REVIEW

The Lights and the Shadows of Controlled Sting Challenge With Hymenoptera

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J Investig Allergol Clin Immunol 2022; Vol. 32(5): 357-366
doi: 10.18176/jiaci.0838

Abstract

Hymenoptera venom immunotherapy (VIT) is effective for protecting individuals with systemic allergic reactions caused by Hymenoptera stings. The need for a tool that shows the degree of protection afforded by VIT and the lack of useful biomarkers have made the sting challenge test (SCT) the gold standard for this disorder, although its use has both lights and shadows. SCT with Hymenoptera involves causing a real sting in a patient diagnosed with allergy to the venom of the stinging insect and who is undergoing treatment with specific immunotherapy. In Spain, SCT is included in the list of services offered by some hospitals and forms part of their daily clinical practice. This review aims to analyze the strengths and weaknesses of this test and to describe the standardized procedure and necessary resources, based on the experience of a group of Spanish experts and a review of the literature.

Key words: Sting challenge test. Hymenoptera venom allergy. Venom immunotherapy.

Resumen

La inmunoterapia con veneno de himenóptero (ITV) es un tratamiento que se ha mostrado eficaz en la protección de sujetos con reacciones alérgicas sistémicas por picaduras de himenópteros. La necesidad de una herramienta que demuestre el grado de protección proporcionada por la ITV, y la ausencia de biomarcadores útiles, convierte a la Prueba de Provocación con Repicadura (PPR) en el *gold standard* en esta patología, con sus luces y sus sombras. La PPR con himenópteros es una prueba que consiste en provocar una picadura real, a un paciente que ha sido diagnosticado de alergia al veneno del insecto picador y habitualmente está en tratamiento con inmunoterapia específica. En España, la PPR se incluye en la cartera de servicios de algunos hospitales, formando parte de su práctica clínica habitual. Esta revisión trata de analizar las fortalezas y debilidades de esta prueba, integrando el procedimiento estandarizado y recursos necesarios, basándose en la experiencia de un grupo de expertos españoles y en la revisión de la literatura.

Palabras clave: Prueba de provocación con repicadura. Alergia a veneno de himenóptero. Inmunoterapia con veneno.

Introduction

IgE-mediated allergy to Hymenoptera venom manifests as a generalized allergic reaction of variable severity that is potentially life-threatening and occurs following an insect sting [1]. Hymenoptera venom immunotherapy (VIT) is effective in protecting allergic individuals from stings in 77%-85% of cases of bee venom allergy and in 91%-96% of cases of vespid venom allergy [2], reducing both morbidity and mortality and improving the patient's quality of life [3]. During VIT, patients tolerate doses of venom greater than that contained in the venom sac of the insect; however, there is no guarantee that an individual patient will tolerate a live insect sting [4]. This, together with the uncertainty that the absence of spontaneous stings generates in some patients, highlights the need for a tool to demonstrate the degree of protection provided by VIT.

The sting challenge test (SCT) with Hymenoptera involves causing a real sting in a patient who has been diagnosed with allergy to the venom [4,5]. It is currently only recommended in patients undergoing VIT.

SCT has been used to assess the efficacy of immunotherapy since it was first applied in the 1950s by Fackler and Loveless [6]. In 1978, it was used to compare VIT with purified venom against body extract [7]. Since then, it has been used in studies that monitor the time course of protection in patients treated with VIT, including follow-up after discontinuation of treatment [8,9], and as the reference technique for the phenotyping of patients allergic to bee venom [10]. Studies of patients not treated with VIT but undergoing SCT have also been published; mention must be made of a series of 138 patients in whom the risk factors for reactions following stings were analyzed [11]. The value of SCT as a diagnostic tool has also been studied [12], although the ethical debate surrounding this practice is a limiting factor [1,13] (see below). For this reason, SCT is not currently indicated for diagnosis.

In Spain, the diagnosis and etiologic and preventive treatment of allergic reactions due to Hymenoptera stings are the responsibility of the allergologist [14,15]. SCT is included in the list of services offered by some hospitals, especially those with more experience in the management of allergic reactions to stings, and thus forms part of their daily clinical practice [16].

