ORIGINAL ARTICLE

Longitudinal Validation of the Spanish Version of the Health-Related Quality of Life Questionnaire for Hymenoptera Venom Allergy (HRQLHA)

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Abstract

Background and Objective: The Spanish version of the health-related quality of life questionnaire for allergy to hymenoptera venom (HRQLHA) has been shown to be reliable, internally consistent, and externally valid. The aim of this study was to complete the validation of the HRQLHA by analyzing its sensitivity to changes (longitudinal validity) using the sting challenge test (SCT) as the variable of change.

Patients and Methods: Patients over the age of 17 years with a systemic allergic reaction to *Apis, Vespula*, or *Polistes* venom were included during their first year of venom-specific immunotherapy. Patients were assigned to either a group that underwent the SCT or a control group that did not. All patients completed the HRQLHA at baseline and after a period of 2 to 4 months, during which time the SCT was performed in the active group, with no intervention in the control group.

Results: Fifty patients were included in the study: 25 in the SCT group and 25 in the control group. The patients in the SCT group showed a significant improvement in mean HRQLHA score (+0.35, *P*=.03) after the SCT, while those in the control group showed no significant changes in questionnaire scores.

Conclusions: Our results demonstrate the sensitivity of the HRQLHA to changes and thus complete the longitudinal validation of the questionnaire. A well-tolerated SCT improves the quality of life of venom-allergic patients as it reduces anxiety associated with the fear of being stung.

Key words: Hymenoptera venom allergy. Quality of life questionnaire. HRQLHA. Sting challenge test. Longitudinal validation.

Resumen

Introducción y objetivo: El cuestionario de calidad de vida en español para alérgicos a veneno de himenópteros (HRQLHA) ha demostrado su fiabilidad, consistencia interna y validez externa. El objetivo de este estudio era completar la validación del HRQLHA mediante el análisis de su sensibilidad al cambio o validación longitudinal, considerando como variable de cambio la prueba de repicadura controlada intrahospitalaria (RIH).

Pacientes y Métodos: Se incluyeron pacientes mayores de 17 años con reacción sistémica por alergia a veneno de Apis, Vespula o Polistes, en el primer año de tratamiento con inmunoterapia. Los pacientes se distribuyeron en un grupo sometido a RIH y un grupo control no sometido a esta prueba. Los pacientes cumplimentaron el HRQLHA basal y después de la repicadura o después de un periodo de 2-4 meses si pertenecían al grupo control.

Resultados: Se incluyeron 50 pacientes en el estudio. 25 en el grupo de RIH y 25 en el grupo control. Los pacientes del grupo RIH presentaron una mejoría significativa en la puntuación del cuestionario HRQLHA después de la repicadura de + 0,35 (p=0,03), mientras que los pacientes del grupo control no mostraron cambios significativos en la puntuación del cuestionario.

Conclusiones: Los resultados obtenidos demuestran la sensibilidad al cambio del HRQLHA y permiten completar la validación longitudinal del cuestionario. La prueba de repicadura controlada intrahospitalaria bien tolerada mejora la calidad de vida de los pacientes alérgicos a venenos ya que disminuye su ansiedad ante una nueva picadura.

Palabras clave: Alergia a veneno de himenópteros. Cuestionario calidad de vida. HRQLHA. Prueba de repicadura controlada intrahospitalaria. Validación longitudinal.

Introduction

Quality of life questionnaires are useful tools in daily clinical practice as they assess health and treatment outcomes in terms that are relevant to the patient [1-3]. As demonstrated by the Vespid Allergy Quality of Life Questionnaire (VQLQ) developed in 2002 by Elberink and colleagues [4], the quality of life of patients allergic to hymenoptera venom is impaired by feelings of anxiety associated with the fear of being stung.

Between 2008 and 2011, the Hymenoptera Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC) carried out a study in which the English version of the VQLQ was translated into Spanish, adapted to Spanish cultural norms, back-translated, and validated as the Spanish version of the quality of life questionnaire (HRQLHA).

The HRQLHA proved to have high reliability, external validity, and internal consistency, and furthermore, it was validated for patients allergic to *Apis, Vespula,* and *Polistes* venom, unlike the original questionnaire, which was validated only for *Vespula* venom [5].

