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Improving allergy testing and diagnosis: impact of skin prick testing intra-head device variability on clinical performance

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Abstract

Background: Multiple head skin prick test (SPT) devices designed for percutaneous allergy testing suffer from intra-head device variability, which may lead to misinterpretations by testing physicians impacting allergy treatment. It is proposed that detailed, high-magnification inspection during the verification stage of the design and development process of SPT devices would improve clinical accuracy and performance.

Objectives: This pilot study aimed to examine the impact of physical characteristics, including consistency of length and the precision of the tips of the applicator tines of two FDA commercially available SPT devices, on clinical performance. It was hypothesized that devices with lower finished product variability would improve clinical performance.

Methods: Visual inspection the Lincoln Multi-Test II (LM) and the ST-9® multiple head applicator (ST-9) were obtained by dimensional measurement using 160X magnification. A total of 8 subjects completed this pilot study. SPT with histamine (HIS; 1 mg/mL base) and saline glycerin (GLY) were applied on the volar surface of one forearm LM and ST-9 devices using on the opposite forearm. Data were obtained from 72 histamine sites for the ST-9 device and 64 histamine sites for the LM device with 72 negative control GLY sites recorded for the ST-9 device and 64 glycerinated GLY sites for the LM device.

Results: T-test revealed that the ST-9® employed a statistically significant shorter tine length (1.94 ± 0.02) and showed less variability of tine length ($P < 0.05$) compared with the LM (2.12 ± 0.03). The ST-9 showed a smaller tip diameter and significantly less tine point diameter variability (0.037 ± 0.006) ($P < 0.05$) compared to LM (0.042 ± 0.009). The ST-9™ displayed significantly ($P<0.05$) less wheal reaction to the negative control glycerin GLY solution than LM.

Conclusion: The lower variability of ST-9® suggests less likely operator misinterpretations. Although considered an engineering design and manufacturing problem, precision and high magnification inspection during the verification stage of SPT devices may have important clinical implications. Studies on optimizing the magnification process to improve the precision and performance of SPT devices in the clinical setting are warranted.

Keywords: Skin Allergy Testing, Allergy and Immunology, Equipment and Supplies, Tine Length, Skin tests.

Introduction

Allergies, affecting 2 in 5 Americans, are one of the most salient chronic health problems accounting for over 17 million physician visits, 30,000 emergency visits, and hundreds of deaths annually.[1-3] Allergies increase a person's risk of other diseases, including asthma which adds a significant clinical and economic burden to the healthcare system.[4,5] The annual cost of allergies is nearly incalculable, given the number of medical visits, pharmaceutical prescriptions, and lost work added to the intangible agonies that each allergy sufferer endures.[3,4] Interestingly, an allergy is a hypersensitivity disorder of the immune system, specifically when a substance that causes a reaction, namely an allergen, triggers the immunological

response. Allergic reactions are usually acquired, predictable, and rapid. Hence, testing and identifying the underlying allergen trigger is considered the primary strategy for diagnosis and treatment.[6-10]

Charles Blackley presented the use of skin prick tests (SPT) to diagnose allergic disease in the 19th century; Lewis and Grant proposed the SPT to investigate immunological skin reactions in the first half of the 20th century.[11,12] With the continuous improvements of diagnostic tools added to the critical need to test for several allergens simultaneously, there was a trend toward using SPT devices with multiple heads allowing clinicians to test various allergens efficiently while potentially reducing patient discomfort.[11] It is worth mentioning that using a device that provides safe and reliable results allows physicians to develop more precise allergen avoidance plans and/or write allergen specific immunotherapy (AIT) prescriptions for their patients with allergic conditions.[1]

There is, however, significant differences between SPT diagnostic devices, adding variability to the device performance, an aspect with important clinical implications.

It has been reported that multiple head SPT devices designed for percutaneous allergy skin testing suffer from intra-head device variability, which may lead to misinterpretations by testing physicians and potentially erroneous and ineffective allergy treatment.[13,14] Inter or intra-test variability in a manufactured component can be attributed to many factors, most prominent from an engineering perspective, relating to the tooling mold's precision, the molding equipment's quality and the manufacturing controls during the molding process. The result of the above factors is reflected in a precise dimensional analysis of the finished product. However, the current literature has scant information about the efforts to address engineering issues and how they impact the device's clinical performance. Therefore, it is proposed that detailed, high magnification inspection during the verification stage of the design and development process of skin testing medical devices would uncover potential tooling and process errors that result in this identified intra-device variability factor that can negatively impact clinical performance.