The aims of this paper are to review the strengths and weaknesses of SCT in Hymenoptera venom allergy and to establish the standardization of the technique from the point of view of safety, availability, and applicability in daily clinical practice based on the experience of a group of Spanish experts and a review of the literature.

2. Indications and Contraindications for SCT

The test is currently used in patients undergoing VIT who have reached the maintenance phase. It is performed several years after initiation of VIT to monitor the efficacy of therapy [17]. Given the lack of in vitro biomarkers capable of predicting the effectiveness of VIT, SCT is considered the gold standard for evaluating the risk of systemic reactions during and after specific immunotherapy [1]. The indications and the contraindications for the SCT are listed in Table 1.

Table 1. Indications and Contraindications for the Sting Challenge Test

Indications
– Patients allergic to Hymenoptera venom in different phases of active treatment with VIT, with at least 2 months of good tolerance to treatment.
– To assess the decision to suspend this treatment (if the patient has had no spontaneous stings).
– In the case of a reduction in quality of life as a result of uncertainty caused by the risk of a reaction due to a spontaneous sting.
– Patients who have risk factors for the failure of treatment (those allergic to bee venom and those with systemic mastocytosis).
– To verify that beekeepers and other high-exposure professionals are protected before being re-exposed.
– Patients who have discontinued VIT to evaluate the level of protection afforded by the years of treatment
Contraindications
– Patients not receiving VIT.
– Patients treated with VIT for whom the following apply:
– Previous systemic reaction following a spontaneous sting.
– Current systemic reactions with VIT
– Severe or uncontrolled cardiorespiratory disease (FEV_1<70%)
– Pregnancy
– Acute inflammatory disease.

Abbreviation: VIT, venom immunotherapy.

3. Procedure and Necessary Resources

3.1. Obtaining and Handling the Insects

The Hymenoptera responsible for the immense majority of stings in Spain are the honey bee (*Apis mellifera*) and the wasps *Polistes dominula*, *Vespula germanica* [18], and *Vespula vulgaris*. More rarely, stings are caused by *Vespa crabro*, *Dolichovespula* species, and *Bombus* species (bumblebee). The recent arrival of other species, such as *Vespa velutina*, in the north of Spain poses a diagnostic and therapeutic challenge to which allergologists must respond [19].

The SCT is performed with the species of insect responsible for the clinical reaction, preferably at the time of year when the insect responsible for the sting is available. The species most frequently used for SCT are *A mellifera* and vespids (*V germanica*, *P dominula*). Appropriate entomological identification is essential.

One Spanish company [20] currently supplies exemplars of *A mellifera* and vespids (*V germanica*, *P dominula*), thus ensuring correct identification of genus and species. This

company is run by an entomologist who captures, identifies, and supplies Hymenoptera throughout Spain. Currently, it does not make international shipments.

The bees should be obtained from hives and not the open countryside. Specimens used for SCT should be workers more than 2 days old. Beekeepers may help to obtain live honeybees, or they could be supplied by the company mentioned above. The bees must be kept in an appropriate plastic container with a small opening through which they can breathe and with feeding material (water and honey from the same hive or a sucrose concentrate), which will allow them to survive for a few days if the test is not to be performed the same day.

The identification of wasps is a much more complex matter, particularly in regions where more than 1 species of allergenic vespid coexists. The insect should be identified by an expert (entomologist, biologist, or trained allergologist). No notable differences have been observed between SCT with insects obtained at the end of spring or in the middle of autumn [12].

It is important to have a sufficient number of specimens of vespids in an appropriate plastic container with a small hole so they can breathe. A part of the nest should be included as a food source to increase survival (this is possible only with aerial nests such as those of *P dominula*, because extraction of subterranean nests it is not practical). The container must be kept in a cool and dark room, thus enabling the insects to survive for up to 4 weeks. The specimens used in the test should be warmed up gradually and allowed to become active [21].

The insects must be handled in a well-ventilated room and made lethargic by the application of CO_2 (used in the hospital for laparoscopy) applied through the ventilation holes in the containers for a few seconds until the insects remain immobile. Their wings and hind legs are removed to avoid accidents inside the hospital. This same effect can be obtained by exposing the insects to cold. The insects are then placed in individual ventilated plastic tubes until their use in the SCT.