The HRQLHA consists of 14 questions rated from 1 to 7. Lower scores indicate worse quality of life. Most of the questions in the HRQLHA are related to emotional aspects of the patients' lives, but there are also some questions that address work, leisure, and outdoor activities. The questionnaire is valid for patients over the age of 14 years who have had a systemic reaction to hymenoptera stings. It is not valid for beekeepers, as in this case the disease would be occupational in nature and patients would have a different perception of their disorder [5-6] (Appendix 1).

Once the cross-sectional validation had been completed, what remained to be done was the longitudinal validation or analysis of the sensitivity of the HRQLHA to changes over time. The variable of change analyzed in the longitudinal validation of the original questionnaire, the VQLQ, was administration of immunotherapy. Specifically, changes in VQLQ score after 1 year of follow-up were compared between a group of patients who had received immunotherapy and a control group who only had access to adrenaline as rescue therapy. The study found significantly improved VQLQ scores in the patients in the immunotherapy group [6-8].

Our group carried out the longitudinal validation of the HRQLHA using the sting challenge test (SCT) as the variable of change. Given that the quality of life of patients allergic to venom is reduced by the uncertainty of how they would react to a new sting [4], our hypothesis was that a well-tolerated SCT would improve quality of life, as it would make patients feel safer when exposed to risk situations. On the basis of this hypothesis, we analyzed HRQLHA scores before and after an SCT and compared the results with those of a control group who did not undergo this challenge. In this article, we describe the process of the longitudinal validation of the HRQLHA.

Patients and Methods

To assess the longitudinal validity of the HRQLHA, the SEAIC Hymenoptera Allergy Committee conducted a controlled, prospective multicenter study in which changes in HRQLHA score were compared between a group of patients who underwent an SCT and a control group who did not. The study was performed between 2011 and 2014.

We recruited consecutive patients over the age of 17 years who had had a systemic allergic reaction to *Apis, Vespula,* or *Polistes* venom and who were in their first year of treatment with venom-specific immunotherapy. Beekeepers were excluded as the HRQLHA is not validated for this group, as were patients who had difficulty reading or understanding the questionnaire. Patients who had been accidentally stung after beginning immunotherapy were also excluded.

Patients were assigned to one of 2 groups: an SCT group and a non-SCT, control, group. Assignment to either group was based on the usual clinical practice of the participating centers, that is, centers that performed SCTs assigned all their patients to the SCT group, while centers with no experience in SCTs assigned all their patients to the control group.

The SCTs were carried out following the procedure described by Moreno et al [9]. After determining the patients' vital signs and placing a peripheral IV catheter, the test was performed using entomologically identified insects. Patients' reactions and vital signs were monitored for 2 hours after the test.

All patients filled in the HRQLHA at baseline. The patients in the SCT group filled in the questionnaire again a week after they had undergone the SCT (2-4 months after baseline). The control group also completed the questionnaire 2 to 4 months after baseline.

The study was approved by the ethics and clinical research committees at the participating hospitals, and all patients were informed about the study and gave their consent to participate.

Statistical Analysis

Statistical analysis was performed in collaboration with the Institute of Biomedical Research in Lleida. The Wilcoxon signed rank test was used to compare the means of matched

groups, the Mann-Whitney test to compare means from independent groups, and the Fisher exact test to compare independent dichotomous variables. Linear multivariate regression was used to analyze the influence of the different variables, and the Pearson correlation coefficient was used to establish the linear relationship between quantitative variables. All data were analyzed using statistical software from the R-project.

Results

Six hospitals from different parts of Spain, including Madrid, Castilla la Mancha, and Catalonia, participated in the study (Figure 1). Fifty-three patients with a mean (SD) age of 47.4 (12.44) years (range, 21-69 years) were included. Most of the patients (86.8%) were men. A majority (64.15%) lived in rural areas, defined as towns with fewer than 10 000 inhabitants. The main occupations were in agriculture (15.1%), the building industry (9.4%), and maintenance (9.4%); 13.2% of the patients were retired.

The patients were allergic to *Polistes* venom in 71.7% of cases, *Apis* venom in 18.9%, and *Vespula* venom in 9.4%. According to the classification of systemic reactions to insect stings by Mueller [10], 35.8% of the reactions were grade IV, 26.4% grade I, 20.7% grade II, and 17% grade III.

The mean (SD) HRQLHQ score for all the patients was 4.8 (1.36). No significant differences were found when the questionnaire scores were compared by age or severity of reaction. However, a significant difference was found when the data were analyzed by sex, with men presenting a significantly higher score (better quality of life) than women (4.96 vs 3.71, *P*=.014) (Table).