Objectives

The present study objectives were to test the impact of physical characteristics such as consistency of length and the precision of the tips of the applicator tines of two SPT Food and Drug Administration (FDA) registered devices, on clinical performance. The study tested the hypothesis that devices with lower finished product variability would improve clinical performance.

Methods

Study Design

The preset study comprises two sets of comparisons: microscopic visual inspection and measurement (bench), and a clinical performance portion.

Microscopic Comparative Device Study

Visual inspection of the Lincoln Multi-Test II (LM) and the ST-9® multiple head applicator (ST-9) were obtained by dimensional measurement, in triplicates, using a Coordinate Measuring Machine (Croma; Serein metrology co.,ltd, Shenzhen, China) [Figure 1]. Briefly, inspection of the tested devices applicators was assembled on the testing trays by a technician blinded to the devices' types (LM vs. ST-9). Once the applicator was enabled, the machine monitor displayed an image of the time being magnified by 120X, and the actual length and diameter was recorded.

Figure 1. Coordinate Measuring Machine set up in preparation of tine length and diameter measurements.

Clinical Performance: Applied Comparative Device Study

Nine healthy subjects (F=6) aged 18-65 consented to participate in this study. Subjects were excluded if they had a history of anaphylactic shock, acute fever, chronic systemic disease manifestations, pregnancy or chronic skin conditions. Subjects were requested to withhold antihistamines, Leukotriene antagonists and H2 antagonists for at least 1 week before testing to avoid masking the histamine reactions on the skin. The applications per subject were carried out in one testing session per subject and performed by a proficient skin testing technician who was blinded to the treatment (glycerin GLY [GLY] or histamine [HIS]) and measured by a separate skin testing technician.

Applications were performed equally with HIS (1mg/ml manufactured by ALK-Abello (Port Washington, NY) as a positive control on the right and left volar regions of the forearms, and the other is with GLY solution as the negative control manufactured by ALK-Abello (Port Washington NY) and also performed on the right and left volar regions of the forearms, as previously described.[8] Using new, sterile ST-9 applicators and Lincoln comparison applicators for each location, the HIS was applied to the two locations, left and right volar surfaces of the upper and lower forearms, the GLY applications are rotated to the left and right volar surfaces of the upper and lower forearms and all applications have at least two centimeters of distance, side to side, maintained between the HIS and GLY to avoid potential HIS positive control reactions contaminating the GLY negative control test sites. With the devices examined, this resulted in 34 individual pricks per subject per session. The testing technicians were both blinded to which applicators have the positive control HIS and GLY to avoid bias in the pressure performed for each applicator and test site.

The performance elements examined and compared included wheal diameter in millimeters of each test site. Wheal measurements are to be initiated and recorded at the 15th minute and concluded by the 20th minute after the test application. To maintain objectivity, the technician who performed all of the tests were blind to the contents of the test solution, either HIS or GLY. A second technician who was not in the room during application of each device recorded the results.

Statistical analysis

Descriptive and inferential statistics were conducted using SPSS version 21.0 (IBM, Chicago IL). Student's *t*-test was used for statistical comparisons between the devices for both tine length and diameter and to compare wheal reactions. $P<0.05$ was considered statistically significant.

Ethical considerations

The volunteer feedback data was collected under written informed consent following the ethical statutes of the Declaration of Helsinki. This project was an ancillary study of Protocol 30-094 approved by Lake Erie College of Osteopathic Medicine Institutional Review Board.

Results

Microscopic Comparative Device Study

Data are presented as Mean±SD unless otherwise indicated. Bench data for the LM and ST-9 devices were obtained by dimensional measurement using 120 X magnification. Descriptive statistics for tine length and diameter are in Table 1 and Table 2, respectively.

The ST-9 showed less variability of tine length ($P<0.05$) [Figure 2 A and B] and employed a slightly shorter tine length (1.94±0.02) compared with the LM (2.12±0.03) [Figure 3A]. The ST-9 showed significantly less tine point diameter variability [Figure 2 C and D] and showed a smaller (0.037±0.006) ($P<0.05$) tip diameter compared to LM (0.042 ± 0.009) [Figure 3 B].