3.2. Clinical Setting and Patient Preparation

SCT requires an appropriate healthcare setting and controlled conditions. Although the technique is safe, the need to control risks requires SCT to be performed in hospitals with staff trained both in the technique and in the management of severe allergic reactions [22,23].

Table 2. Preparation of the Room, Material, and Staff

The test will be performed in the allergy day hospital, with full availability of cardiopulmonary resuscitation equipment.
In patients at risk of comorbidities, the room must have direct access to the intensive care unit/resuscitation room/emergency department.
Direct supervision by an allergologist and nursing staff trained in emergency situations.
Material: – Insects. – Transparent plastic containers with lids. – CO2 cylinder with reducing valve and application pistol. – Standard dissection tweezers. – Entomologic scissors.
The test will last approximately 120 min.

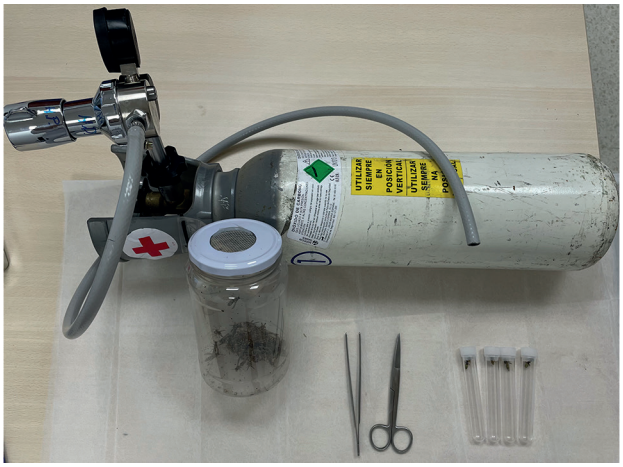

Figure 1. Material necessary for performing the sting challenge test.

The room for the test, the material (Figure 1), and the necessary staff are listed in Table 2.

Bearing in mind the indications and contraindications for this test, the patients selected should be informed in detail of the possible risks and consequences and should sign the corresponding specific informed consent form.

Patients should undergo an initial assessment and examination, and it is necessary to suspend for an appropriate length of time those drugs that might inhibit the reaction, such as corticosteroids, antihistamines, and anti-IgE antibodies. Recent studies have shown that treatment with angiotensin-converting enzyme inhibitors and ß-blockers does not increase the severity of reactions following spontaneous or controlled stings [24].

We recommend that patients do not smoke or drink alcohol or consume fats for 6 hours prior to the test and for 1 hour afterwards.

Chronic diseases should be controlled. Patients should not have been stung recently and must be able to tolerate VIT.

Heart rate, blood pressure, and oxygen saturation should be monitored. In the case of patients with asthma, PEF and FEV_1 should be measured before the test. In all cases, a peripheral intravenous catheter should be placed in the opposite arm to that being used for the SCT.

After the peripheral line has been set up, a sample of peripheral blood should be taken for the determination of baseline levels of mediators such as tryptase.

3.3. The SCT

When the insect has recovered its baseline level of activity, it should be held by the thorax with tweezers and placed on the volar forearm, with slight pressure on the abdomen against the skin so as to force the sting.

In the case of bees, the stinger remains embedded in the skin owing to the lateral barbs, which give it the shape of a harpoon, and the stinger attached to the venom sac continues to inject venom. The insect should be left in place for 30 seconds, and the body and the venom sac of the bee should then be