Of the 53 patients included in the study, 28 were assigned to the SCT group and 25 to the control group. We found no significant differences for age, sex, grade of reaction, or time on immunotherapy between the 2 groups (Table). Of the 28 patients in the SCT group, 24 were stung by *Polistes* and 4 by *Apis*. Three of the patients in the SCT group were considered to not tolerate the test; 2 developed an extensive local reaction (larger than 10 cm), and the third developed a systemic grade I reaction. All 3 patients had been stung by *Polistes*. They were excluded from the study as we believed that their poor tolerance of the SCT might negatively affect the score on the second questionnaire. As a result, 50 patients (25 in each group) were finally included in the study.

Figure 1. Participating centers and number of patients.

The mean (SD) time between the beginning of immunotherapy and completion of the first questionnaire was

Table. Demographic Data and Study Results

Patients, No.		53
Age, mean (SD), y		47.40 (12.44)
Sex		
Female, No. (%)		7 (13.2)
Male, No. (%)		46 (86.8)
Venom involved		
Apis, No. (%)		10 (18.9)
Vespula, No. (%)		5 (9.4)
Polistes, No. (%)		38 (71.7)
Severity of reaction (Mueller)		
Grade I, No. (%)		14 (26.4)
Grade II, No. (%)		11 (20.7)
Grade III, No. (%)		9 (17)
Grade IV, No. (%)		19 (35.8)
Characteristics by group	SCT group	Control group
Patients, No.	28	25
Age, mean (SD), y	46.4 3 (10.89)	48.48 (14.13)
Sex		
Female, No. (%)	4 (14.3)	3 (12)
Male, No. (%)	24 (85.7)	22 (88)
Severity of reaction (Mueller):		
Grade I, No. (%)	9 (32.1)	5 (20)
Grade II, No. (%)	8 (28.6)	3 (12)
Grade III, No. (%)	4 (14.3)	5 (20)
Grade IV, No. (%)	7 (25)	12 (48)
Time on immunotherapy up to Q1		
Days, mean (SD)	187.03 (137.60)	155.52 (106.50)
Results of longitudinal validation		
HRQLHA score, mean (SD)		4.8 (1.36)
HRQLHA score by sex, mean (SD)		
Men		4.96 (1.36)
Women		3.71 (0.66)
Time between questionnaires, mean (SD), d		
Between beginning of immunotherapy and Q1		172.17 (123.77)
Between Q1 and SCT		98.75 (39.49)
Between SCT and Q2		6.75(1.57)
Questionnaire scores by group, mean (SD)		
SCT group		
Q1	4.95 (1.26)	
Q2	5.30 (1.11)	
Q2-Q1	+ 0.35	
Control group		
Q1	4.71 (1.53)	
Q2	4.59 (1.56)	
Q2-Q1	-0.12	

Abbreviations: SCT, sting challenge test; Q1, questionnaire 1 (completed at baseline); Q2, questionnaire 2 (completed 2-4 months after baseline, and approximately a week after the SCT in the case of the SCT group).

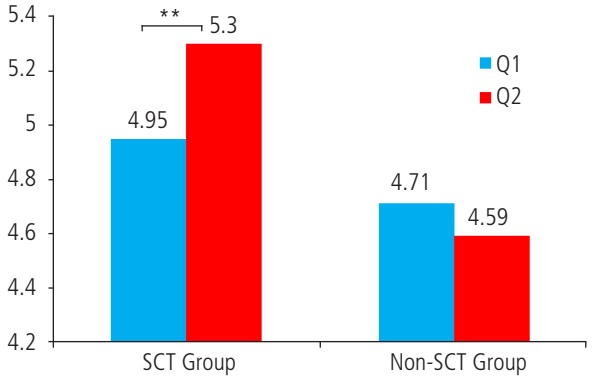

Figure 2. Mean scores for the first (Q1) and second (Q2) questionnaire in the sting challenge test (SCT) group and non-SCT group. ** *P*=.03

172.17 (123.77) days. On average, 98.75 (39.49) days elapsed between completion of the questionnaire and the SCT and 6.75 days (1.57) elapsed between the SCT and completion of the second questionnaire.

