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Short Communication Open Access

Application of Wireless Temperature Monitors in Vaccine Clinical Trials and the Statistical Concerns Related to the Continuous Dependent Data

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Short Communication

In medical practices, researchers are developing tele-operated robots, prostheses, and smart monitoring systems to benefit services such as medical interventions, and studies [1]. For example, The remote monitoring of body temperature now wildly used in Intensive care units have enabled the real-time monitoring of the patients' body temperature [2], which make it possible for the nurses and doctors to collect the temperature information and grasp the physical condition dynamics timely. However, there were few vaccine clinical trials applied the remote real-time measuring approach until we brought an innovation to introduce the remote measuring platform into the field of vaccine clinical trials.

As we described in our previous study [3], we applied the wireless temperature platform in the phase I clinical trial designed to assess the safety and immunogenicity of a novel Ebola vaccine [4], there were two main purposes: first to provide more information for the safety evaluation and dose-selection of the Ebola vaccine, then to explore the application of the remote real-time temperature measuring platform in vaccine clinical trials. In this paper, we aimed to discuss the feasibility and practicality of the temperature measuring platform, and also, to introduce the data management and statistical concerns of the temperature data generated from the platform.

Study Design and Participants

This was a secondary research based on the randomized, double-blinded and placebo-controlled phase-I Ebola vaccine clinical trial, a total of 120 healthy participants were enrolled and randomly assigned into 3 treatment groups: low-dose group, high-dose group and the placebo group. This research was approved by the institutional review board of Jiangsu Provincial Center for Disease Control and Prevention.

Results and Discussion

The remote real-time temperature measuring platform

The temperature measuring platform was developed by TOSHONG Technologies, Nanjing, China. The main components of the platform were remote wireless thermometers, temperature measuring stations, software and server. The remote thermometer which carried infrared sensor was placed on the skin surface of the participant, at the intersection of left mid-axillary line and the third intercostal space, secured with adhesive tapes. The wireless thermometers measured the body axillary temperature and emitted the digital signal every two minutes. The temperature measuring stations picked up the signal transmitted by the wireless thermometers, the effective receiving distance was about 30 meters. The software was running on the server, which realized the function of processing, real-time displaying and early warning of the temperature data.

Compared with the traditional mercury thermometers, there were several advantages of wireless temperature measuring platform in vaccine clinical trials. In vaccine clinical trials, as required by the ethics principle, the participants should be benefit at greatest degree and avoid harm as much as possible, especially in phase-I trials , in which new vaccines are tested in people for the first time, so in the phase-I Ebola vaccine clinical trial, both wireless temperature measuring platform and traditional mercury thermometers were adopted, on the one hand, traditional thermometers are stable and conservative, we could analyze the fever reactions in the traditional way according to the protocol , on the other hand, wireless thermometers continually measured the temperature every two minutes and displayed the body temperature variation curves of the participants on the LCD screen located at the clinical trial site, which helped the staff to grasp the real-time information and carry out emergency settlement when real adverse events were to emerge.

However, there were some potential limitations of the wireless measuring platform, firstly, the transmission of signal rely on the condition of the wireless network and transfer distance, while signal-loss problems happened occasionally would result in the lack of data. Secondly, as described in our former paper [3], the wireless thermometers used in the Ebola vaccine clinical trial were hold on the skin surface with tapes, during a long measuring time, varying degrees of erythema and itch on the skin appeared in some of the participants, which urged the researchers to pause the usage of wireless thermometers, so we concluded that, wireless ear thermometers measuring the tympanic temperature would be tested instead in the subsequent vaccine clinical trials.

Statistical concerns related to continuous temperature data

Data management and visualization: The wireless measuring platform recoded the temperature and the corresponding time points, which were too messy for statistical analysis, so we first subtracted the vaccination time point from the measuring time points to get the intervals before or after vaccination for each participant. There were some occasional different temperature data at the same time point from the same person, in which case we considered taking more conservative stance to choose the maximum values. Missing values also existed throughout temperature measuring process which might be relevant to signal loss, the proportion of the missing data was 14.22%.In addition, any data less than 36.0°C, which may ascribed to

loose contact, were deleted. We then imputed the missing temperature data with last observation carry-forward (LOCF) method [5-7].

Time line charts were initially considered to demonstrate the temperature change through time, however we found the temperature line chats with irregular lines from different participants seemed so chaotic, in order to show the fever data at some time points intuitively, we used heat maps [8,9] which originated in 2D displays of the temperature values in a data matrix, fever values were represented by small red squares, normal values by light gray squares and missing values by white squares (part of the data shown in Figure 1). Whereas we left out the heat maps in our original research paper in consideration of space.

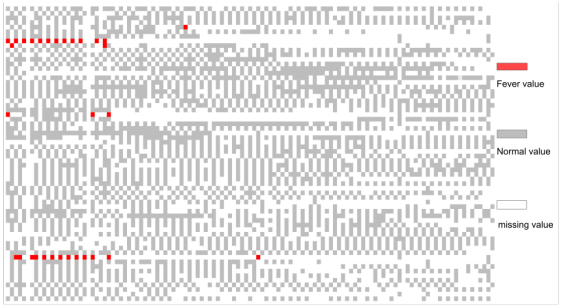

Figure 1: Heat map of the temperature data from each participant (part of the dataset).