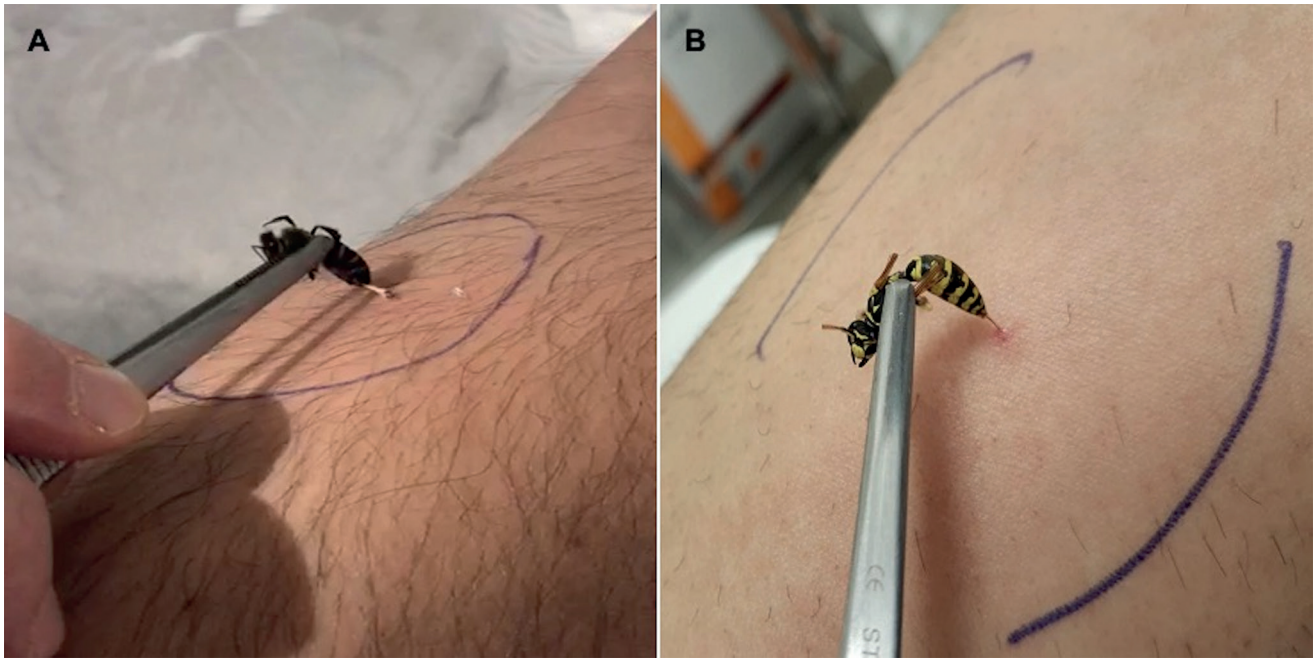

Figure 2. Sting challenge test with *Apis mellifera* (A) and *Polistes dominula* (B).

removed. Bees only sting once and die from eventration as the stinger is left embedded (Figure 2A).

In the case of wasps (Figure 2B), when the patient notices the sting, the insect should be forcibly held against the forearm for 30 seconds so that sufficient venom is injected, since the wasp does not usually leave the stinger embedded, although in some cases with *Vespula* species it does [25]. Thus, the wasps can normally make several stings in the forearm by moving the abdomen.

The clinical status of the patient should be monitored for 2 hours, at 15, 30, 60, and 120 minutes after the sting. If symptoms appear, vital signs should also be taken at that point.

3.3.1. Outcome of the SCT

The development of an erythematous reaction in the area of the sting after a few minutes is the only objective indicator of the actual inoculation of the venom; if this reaction does not occur, we should interpret this as the venom not having been injected, and the tests should not be considered valid [22]. The papule can be measured quantitatively after 15 minutes. The appearance of a local or extensive reaction is usual after a re-sting. A positive response consists of the appearance of systemic symptoms typical of an IgE-mediated skin and/or anaphylactic reaction, in general reproducing those experienced by the patient in previous reactions. The symptoms should be graded following the classification for systemic reactions, serum tryptase levels should be determined during the acute episode, and the patient should be reassessed to determine the need for changes in the protocol, VIT dose, and duration of VIT.

A negative response indicates the absence of systemic symptoms.

4. The Lights of Controlled Sting Challenge With Hymenoptera

4.1. SCT as a Possible Biomarker

Useful biomarkers have been sought for monitoring of the effectiveness of VIT.