Table 1. Tested devices descriptive statistics in tine length

Device	N	Mean	Median	SD	CV%	Range	Minimum	Maximum
Lincoln	24	2.12	2.12	0.030	1.26	0.11	2.06	2.17
ST-9	27	1.94	1.94	0.025	1.23	0.10	1.88	1.98
Total	51	2.06	1.98	0.093	4.63	0.29	1.88	2.17

Table 2. Tested devices descriptive statistics in tine point diameter

Device	N	Mean	Median	SD	CV%	Range	Minimum	Maximum
Lincoln	24	0.041	0.041	0.009	22.00	0.030	0.028	0.058
ST-9	27	0.036	0.036	0.005	16.67	0.028	0.022	0.050
Total	51	0.038	0.037	0.007	20.61	0.036	0.022	0.058

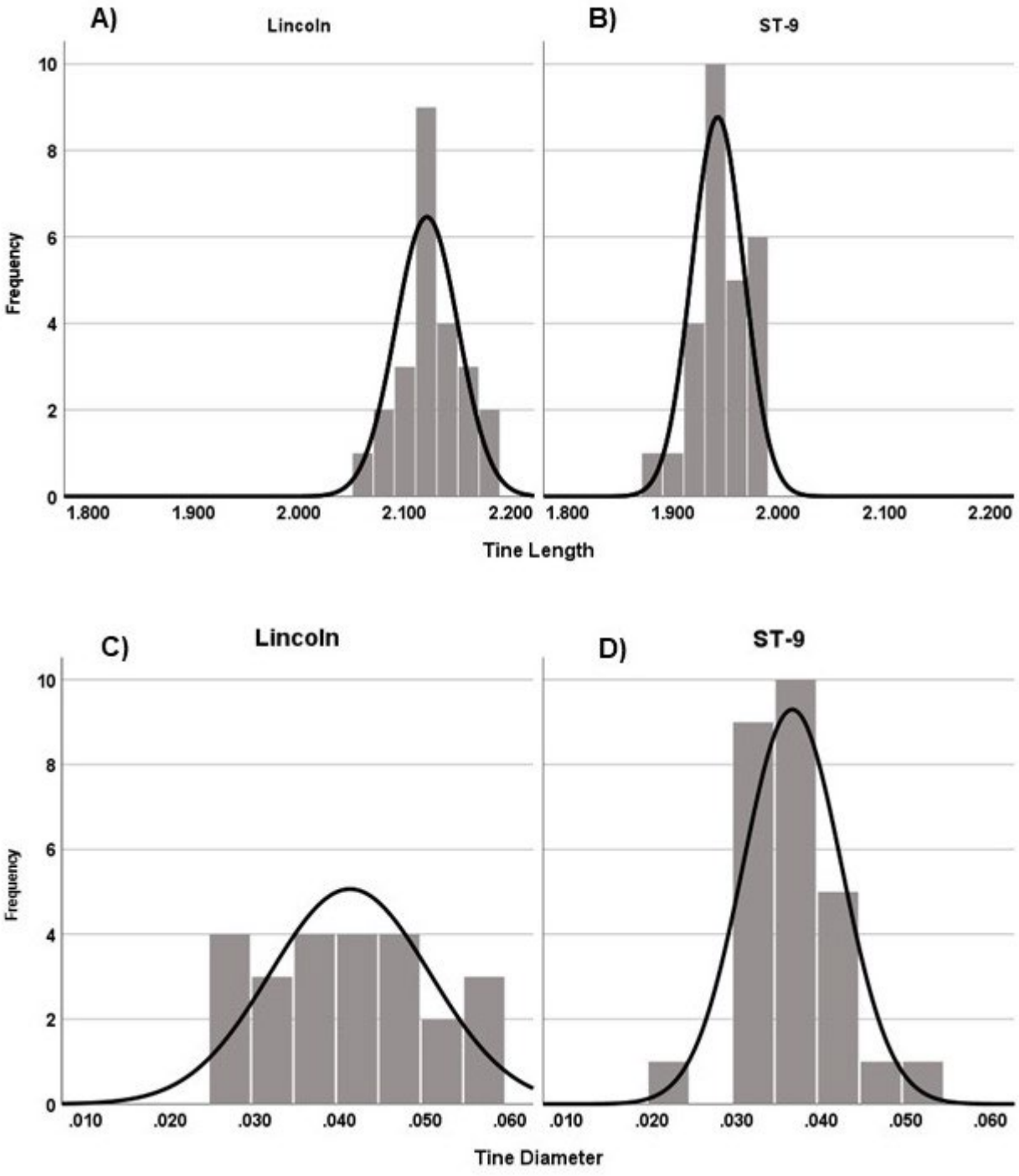

Figure 2. Tine length and diameter device variability among the compared devices

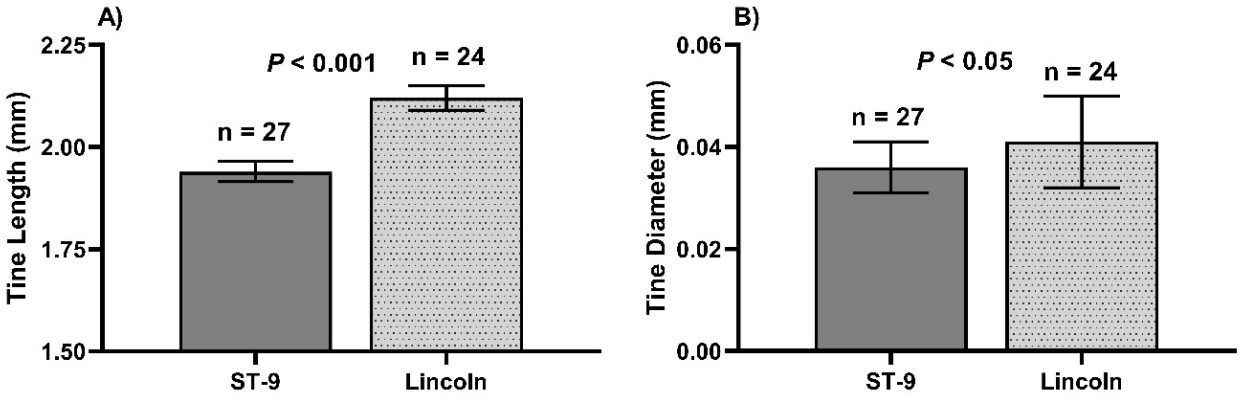

Figure 3. Comparison of tine length and diameter between tested devices

Clinical Performance: Applied Comparative Device Study

One subject was excluded due to self-reported antihistamine use within 72 hours of the pilot study. The SPT tests with histamine HIS (1 mg/mL base) and glycerin GLY were applied to 8 adults using Lincoln Multi-Test II on the volar surface of one forearm and the ST-9™ multiple head applicator (ST-9) on the opposite forearm. Data were obtained from 72 HIS sites for the ST-9 device and 64 HIS sites for the LM device. 72 negative control GLY sites were recorded for the ST-9 device and 64 GLY sites for the LM device. Observationally, the ST-9 showed significantly ($P < 0.05$) less wheal reaction to the negative control GLY solution compared to LM [Figure 4A]. Although both devices produced a positive response of over 3 mm wheal size, LM produced a larger wheal size in the HIS test than ST-9, it was not statistically significant, but might be clinically relevant.

