment for those patients requiring a rapid protection.

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