4.1.1. Specific IgE (sIgE)

sIgE to venom initially rises and a subsequently decreases during VIT, remaining at low levels for several years following interruption of treatment [26,27]. A decrease in levels of sIgE against individual allergens in relation to VIT has also been observed [28]. Nevertheless, these values rarely become negative [26]. The coexistence of detectable sIgE levels and tolerance of stings in some patients receiving treatment and the lack of differences in changes in sIgE between successfully and unsuccessfully treated patients render this biomarker inappropriate for monitoring the risk of patients undergoing VIT for future stings [1,3,29].

4.1.2. Specific IgG4 (sIgG4)

sIgG4 tends to rise during VIT to a variable extent from one patient to another [30]. Some studies have linked the rise in sIgG4 with the effectiveness of VIT [31]. While sIgG4 levels have been reported to decrease following interruption of VIT, such a decrease has been found to have no effect on the protection obtained against stings [31]. In any case, there is no evidence for a correlation between the results of the SCT and levels of sIgE and sIgG4 or the ratio of sIgE to sIgG4 [32].

4.1.3. The basophil activation test

The results of the basophil activation tests (BAT) correlate well with those of spontaneous stings [33] and SCT [34]. However, given the lack of standardization and methodological complexity, use of the BAT is currently restricted to research [35]. In their study, Hausmann et al [36] found a sensitivity and a negative predictive value of 100%, although the specificity and positive predictive values were 87% and 50%, respectively, when the BAT was compared with SCT using live insects, which led the authors to conclude that the BAT could replace SCT in cases with formal contraindications [36]. A parallel situation has been observed between the expression of CD63 by basophils and the protection afforded by VIT in children allergic to bee venom; this may predict reactions to bee venom in new stings once immunotherapy is complete [34,37].

Although sIgE, sIgG4, and BAT have proven useful with respect to the tolerance of stings by patients treated with VIT, none of these techniques provides the same information as SCT, which is why SCT is considered the gold standard for monitoring the effectiveness of VIT and remains—at least for the present—an irreplaceable tool [1].

4.2. SCT as a Programmable Procedure

Some authors have based the effectiveness of VIT on the response to spontaneous stings. However, we do not know when this occurs or, indeed, if it will ever occur. Furthermore, a spontaneous sting may not guarantee a sufficient amount of venom, given that the patient frightens the insect away rapidly on being stung in the case of bees and that the sting lasts only 1-2 seconds in the case of wasps.

One of the advantages of the SCT is that it can be programmed for patients undergoing VIT at different time points after the maintenance dose has been reached in order to assess its efficacy. Tests have been performed as early as a week after the maintenance dose is reached [38] to several years after its first use [26,39] and in general before finishing VIT [40]. In these cases, a positive SCT result allows the factors associated with the failure of the VIT with bee venom to be identified [41] and strategies to be modified. SCT can also be programmed 1 or several years after discontinuation of immunotherapy with the aim of verifying the patient's degree of protection [40].

4.3. SCT Allows Adjustment of the VIT Dose

A positive SCT in patients undergoing VIT makes it possible to identify those who need a larger dose then the conventional 100 µg and therefore to increase the dose to 200 µg or more to ensure that therapy is protective [42]. In such cases, SCT allows the effectiveness of the dose to be verified.

4.4. SCT is a Safe Procedure in Patients Undergoing VIT

Much has been written about the possibilities of SCT causing serious anaphylactic reactions. This issue will be dealt with in the shadows section. However, here we would like to mention that, to our knowledge, no fatal reaction caused by SCT has been reported in patients treated in a hospital setting. Furthermore, it has been documented that most systemic reactions caused by SCT have been shown to be less severe than the index sting [21,43]. Controlled SCT in a hospital setting will always be safer than a spontaneous sting in an uncontrolled setting, and the option of not performing the test under clinical conditions that do not allow it is always possible.

The SEAIC has issued documentation on diagnostic and therapeutic procedures (RESCAL), classifying them into 3 levels of risk (A, B, and C). SCT performed in uncomplicated cases of patients treated with immunotherapy has been classified as being at risk level B (more complicated procedures, procedures lasting more than 2 hours involving a moderate-to-high risk). SCT is assigned level C in patients with comorbidities (highly complex tests requiring constant supervision and monitoring by specialist nursing and medical staff and/or extreme risk for a severe reaction or the presence of comorbidities) [16].

