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Local thermal reaction after influenza vaccination: Quantification by infrared imaging and biometric considerations

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ABSTRACT

Background: Extensive clinical investigations are mandatory to evaluate the safety and reactogenicity of vaccines. The recording of common adverse events like injection site soreness or general discomfort derives from individual subjective perceptions. Thermal imaging at the injection site possibly provides a non-subjective and a non-invasive approach to supplement this evaluation.

Results: A protocol for quantified injection-site infrared imaging included 86 participants during a flu vaccine campaign, 40% of whom had a thermal reaction of 1 °C; 25–30% had no thermal response. There was little subjective pain reporting and no clinical correlations were observed except with post-vaccination erythema.

Higher responses were linked with advanced age and multiple previous vaccinations.

Conclusion: Evan if influenza vaccine was only moderately reactogenic, a thermal response was detectable in about 70% of vaccinees, though no relationship to reactogenicity was seen.

Infrared imaging might however be a prospective tool for individual studies of vaccine-induced vascular responses.

1. Introduction

Vaccines are given to individuals to prevent a disease that often does not pose an immediate threat. Thus safety and tolerability always remain in the focus of attention and vaccines undergo stringent safety tests and clinical studies covering a considerable number of people [1–3]. Furthermore, post licensing observational studies could be initiated [4,5]. In contrast to the rare severe adverse events, mild and less important adverse events such as local swelling, redness, soreness or other subjective complaints appear more frequently, and may influence the individual acceptance of a vaccination [6–8] An additional approach based on high-resolution infrared imaging was proposed to reduce subjective aspects. It allows detailed mapping of local thermographic changes after vaccination caused by an increased blood flow.

The imaging protocol is based on recommended standards by Ammer and Ring [9]. A preceding pilot test covering five subjects after influenza vaccination for a timeline of 54 h revealed that a maximal thermal response occurs on the first day post vaccination with a mean of 0.70 °C, which drops down to 0.32 °C the next day (own data, unpublished). This time period is similar in studies regarding the occurrence of mild and less important adverse events after influenza vaccination in the first few days [10–13].

This study has two main objectives: firstly, to develop and verify a procedure to obtain relevant thermographic data after influenza vaccination; and secondly, to determine whether the thermal response correlates with adverse reactions. The seasonal influenza campaign for employees at a health care facility provides an opportunity to involve a sufficient high number of participants for a limited period [14,15].

2. Methods

The study protocol was reviewed and approved by the Ethics Committee of the Goethe University Faculty of Medicine (reference no. 64/12). 86 individuals working at medical facilities located in the Frankfurt area (Germany) participating at the seasonal influenza vaccination campaign were involved. All participants read and signed a consent form prior to participation. A first thermographic picture was taken before vaccination in the immediate vicinity of the vaccinator's room. The vaccine brand was selected by the health facility paying for the vaccination.

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The next day, after the second thermographic investigation, appearance of clinical signs, such as soreness, fatigue, itching, headache, fever and hoarseness were enquired.

In the case of local pain, a classification on a scale of 1–4 (without reaction, slight soreness, considerable soreness, and severe soreness with reduced mobility) was documented. The size of any local swelling or erythema was recorded. In addition, the numbers of past influenza vaccinations, age, and gender were noted. Subjects who obviously showed a deviation in the functional or morphological lateral symmetry on the upper arm were explicitly excluded.

2.1. Infrared imaging

The investigation took place in a draft-free room protected from direct sunlight with a mean temperature between 21 °C and 23 °C and a relative humidity between 40% and 65%. For thermal equilibration, all subjects had to stay with arms and shoulders naked for at least 10 min. The vaccination site, located on the upper arm, was marked with a small metallic circle using an Edding 750® paint marker. The same area at the unvaccinated site was marked with a "K". For thermal imaging, the Jenoptik VarioCAM High Definition infrared camera (InfraTec, Dresden, Germany) was used throughout. The distance from the camera to the upper arm was approximately 1–1.5 m. To ensure a standardised position, the TFT flat screen monitor from the infrared camera was superimposed with a transparent template to facilitate positioning the subjects' upper arms at a similar area.