In the SCT group, significant differences were found between mean baseline score (4.95 [1.26]) and mean post-SCT score (5.3 [1.11]) (significant difference of +0.35, *P*=.03). However, in the control group, no significant differences were found (baseline score of 4.71 [1.53] vs second questionnaire score of 4.59 [1.56], ie, nonsignificant difference of -0.12; *P*=.47). Our findings thus show that patients in the SCT group had significantly improved HRQLHA scores as compared with patients in the control group over the same time period (Figure 2).

Furthermore, when we compared the magnitude of the change in scores in both groups, a significant difference (*P*=.04) was found, indicating that the patients in the study and control groups had statistically different changes in questionnaire scores.

The mean baseline score for the 3 patients who did not tolerate the SCT was 4.3 (0.12) compared with 4.19 (0.98) after the test. Thus, their scores decreased (-0.11), although the differences were not significant given the small number of individuals.

Multivariate analyses revealed that none of the other variables (age, sex, place of residence, venom, grade of reaction, time between questionnaires, and time on immunotherapy) significantly contributed to explaining the differences in questionnaire scores and strongly suggest that this change was due exclusively to undergoing the SCT.

These results demonstrate the sensitivity of the HRQLHA to change and allow the longitudinal validation of the questionnaire to be completed. At the same time, they confirm that the SCT is capable of improving patients' quality of life.

Discussion

Patients allergic to hymenoptera venom have impaired quality of life because they have to be alert to the presence of insects and are uncertain how they might react to a new sting. Based on the hypothesis that a well-tolerated SCT would improve patients' quality of life by making them feel safer in risk situations, we designed a study to assess the longitudinal validity of the HRQLHA by analyzing changes in questionnaire scores following an SCT.

Most of our patients were men from rural areas with jobs involving a high risk of exposure to stings (agriculture, building, and maintenance). The predominance of these typically male professions explains why men outnumbered women in our study.

The most frequent venom was from *Polistes*, which is the most common hymenoptera in the center and south of Spain [11]. The inclusion of patients allergic to *Polistes* venom is a major advance, as similar studies in Europe have not included this insect due to its low prevalence [7,12].

The mean overall baseline HRQLHA score observed was 4.8 (1.36), which is higher than previously reported by our group [5], and therefore indicates a better perception of quality of life in our series of patients. The mean HRQLHA score was also significantly higher in men than in women (4.96 vs 3.71, *P*=.014), although previous studies have shown conflicting results in this respect [5]. Like other studies [4,5], no relationship was found between questionnaire scores and age or severity of reaction.

A significant improvement in HRQLHA scores was observed in the SCT group but not in the control group. Furthermore, we found that the magnitude of the change was significantly different between the 2 groups (Figure 2). Patients who did not tolerate the SCT showed a decrease in questionnaire scores, although the results were not significant given the small number of patients. Our results demonstrate the sensitivity of the HRQLHA to change and complete the longitudinal validation of the questionnaire, which can now be used in clinical practice. Furthermore, we have also confirmed the hypothesis that a well-tolerated SCT improves the quality of life of patients allergic to hymenoptera venom.

The SCT is normally used to monitor the efficacy of immunotherapy [13], but our study shows that the test might have a new indication, that is, it could be used to improve the quality of life of patients treated with immunotherapy who live in fear of being stung.

This is the first controlled study to analyze changes in scores from a specific quality of life questionnaire in patients undergoing SCT. Two studies have reported significant improvements in VQLQ scores in patients after an SCT, but because neither of them included a control group, it is impossible to establish whether the improvement was due to the SCT or to confounding factors [14,15].

The HRQLHA may also be useful in the initial stages of managing patients allergic to venom in daily clinical practice, as more effort may be required to reassure patients with a very poor quality of life about their situation and to explain the benefits of treatment with specific immunotherapy. It has been proposed that the decision to begin immunotherapy in patients with systemic grade I reactions may depend on other factors, such as quality of life impairment [16]. Furthermore, previous studies have shown that specific immunotherapy improves patient quality of life [7,8] and thus in patients with a systemic grade I reaction a low HRQLHA score may guide the decision on the need for immunotherapy. Finally, based on the results of this study, the SCT may help to improve the quality of life of patients on immunotherapy with a low HRQLHA score.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

These data were presented as an oral communication at the session "Quality of Life" at the International Symposium on Allergy to Hymenoptera held in Granada, Spain in October 2013.

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