4.5. SCT is Useful in Patients With Mastocytosis

VIT is recommended indefinitely in patients allergic to Hymenoptera venom with mastocytosis [44], and the need to know its efficacy by SCT is even more important than in other patients, given the severity of reactions in this group. In such cases, the technique should be performed with the same safety measures as in other patients [41,45].

Although mastocytosis has been identified as a risk factor for the failure of VIT, studies in which SCT has been performed conclude that systemic reactions, when they occur, are less severe and that VIT confers greater protection if the maintenance dose is increased [44,46,47].

4.6. SCT Enables In Vivo Research

SCT also opens up the possibility of studying the pathophysiology of anaphylaxis in vivo by objective monitoring of the clinical, immunologic, and biochemical events that occur in a programed generalized allergic reaction [48,49]. This technique has led to the generation of FXIIa-C1inh and kallikrein-C1inh complexes, as well as the degradation of high-molecular-weight kininogen [50]. Levels of mediators such as histamine and tryptase and endogenous vasopressors can also be monitored [11,51]. These would compensate for the vasodilation and extravasation of fluids which occur in anaphylaxis and would explain the ability of some patients to spontaneously recover without treatment [48]. The SCT has been used to study the natural history of allergy to venoms, although this is not the most widely accepted recommendation. In their study, Golden et al [12] analyzed the frequency and severity of reactions to stings of different species of *Vespula* in 111 adults, most of whom had experienced slight-to-moderate systemic reactions due to *Vespula* stings and were therefore sensitized to this venom. A total of 175 serial SCTs were performed, with 72% being negative and the remainder less severe than the previous spontaneous stings. In another study [52], 92 children allergic to Hymenoptera venom underwent serial SCT, after which vaccination was recommended in 13, thus confirming, thanks to the use of SCT, a trend towards spontaneous resolution of the disorder in

a large part of the population evaluated. Controlled exposure to Hymenoptera venoms has also been used in laboratory animals to determine the role of the adaptive type 2 immune response. The findings support the hypothesis that IgE and mastocytes help to protect the host against the toxic effects of the venom [53].

4.7. SCT Improves Quality of Life

Another point in favor of SCT is its influence on the quality of life of patients who have experienced systemic reactions to Hymenoptera stings and who live and work in settings where insects are present. Anaphylactic reactions following a bee or wasp sting can lead to a considerable decrease in the quality of life of people who experience them. These reactions have a substantial impact on daily activities in the open air (including professional activities) and may lead to symptoms of anxiety or depression [54]. This reduction in quality of life in people who have experienced systemic reactions after Hymenoptera stings can be evaluated using questionnaires that examine general aspects of health (Health-related Quality of Life Questionnaire for Hymenoptera Venom–Allergic Patients) or specific issues (Vespid Allergy Quality of Life Questionnaire) [55]. Application of validated questionnaires recently demonstrated that vaccinated patients who tolerated SCT had a better quality of life than patients receiving VIT who had not undergone this test [56,57].

5. The Shadows of Controlled Sting Challenge With Hymenoptera

5.1. SCT as a Diagnostic Tool

The usual diagnostic tools may not be sufficient to confirm a diagnosis; therefore, the usefulness of SCT as a diagnostic tool is a matter of debate [1].

A negative isolated SCT does not predict that subsequent test results will also be negative [23,29,58]. In the case of untreated allergic patients, the risk of a serious reaction produced by SCT could be compounded by the uncertainty of an isolated negative result. Therefore, the decision to restrict immunotherapy in a patient with an isolated negative SCT result could have serious consequences.