Statistical Concerns

The temperature data from the same participant were likely to be correlated, but the data from different participants were assumed in general to be independent [10]. For example, in this study, temperature data from 113 participants accounting for 17412 effective records were obtained in the first 6 hours after vaccination. Generalized estimating equations (GEE) was used in our study to explore the relationship between fever and dose groups, demographical features such as sex, age and BMI. The results indicated that there was no statistical significant difference between high-dose group, low-dose group and the placebo group (Table 1). Male gender was a significant risk factor for fever compared with female gender (adjusted incidence rate ratios (IRRs) of 2.93 and 7.62 for any-grade fever or grade-2 fever respectively, P<0.001) [11].

GEE was forward by Liang Zeger [12] which is an extension of generalized linear models that provides a flexible approach to analysis of data from a longitudinal study. The key issue in the analysis of this kind of longitudinal data is that temperature values measured repeatedly within the same subjects tend to be correlated, and this correlation structure needs to be taken into account in the statistical analysis [13], the intra-participant correlation structure in our research was assumed to be exchangeable. In addition, GEE can cope with data with missing values, Liang has proved that if there are not too many missing values and missing is random, the GEE estimation is robust [14], the results of our analysis also indicated this, both datasets with missing data and imputed data with LOCF method were analyzed, and the differences between the statistical result were minimal.

Variables	Any (≥ 37.1°C)		Grade-2 (37.6-39.0)	
	IRR (95%CI)	P	IRR (95%CI)	P
Group 2low-dose *vs.* placebo	0.713(0.575-0.884)	0.002	0.996(0.615-1.612)	0.986
Group 3high-dose *vs.* placebo	0.673(0.551-0.822)	<0.001[a]	1.442(0.966-2.152)	0.073b
Sexmale *vs.* female	2.932(2.427-3.541)	<0.001	7.624(4.686-12.404)	<0.001
Age group	1.071(0.984-1.166)	0.113	0.783(0.668-0.919)	0.003
BMI	1.034(0.999-1.070)	0.054	0.667(0.613-0.726)	<0.001
Base-temperature	2.177(1.635-2.900)	<0.001	2.842(1.581-5.107)	<0.001
Time	1.003(1.003-1.003)	<0.001	1.006(1.004-1.008)	<0.001
ab				

Table 1: Generalized estimating equations results for analysis of risk factors of fever.

Further Work in the Future

Wireless ear thermometers measuring the tympanic temperature would be tested instead in the subsequent vaccine clinical trials. Furthermore, more details of the relationship between the febrile reaction and the indicators of the immunity level such as antibody titres and T-cell responses should be studied in the future.

References

1. Gonzalez FC, Villegas OO, Ramirez DE, Sanchez VG, Dominguez HO (2014) Smart multi-level tool for remote patient monitoring based on a wireless sensor network and mobile augmented reality. Sensors 14: 17212-17234.
2. Kim Y, Lee SK (2014) Energy-efficient wireless hospital sensor networking for remote patient monitoring. Information Sciences 282: 332-349.
3. Dai Q, Qi L, Hu Y, Meng F, Li J, et al. (2017) The early-onset febrile reaction following vaccination and associated factors: An exploratory sub-study based on the Ebola vaccine clinical trial. Human Vaccines Immunother 13: 1-6.
4. Feng-Cai Z, Li-Hua H, Jing-Xin L, Shi-Po W, Pei L, et al. (2015) Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial. The Lancet 385: 2272-2279.
5. Cismondi F, Vieira SM, Reti SR, Finkelstein SN (2013) Missing data in medical databases: Impute, delete or classify? Artificial Intelligence in Medicine 58: 63-72.
6. Siddiqui O, Ali MW (1998) A comparison of the random-effects pattern mixture model with last-observation-carried-forward (LOCF) analysis in longitudinal clinical trials with dropouts. Journal of Biopharmaceutical Statistics 8: 545-563.
7. Boers M (2008) Missing data in trials: do we have to keep carrying the last observation forward? Arthritis Rheum 59: 2-3.
8. https://en.wikipedia.org/wiki/Heat_map2017.
9. Pleil JD, Stiegel MA, Madden MC, Sobus JR (2011) Heat map visualization of complex environmental and biomarker measurements. Chemosphere 84: 716-723.

10. Chen F (2015) Statistical Methods for Dependent Data.
11. Dai Q, Liang Q, Hu Y, Meng F, Li J, et al. (2017) The early-onset febrile reaction following vaccination and associated factors: An exploratory sub-study based on the Ebola vaccine clinical trial. Hum Vaccin Immunother 13: 1-6.
12. Diggle PJ (1997) Introduction to Liang and Zeger (1986) Longitudinal Data Analysis Using Generalized Linear Models: Springer New York.
13. Verbeke G, Molenberghs G, Rizopoulos D (1986) Random Effects Models for Longitudinal Data2010. Biometrics 963-974.
14. Liang KY, Zeger SL (1986) Longitudinal data analysis using generalized linear models. Biometrika 73: 13-22.