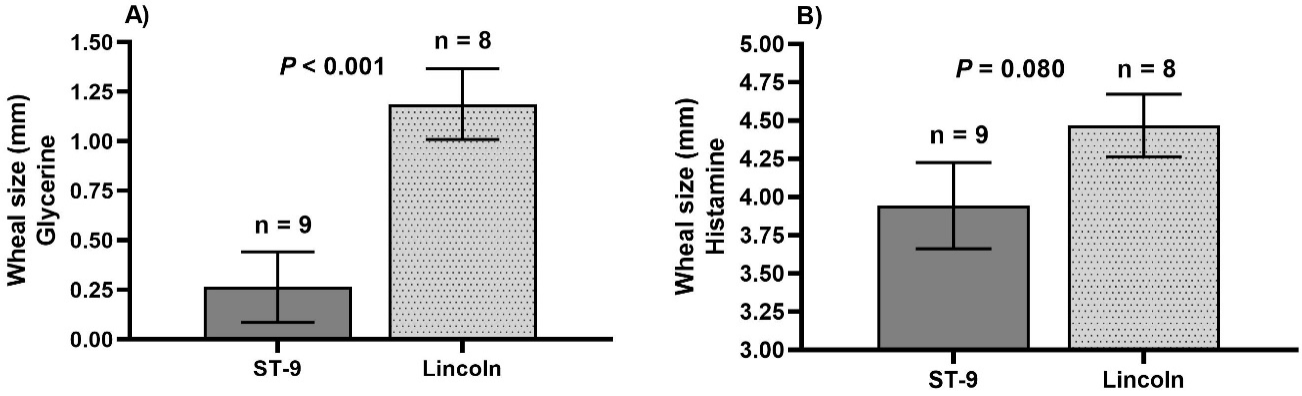

Figure 4. Wheal size comparisons between tested devices

Discussion

The present work sought to examine and compare the physical characteristics, such as, the consistency of length and the precision of the tips of the applicator tines of two similar FDA-cleared and commercially available allergy SPT devices. The results of the present study demonstrate that the ST-9 is dimensionally less variable with more consistent tine lengths and has smaller and more consistent tine tips. Consequentially, the ST-9 produced less wheal reaction to the negative control GLY solution than LM possibly leading to less false positive skin reactions. The lower Variability of ST-9 seems to suggest a less likelihood of misinterpretations by testing physicians with the potential to improve accuracy of allergen identification in the clinical setting.

The SPT or scratch test, is an efficient way of testing for immediate IgE-mediated allergic diseases to many different substances (allergens) as it is usually conducted simultaneously. SPT offers advantages such as relatively low cost, ease of implementation, good diagnostic value, minimal invasiveness, and low pain when performed by a trained professional in a standardized method.[15-17] It has

been reported that the apparent variability in SPT results depends on the device used after controlling for the variation between users and receivers as well as other human factors.[18,19] Moreover, the reported specificity and sensitivity of the SPT to airborne allergens is about 70–97%, and to food allergens, it is 30–90%.[19,20] Thus, correctly performed by a trained individual with a well-manufactured device can lead to proper identification of the disease-triggering allergen and designing the appropriate course of treatment.[21]

It is worth noting that diagnostic test errors can significantly impact patient safety and the allergy treatment's efficacy, compromising the quality of care.[20,21] The quality control procedures in the manufacturing department of in vitro diagnostic products ensure the consistent and reproducible manufacturing of the products with less variability and improved clinical performance of the device.[22,23]

An important observation from our study is that skin testing is not a noticeably painful procedure. In fact, pain scores were minimal (1 on a scale of 0 = no pain to 10 = severe pain) and thus were not included in the results as no variation between devices and subjects was observed. These results are in agreement with those of Cox et al. [1] On the other hand, wheal size was statistically significantly different between the devices in the control condition (ST-9~1 mm less), which may have important clinical implications as it might be the difference between a negative or a false positive tests.

The present work has some limitations that need to be pointed out. There was a limited sample size for the clinical portion of the study conducted in relatively healthy adults and the location of the devices studied was limited to the forearms only. There are other commercially available SPT devices that were not compared during this study. Tine length and diameter measurements would benefit from a separate laboratory to replicate the work and compare the results. Furthermore, the present work did not consider other potential parameters affecting clinical performance, such as tine length inclination. However, the selected parameters of length and diameter are the most commonly measured during the device's manufacturing and quality control processes.

Conclusions

The ST-9 is dimensionally less variable with more consistent tine lengths and has smaller and more consistent tine tips. The ST-9 produced less wheal reaction to the negative control glycerin GLY solution than LM possibly leading to less false positive reactions in the ST-9 device. The lower variability of ST-9 seems to suggest a more consistent device. Although considered an engineering design and manufacturing problem, precision and high magnification inspection during the verification stage of SPT medical devices may have important clinical implications. Optimization of the magnification process as well as more clinical studies aimed at improving the precision of these devices in the clinical setting are warranted.

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Competing interests

Marvin Smollar and Troy Grogan are shareholders and senior management at MedScience Research Group, Inc., the owner of the patents, trademarks and FDA 510k clearance and the manufacturer of the ST-9 device.

Abbreviations

Skin prick test: SPT; Lincoln Multi-Test II: LM; Saline glycerin: GLY; Histamine: HIS; Allergen specific immunotherapy: AIT; Food and Drug Administration: FDA.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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None.

Ethics approval and consent to participate

This project was an ancillary study of Protocol 30-094 approved by Lake Erie College of Osteopathic Medicine Institutional Review Board.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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