With the aim of evaluating the diagnostic value of SCT and recommending immunotherapy in Hymenoptera venom–allergic patients who experience systemic reactions, several authors have performed tests sequentially on the same patients to assess the reproducibility and negative predictive value of SCT, comparing the results with a second SCT or stings in the field. Golden et al [12] demonstrated that up to 11 of 37 patients with allergy to *Vespula* venom, a negative result in their first SCT, and no VIT presented systemic reactions following a second SCT. In a study by Franken et al [59], 61 untreated *Vespula* venom–allergic patients had negative results in their first SCT; of these, 21% had a positive result on a second SCT. Blaauw et al [60] performed SCT on 136 patients allergic to bee venom, of whom 76 had a negative result; of these, 41 patients subsequently received a sting in the field, and 6 of them (14.6%) experienced a reaction. The authors also performed an SCT on 343 patients allergic to wasp venom, of whom 284 had negative results; of these, 127 patients were stung in the field and 13 (10.2%) had a reaction. Based on these results, the authors report that the negative predictive value of an SCT for subsequent stings in the field is 85.4% in the case of bees and 89.9% for wasps.

5.2. Risk of SCT in Patients Not Undergoing VIT

When faced with the decision of indicating an SCT for a patient allergic to Hymenoptera venom, it is crucial to bear in mind aspects related to safety, including the possibility of boosting sensitization.

Large series of patients allergic to Hymenoptera venom have demonstrated that the reaction untreated patients experienced in the SCT is less severe than that reported by the patients in the clinical history and that the severity of the expected reaction is greater in patients with a history of previous severe reactions [12,60]. In this regard, Blaauw et al [60] found that the prevalence of severe systemic reactions (grade III and IV in the Müller classification) following SCT was 24% for *A mellifera* and 8% for *Vespula* species. In patients with a history of severe reactions, the SCT reaction was as severe as the previous reaction in 25% of patients allergic to *A mellifera* and in 15% of those allergic to *Vespula* species. In the study by Franken et al [59], 46% of patients who reacted with their second controlled SCT, but not with the first, experienced anaphylactic shock requiring vasoactive drugs.

Given the data presented in the last 2 sections, SCT is not habitually used as a diagnostic tool in patients not receiving VIT.

5.3. SCT Could Cause Aversion

Not all patients with a history of allergy to Hymenoptera venom agree to undergo SCT with a live insect. One study reports that 26% of patients refused [8], although no in-depth study has been performed into the reasons for refusal. In any case, we believe that the key factor is the amount of information given to the patient and the confidence that patients have in their health care setting.

5.4. Use of a Live Insect

Another problem with SCT is the need to use live insects. SCT differs from other allergology challenges because the live insect has certain irreplaceable biological properties and because it presumably inoculates the entire content of its venom sac in a single motion. It is considered that least 90% of the venom sac contents are delivered within 20 seconds [61].

Attempts made to reproduce the sting using subcutaneous and intracutaneous injections have yielded poor results [21]. Better results have been obtained using injections with a microsyringe (0.5 µL of pure venom) at a depth of 2 mm, which could correspond to the conditions of a spontaneous sting, although the technique is arduous [13].

The reason why the venom of the live insect reproduces the reactions better than purified venom is unknown, although it has been postulated that the presence of low-molecular-weight substances, such as vasoactive amines, influence the development of the allergic reaction [62].

SCT is affected by 2 important aspects:
– Obtaining the insect and identifying it correctly (see above).
– Lack of quantification of the venom in SCT.

Unlike other controlled challenge techniques, SCT cannot be performed progressively by quantifying the amount of venom administered by the insect [22], and it is impossible to conduct blinded studies.

Differences between insects (eg, bees and wasps) may affect the result of SCT [1]. With each sting, bees inject a volume of venom of between 50 and 140 µg, a quantity much larger than vespids (1.7-3.1 µg for *Vespula*, 2.4-5 µg for *Dolichovespula*, and 4.2-17 µg for *Polistes*) [63,64]. The size of insects from the *Vespa* genus would seem to indicate that a greater volume of venom is injected, although there are no data to confirm this hypothesis. It has been reported that SCT results with *Vespula* species are less reliable than those obtained with *A mellifera*; this is because the amount of venom released by the vespid is more variable than that injected by *A mellifera* [13]. Furthermore, vespids can sting several times, with the venom sac partially depleted, whereas a bee stings only once and then dies from eventration. Differences have even been found within the same genus. In patients allergic to *Vespula* species not receiving VIT, one study found a more aggressive attitude and a deeper sting with *Vespula maculifrons*, for which the reaction was more severe than that of *V germanica* [12].