2.2. Image processing and biometric considerations

Further processing of the infrared data was performed by thermo-analytic imaging software EXAM 5.7 and 5.8 (InfraMedic GmbH, Moerfelden-Walldorf, Germany). Firstly, the thermographic picture appears as a varying landscape of warmer and colder areas. For further processing of image data, a 'region of interest' was defined by inserting an elliptic template covering the area from the upper edge of the shoulder and the midpoint of the upper arm axis (Fig. 1). This selected part of the infrared image consists of approximately 3–5 thousand pixels, each representing a single temperature value. Based on these data, both the mean and the 80th percentiles were calculated for later comparison. If only the mean had been used, subjects with high peak temperatures on rather small areas could have been underestimated compared to subjects with comparable peak temperature but larger areas affected. To obtain one value describing the local rise in temperature after vaccination, at least two methods are possible. The simplified way was comparing the readout on the vaccinated (V) and the non-vaccinated control sides (C) 24 h later by their difference $\mathbf{(V_{24}\text{-}C_{24})}$, and only one appointment for the investigation was needed. However, because of a presumed bias caused by thermal left-right asymmetry, an additional first infrared image was taken immediately prior to vaccination. It led to a calculation according to the formula $\mathbf{(V_{24}\text{-}V_0)} - \mathbf{(C_{24}\text{-}C_0)}$ applicable both to means or percentiles of the individual readout.

2.3. Analysis methods

A two-sided significance level $\alpha = 0.05$ was used for all statistical tests. Significance of increase in temperature for each calculation method was evaluated using a one-sample *t*-test. Differences between subjects with or without erythema regarding the mean temperature change were tested using a two-sample *t*-test. The comparison of age groups (<25 years, 25–34 years, 35–44 years, 45–54 years, and 55 years and older) and different numbers of pre-vaccinations (0, 1, or ≥2) was done with a one factorial analysis of variation (ANOVA). A cut-off for the difference in mean temperatures was determined using a receiver operating characteristic (ROC) function. The statistical analysis was performed using SAS/STAT software, version 9.4, SAS System for Windows.

3. Results

This study involved 86 individuals employed at Frankfurt University Hospital (N = 39) or at the Federal Agency for Vaccines and Biomedicines (N = 47) located in the Frankfurt area (Germany). The ages varied between 21 and 63 (mean 43.6). A total of 54 female and 32 male participants were investigated during the vaccination campaign in 2013–2014.

In general, the infrared thermography provides a clear visualisation of local warming at the vaccination area (Fig. 1, Tables 1 and 2). The variation of the individual readout was characterised by three frequency distributions displayed in Fig. 2, comparing different algorithms. A reduced approach, Fig. 2 left graph, by

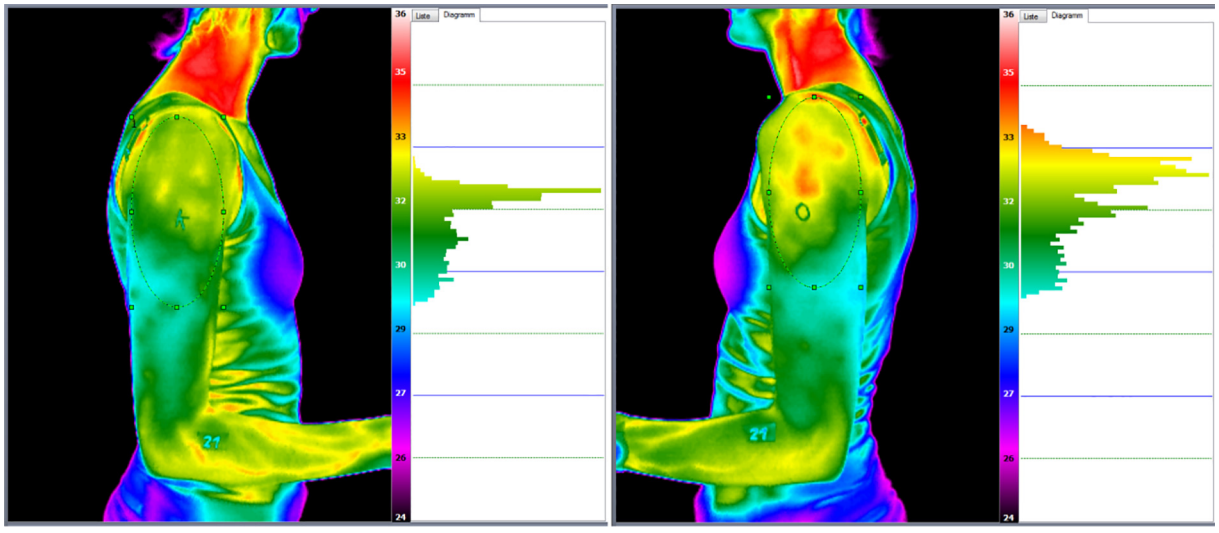

Fig. 1. Female subject 24 h following seasonal influenza vaccination. Left: In the unvaccinated arm, the average temperature in the region of interest, marked by elliptic template was 31.4 °C. Right: In the vaccinated arm, the average temperature was 32 °C. Histogram with frequency distribution of temperature pixels inside the elliptic region.

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