Few data are available on other aspects that affect the differences in the amount of venom inoculated, for example, the time needed to empty the sac in a spontaneous sting, the different sizes of the insects, and the possibility of a previous sting.

5.5. False Safety and Abandonment of VIT

After a tolerated SCT, VIT must continue following the originally established protocol. It is important to bear in mind that a controlled sting does not replace a dose of VIT. A tolerated SCT confirms the success of therapy and, therefore, that the therapeutic dose is effective. However, this success does not mean that the duration of treatment can be shortened (minimum of 5 consecutive years) [1]. Therefore, patients should be informed that, even in the case of a negative SCT result, they must complete VIT to guarantee its long-term efficacy [1]. Similarly, they must continue to carry an adrenaline auto-injector, if previously told to do so [65].

6. Discussion

Despite major advances in the diagnosis of allergies in recent years, there are no reliable biomarkers to monitor the efficacy of VIT. The SCT is the only reliable way of verifying the clinical efficacy of VIT. In both real life and clinical research, the SCT is accepted as the gold standard for measuring the protection provided by VIT [1], with doubts regarding the appropriateness of performing the test in untreated patients remaining owing to the uncertainty surrounding the safety of the procedure [59,60].

The SCT methodology is not standardized. A German publication [66] described the SCT procedure in the authors' care setting. The method adopted by Spanish allergists is based on cooperation with expert entomologists, the characteristics of the Spanish Health System, and experience accumulated over the last 2 decades.

This lack of standardization, which would include variations in the amount of venom injected, as well as differences in the species of insects used and their geographic origin, may account for the limited information available on the reproducibility of SCT results.

When faced with a patient who has experienced an anaphylactic reaction following a Hymenoptera sting without the normal diagnostic tools being able to confirm the underlying allergic mechanism, the SCT may be the best option when attempting to confirm the real need for VIT. However, confirmation of an isolated negative test result does not rule out the possibility of a systemic reaction following a subsequent sting [23,29,58]. Consequently, the decision to start VIT should be taken with great care in these cases.

In treated patients, the negative predictive value of SCT has not been explored, with the result that, where possible, more than 1 SCT should be performed to increase certainty regarding protection. However, the greater safety offered by the SCT in treated patients [21] allows more than 1 SCT

Table 3. Summary of the Lights and the Shadows of the Sting Challenge Test

Sting challenge test	
Lights	Shadows
Possible biomarker Gold standard for efficacy of VIT	Debatable diagnostic tool
Programmable procedure	Unsafe in patients before VIT
Tool for adjusting the dose of VIT	May be a scary experience for some patients
Safe in patients undergoing VIT	Variability in amount of injected venom
Acceptable in patients with mastocytosis	False feeling of safety
Useful for research	Complicated logistics of using live insects
Improves patients' quality of life	Nonstandardized technique

Abbreviation: VIT, venom immunotherapy

to be performed under controlled conditions, thus adding a firm basis to the decision to discontinue successful VIT. The incorporation of SCT into daily clinical practice for patients allergic to Hymenoptera venom undergoing VIT guarantees an excellent level of integrated care, with it being clear that a negative result improves quality of life and a positive result allows the patient to be re-evaluated and improvements to be made to the VIT (protocol, dose, and duration).

SCT is currently the necessary reference for researchers in their search for biomarkers of the effectiveness of VIT and immunological tolerance in general.

The main lights and shadows are summarized in Table 3. As an overall conclusion, the Hymenoptera Allergy Committee of the SEAIC recommends using the SCT under appropriate conditions to assess the response to VIT, including the need to adjust the dose and the appropriateness of maintaining treatment for longer. The Committee is also in favor of more multicenter clinical studies using this technique to improve the current evidence base. Furthermore, the Committee is not in favor of using the SCT for diagnostic purposes in untreated patients.

Acknowledgments

The study was carried out within the framework of the Hymenoptera Allergy Committee of the SEAIC.

Funding

The authors declare that no funding was received for the present review.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received December 29, 2021; accepted for publication June 21, 2022.

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